captopril-reagent derivative adsorbs onto the cartridge packing from toluene and can be eluted with dimethylformamide.

A plasma sample with standard captopril disulfide (2 μg/mL) is run along with samples to compensate for incomplete reduction. If high (off scale) fluorescence readings from the sample are obtained, eluates from the cartridges can be diluted to proper concentration with dimethylformamide.

Recovery experiments were carried out by addition of various concentrations of captopril, captopril disulfide, captopril-cysteine disulfide, or captopril-glutathione disulfide to plasma. These were kept at room temperature for 4 h then stored at 5°C overnight. Results are shown in Table II. Recoveries ranged from 95 to 104%.

Reproducibility was checked by performing six assays of a plasma sample spiked with captopril disulfide at 2 μg/mL (Table III). Precision at this concentration is 1.7% (*CV*).

Results obtained by the fluorometric method were compared with those obtained by the GC–MS method (Table IV). The data were correlated by linear regression analysis, which yielded an intercept of 5.6, a slope of 0.9914, and a correlation coefficient of 0.9949. Agreement between the methods is acceptable.

Although the fluorometric method is very sensitive (because as little as 2 ng of a pure captopril standard/mL of dimethylformamide solution can be accurately measured in a 1-cm cell, without HPLC separation), the method can be used for measuring captopril in plasma containing >200 ng of the drug/mL. Therefore, it is suitable for patients who accumulate captopril during extended therapy and have microgram per milliliter levels of captopril plus disulfide metabolites in plasma. It can be especially useful to the small hospital laboratory which does not have expensive instrumentation (such as GC–MS) available.

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Reverse-Phase High-Performance Liquid Chromatographic Determination of Halogenated 8-Hydroxyquinoline Compounds in Pharmaceuticals and Bulk Drugs

EDWARD J. WOJTOWICZ

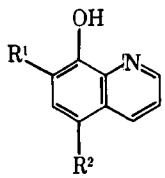
Received August 23, 1983, from the *Food and Drug Administration, 599 Delaware Avenue, Buffalo, NY 14202.* Accepted for publication December 6, 1983.

Abstract □ A reverse-phase high-performance liquid chromatographic (HPLC) method was developed for determining iodochlorhydroxyquin, 5,7-dichloro-8-hydroxyquinoline, and 5,7-diiodo-8-hydroxyquinoline in creams, ointments, shampoos, tablets, and bulk drugs. A column packed with 10-μm phenyl-silica and a mobile phase of 0.001 M $NiCl_2$ in acetonitrile–methanol–water (30:20:50) was used to separate the nickel complexes of the three drugs, with detection at 273 nm. Analysis of creams, ointments, shampoos, and tablets gave results close to the label declarations. Recovery of standard material added to samples was ≥98%. Linearity of response was shown over a range of 30–150% of label claim for standards of the three drug substances. Multiple analyses of iodochlorhydroxyquin and diiodohydroxyquinoline bulk drugs showed purities of 99.96 and 98.77% with *CV* of 1.17 and 0.73%, respectively. The HPLC method offers an alternative to current USP procedures, which lack stability-indicating and specificity characteristics.

Keyphrases □ HPLC—Halogenated 8-hydroxyquinoline compounds □ 8-Hydroxyquinoline—halogenated, HPLC

The current USP XX IR spectrophotometric procedure (1) for determining iodochlorhydroxyquin (I) in creams and ointments has many deficiencies, as reported by Gruber *et al.* (2), who used GC to determine trimethylsilyl ether derivatives of related halogenated 8-hydroxyquinolines. A colorimetric procedure (3) complexed I with nickel ion. However, other 8-hydroxyquinolines, present as impurities, would interfere to give high results. A normal-phase high-performance liquid chromatographic (HPLC) procedure (4) involved esterification of I using a mixture of pyridine–acetic anhydride, an evaporation step, and a reconstitution of the residue in the mobile phase. Procedures using anion-exchange HPLC (5, 6) and reverse-phase HPLC (7, 8) failed to adequately separate I from other 8-hydroxyquinolines.

In this study, a simple and specific reverse-phase HPLC method was developed to separate and quantitate iodochlorhydroxyquin (I), 5,7-dichloro-8-hydroxyquinoline (II), and 5,7-diiodo-8-hydroxyquinoline (III) as their nickel complexes



I, $R^1 = I$, $R^2 = Cl$
II, $R^1 = R^2 = Cl$
III, $R^1 = R^2 = I$
IV, $R^1 = H$, $R^2 = Cl$
V, $R^1 = R^2 = H$
I.S., $(C_6H_5)_2NH$

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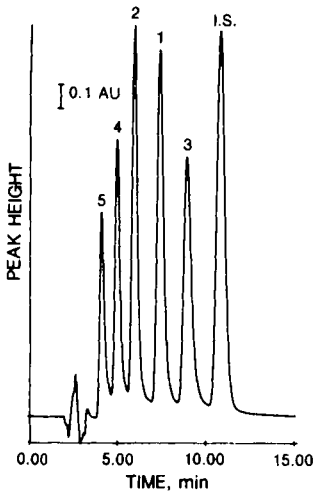

Figure 1—*Chromatogram of a mixture of iodochlorhydroxyquin (1), 5,7-dichloro-8-hydroxyquinoline (2), 5,7-diiodo-8-hydroxyquinoline (3), 5-chloro-8-hydroxyquinoline (4), 8-hydroxyquinoline (5), and diphenylamine (I.S.) determined at a detector setting of 0.1 AU and 273 nm.*

in bulk drug form and in pharmaceuticals. The HPLC system also resolved I, II, and III from 5-chloro-8-hydroxyquinoline (IV) and 8-hydroxyquinoline (V), which are precursors in the syntheses of bulk forms of the drugs.

EXPERIMENTAL SECTION

Materials—Nickel chloride hexahydrate[1], iodochlorhydroxyquin[2], 5,7-dichloro-8-hydroxyquinoline[3], 5,7-diiodo-8-quinolinol[2], 5-chloro-8-hydroxyquinoline[4], 8-hydroxyquinoline[4], and diphenylamine[5] were used as received. Methanol[6], acetonitrile[6], and tetrahydrofuran[6] were distilled in glass.

Chromatographic System—The liquid chromatographic system consisted of a high-pressure pump[7], a variable-wavelength UV detector[8], an integrator-recorder[9], and a phenyl column (10 μm, 30 cm × 3.9 mm)[10]. The mobile phase, 0.001 M $NiCl_2$, was prepared in acetonitrile–methanol–water (30:20:50) and filtered before use. The flow rate of the mobile phase was 1.2 mL/min. The detector was set at 273 nm and at a range of 0.1 AUFS. The integrator-recorder was used at an attenuation setting equal to 8 mV, a threshold value of 3, and a peak width setting of 0.16 in the peak height measuring mode.

Quantitative Procedure for Iodochlorhydroxyquin (I)—Ointment or cream samples containing an equivalent of 30 mg of I were dissolved with heating in 40–50 mL of tetrahydrofuran. The solutions were quantitatively transferred to 100-mL volumetric flasks and diluted to volume with tetrahydrofuran. An accurately weighed 30-mg portion of USP standard I was transferred to a 100-mL volumetric flask and diluted to volume with tetrahydrofuran. Five-milliliter aliquots of sample and standard preparations were transferred to separate 50-mL volumetric flasks. One milliliter of a 10-mg/mL methanolic solution of nickel chloride was added to each flask, and the flasks were shaken to disperse the reagent.

The complex formed between nickel and I produced a yellow solution. An internal standard solution of 80 mg of diphenylamine in 200 mL of methnol was prepared, and 5.0-mL portions were transferred into each 50-mL flask. The petrolatum base in ointments or creams precipitated when the internal standard solution was added. The flasks were diluted to volume with methanol. Injections were made from the final standard and filtered sample solutions. Peak height response relative to the internal standard was used to calculate the amount of I in the samples.

Quantitative Procedure for II—An accurately weighed portion of a shampoo, containing an equivalent of 30 mg of II, was dissolved with heating in 40–50 mL of methanol. The solution was quantitatively transferred to a 100-mL volumetric flask and diluted to volume with methanol. A standard of 30 mg of II was accurately weighed into a 100-mL volumetric flask and diluted to volume with methanol. Two-milliliter aliquots of the sample and standard preparations were transferred into separate 50-mL volumetric flasks. One milliliter of the methanolic nickel chloride reagent and 3.0 mL of the internal standard solution were added to the sample and standard flasks. The solutions were diluted to volume with methanol, and the samples were filtered before HPLC. Peak height response relative to the internal standard was used to quantitate II.

[1] ICN Pharmaceuticals, Inc., Plainview, N.Y.
[2] USP Reference Standard.
[3] Westwood Pharmaceuticals, Buffalo, N.Y.
[4] Pfaltz and Bauer, Stamford, Conn.
[5] Merck and Co, Rahway, N.J.
[6] Burdick and Jackson Laboratories, Muskegon, Mich.
[7] Model 6000A; Waters Associates, Milford, Mass.
[8] Model SF-770; Schoeffel Instruments, Westwood, N.J.
[9] Model 3390A, Hewlett-Packard, Avondale, Pa.
[10] μ-Bondapak; Waters Associates.

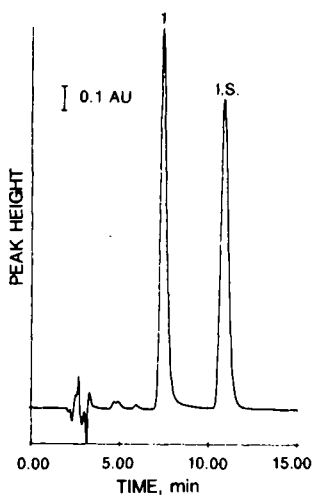

Figure 2—*Chromatogram of ointment preparation of iodochlorohydroxyquin (1) and diphenylamine (I.S.), at a detector setting of 0.1 AU and 273 nm.*

Quantitative Procedure for III—An accurately weighed portion of cream equivalent to 20 mg of III was dissolved with heating in 40–50 mL of tetrahydrofuran. The solution was quantitatively transferred to a 100-mL volumetric flask and diluted to volume with tetrahydrofuran. For the tablet form, 20 tablets were accurately weighed and finely powdered. An accurately weighed portion of the ground composite equivalent to 200 mg of III was transferred to a 250-mL volumetric flask with ~150 mL of tetrahydrofuran. The flask was heated on a steam bath for a few minutes and then shaken for 30 min on a mechanical shaker. After dilution to volume with tetrahydrofuran, a 25-mL aliquot was diluted to volume with tetrahydrofuran in a 100-mL volumetric flask. An accurately weighed 20-mg portion of standard III was diluted to volume with tetrahydrofuran in a 100-mL volumetric flask. Five-milliliter aliquots of the sample and standard preparations were transferred into separate 50-mL volumetric flasks, and 1 mL of the methanolic nickel chloride reagent and 3.0 mL of the internal standard solution were added to each flask. After dilution to volume with methanol, the standard preparation and filtered samples were chromatographed. Peak height response relative to the internal standard was used to quantitate III in the samples.

Quantitation Procedure for Bulk Drugs—Accurately weighed bulk drug

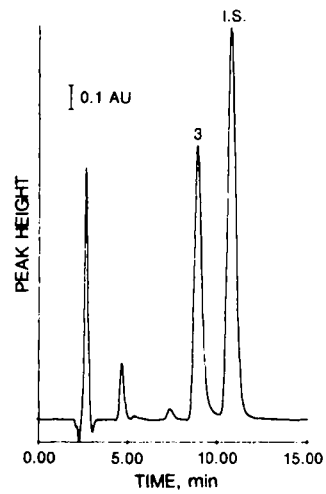

Figure 3—*Chromatogram of cream preparation of 5,7-diiodo-8-hydroxyquinoline (3) and diphenylamine (I.S.), at a detector setting of 0.1 AU and 273 nm.*

Table I—Results of Analyses of Pharmaceutical Formulations

Dosage Form	Active Ingredient	Manufacturer[a]	Found, %[b]
Ointment	3% Iodochlorhydroxyquin	A	3.02, 3.00
Cream	3% Iodochlorhydroxyquin	A	3.00, 3.00
Ointment	3% Iodochlorhydroxyquin plus 0.5% HC[c]	A	3.03, 3.04
Cream	3% Iodochlorhydroxyquin 0.5% HC	A	3.08, 3.04
	3% Iodochlorhydroxyquin plus 1% HC	B	2.92, 2.92
	3% Iodochlorhydroxyquin plus 0.5% HC	C	3.05, 2.98
Shampoo	2% 5,7-dichloro-8-hydroxyquinoline	D	1.98, 1.95
		D	1.96, 1.99
Cream	1% 5,7-diiodo-8-hydroxyquinoline plus 1% HC	E	1.04, 1.02
Tablet	210 mg of 5,7-diiodo-8-hydroxyquinoline tablet	F	208, 209[d]
	650 mg of 5,7-diiodo-8-hydroxyquinoline tablet	F	644, 650[d]

[a] Key: (A) Ciba Pharmaceutical, Summit, N.J.; (B) E. Fougera and Co., Melville, N.Y.; (C) Dome Laboratories, West Haven, Conn.; (D) Westwood Pharmaceuticals, Buffalo, N.Y.; (E) Dermik Laboratories, Fort Washington, Pa.; (F) Vitarine Co., Springfield Gardens, N.Y. for Glenwood Inc., Tenafly, N.J. [b] Each pair of results represents duplicate assays of a different lot of each dosage form. [c] HC = hydrocortisone. [d] mg.

samples were diluted to volume with tetrahydrofuran in 100-mL volumetric flasks and treated similarly to the cream and ointment samples after appropriate dilution.

System Suitability—The HPLC system in this study was suitable when a resolution factor of at least 1.5 was obtained between the sample and internal standard peaks, and a relative *SD* of ≤2% was achieved for the response ratio of the two peaks after five replicate injections.

RESULTS AND DISCUSSION

Early in this study, it was evident that iodochlorhydroxyquin (I) needed to be chemically modified to obtain a satisfactory reverse-phase high-performance liquid chromatogram. This modification had to be quantitative and easy to accomplish for analytical method application.

The formation of chelate complexes of 8-hydroxyquinolates with bivalent inorganic ions was explored. Salts of zinc and bivalent nickel, copper, and cobalt were used as complexing agents for I. Reverse-phase HPLC of methanolic solutions of these complexes, through octadecylsilane columns of 5- and 10-μm particle sizes with mobile phase composed of combinations of methanol, water, acetic acid, and various ion-pairing chemicals, was unsuccessful.

Reverse-phase HPLC has been used with a mobile solvent system containing nickel acetate to determine aniline and its metabolites (9). The use of bivalent metal ion salts in the mobile phase was investigated for the chromatography of chelate complexes of I. When a mobile solvent system of 0.01 M $NiCl_2$ in

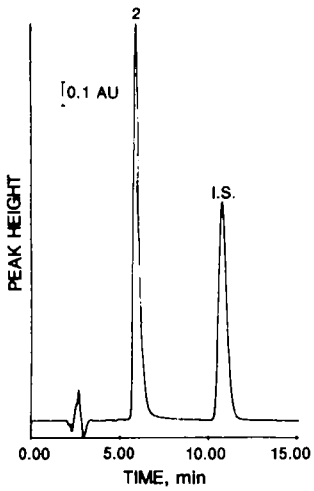

Figure 4—*Chromatogram of shampoo preparation of 5,7-dichloro-8-hydroxyquinoline (2) and diphenylamine (I.S.) at a detector setting of 0.1 AU and 273 nm.*

Table II—Recovery of Added Standards

Product	Standard	Amount Added, mg/g	Amount Found, mg/g	Recovered, %
3% Iodochlorhydroxyquin plus 1% HC[a] cream	I	29.3	29.3	100.0
3% Iodochlorhydroxyquin plus 0.5% HC ointment	I	21.7	21.3	98.2
2% 5,7-dichloro-8-hydroxyquinoline shampoo	II	16.5	16.2	98.2
1% 5,7-diiodo-8-hydroxyquinoline plus 1% HC cream	III	9.7	9.72	100.2
210-mg tablet	III	130.4	129.7	99.5
650-mg tablet	III	126.6	127.0	100.3

[a] HC = hydrocortisone.

methanol–water (75:25) was used, I eluted from a C_{18} column with some tailing.

Substitution of a phenyl-bonded column, addition of acetonitrile to the mobile phase, increase of the water content in the mobile phase to 50%, and reduction of the nickel salt concentration to 0.001 M yielded an HPLC system which separated the nickel complexes of five related standard hydroxyquinolates. This chromatographic system was used to quantitate I, II, and III in pharmaceuticals. Diphenylamine was chosen as the internal standard because it absorbed in the same UV region as the complexes and was adequately separated from the Ni–III complex, which was the last to elute from the column (Fig. 1).

Tetrahydrofuran was chosen as the solvent for petrolatum-based creams or ointments and tablet formulations of I and III. Methanol was used with a shampoo containing II. Warming the samples in the appropriate solvent on a steam bath aided in dispersing the samples and dissolving the active ingredients. Warming the initial standard preparations ensured their complete dissolution.

Addition of the methanolic nickel chloride solution to aliquots of the sample and standard preparations resulted in the immediate formation of the yellow organometallic complex. The metal salt was added in ≥10-fold excess for complete complexation. Addition of the methanolic solution of the internal standard, and dilution with methanol to volume, caused precipitation of the petrolatum in ointment or cream samples and necessitated filtration of these samples before chromatography.

The absorbance maximum for the Ni–I complex was 273 nm; this wavelength was also used in determining the nickel complexes of II and III. The presence of hydrocortisone or formulation excipients in ointments and creams did not interfere with sample analysis. Hydrocortisone eluted in ~4.8 min from the column and had a low absorbance at 273 nm. Figures 2 and 3 are typical chromatograms obtained from ointment and cream preparations of I and III formulated with hydrocortisone. Figure 4 is a chromatogram of a shampoo containing II.

Table I gives the results of duplicate analyses of different lots of preparations containing I, II, and III. Close agreement with label claim is evident. Recoveries for standards added to the prepared samples are listed in Table II. Recoveries of ≥98% were obtained for each added standard.

Linearity of response was tested by preparing a standard curve for five different concentrations of standards of I, II, and III. A correlation coefficient of 0.999 was obtained for each standard over a range of ~30–150% of the label claim, based on sample preparation using the proposed procedure.

Bulk drug samples of I and III were analyzed five times. An average purity of 99.96% with a 1.17% *CV* was obtained for I, while the bulk sample of III had an average purity of 98.77% and a *CV* of 0.73%.

The high selectivity and efficiency achieved by the use of metal ions in mobile solvents for reverse-phase HPLC have been attributed to secondary chemical equilibria (10). These secondary chemical equilibria control retention time and peak symmetry, and, if chromophoric counterions are used, detection will be enhanced. When nickel ion was absent from the mobile phase used in this study, no peaks were detected when a mixture of nickel complexes was injected into the column. Addition of the metal ion and adjustment of acetonitrile content resulted in a well-resolved chromatogram. The solvation effect of the acetonitrile in the mobile phase gave the eluting peaks a symmetry that was lacking in systems of water–methanol solutions of the nickel salt.

The use of metal ion salts in reverse-phase HPLC should find increasing application in research involving biochemical and pharmaceutical substances. The method presented here is stability indicating because possible decomposition products and impurities are separated from the parent compound, and the method is an alternative for the current official USP procedures (1,

11) for assaying and identifying I and III in bulk drug form or pharmaceutical preparations.

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Distribution and Elimination of Coated Polymethyl [2-^{14}C]Methacrylate Nanoparticles After Intravenous Injection in Rats

DANIEL LEU *§, BARBARA MANTHEY ‡, JORG KREUTER §, PETER SPEISER §, and PATRICK P. DeLUCA *x

Received March 11, 1983, from **The University of Kentucky College of Pharmacy, Lexington, KY 40536* and the §*School of Pharmacy, Swiss Federal Institute of Technology, CH-8603 Schwerzenbach, Switzerland.* Accepted for publication October 28, 1983. ‡Present address: Institute of Toxicology, Swiss Federal Institute of Technology, CH-8092 Zurich, Switzerland.

Abstract □ Surfactant-coated polymethyl [2-^{14}C]methacrylate nanoparticles had significantly different time-course distribution patterns in rats than noncoated and albumin-coated particles. Blood concentrations of poloxamer 188-coated particles were 70-fold higher after 30 min, and the particles persisted at higher levels in the circulation for up to 2 h. The initial and final liver levels were significantly lower (38% after 30 min, 51% after 7 d) and spleen levels were significantly higher (21% after 30 min, 23% after 7 d) than noncoated particles (74% in the liver and 5% in the spleen after 7 d) and the albumin-coated particles (84% in the liver and 5% in the spleen after 7 d). Specific activity was somewhat higher for the surfactant-coated particles in other organs such as the lungs, kidneys, testicles, ovaries, and lymph nodes. The bovine serum albumin sorption behavior of polymethyl methacrylate nanoparticles was followed under various conditions, and adsorption was found to increase with increasing protein concentration and increasing temperature, reaching a maximum at the isoelectric point of pH 4.9 after ~12 h of incubation. The zeta potential of the particles decreased with increasing pH, and the change was more pronounced with the albumin-coated particles.

Keyphrases □ Polymethyl methacrylate—^{14}C-labeled nanoparticles, distribution and elimination in rats, intravenous injection □ Distribution—^{14}C-labeled polymethyl methacrylate nanoparticles, intravenous injection, rats □ Elimination—^{14}C-labeled polymethyl methacrylate nanoparticles, intravenous injection, rats

There is growing interest in polymeric drug-delivery systems for parenteral administration to provide sustained release and action, and to increase the stability of easily metabolized drugs (1, 2). Nanoparticles (10 nm–1 μm) have been suggested as new drug-delivery systems (3–6). The goal is to develop a system to direct potent drug molecules to specific organs or cells, thereby limiting the systemic levels and potential toxicity to healthy or normal tissues and cells.

Polymethyl methacrylate has been used in surgery for over 30 years as a material for artificial bones (7). Implanted methyl methacrylate polymers appear to be well tolerated if the implants are monomer-free and under a certain threshold size (8). However, little is known about the biodegradability and the elimination of polymethyl methacrylate particles from the body. Nanometer-size particles exhibit a much larger surface area than the implants used in previous studies (9, 10) and are expected to degrade much faster. Information on the long-term effects of acrylic polymer particles on the living cell, however, is scarce (11).

It is generally accepted that polymers in the form of nanometer-size particles are mainly taken up by the cells of the reticuloendothelial system, predominantly in the liver and spleen. It was found that 70% of polymethyl [2-^{14}C]methacrylate nanoparticle radioactivity localized in the liver of rats 7 d after intravenous administration in phosphate-buffered saline (12). The clearance of labeled polystyrene divinylbenzene microspheres (3–25 μm) from the blood was size-dependent in beagle dogs (13, 14). Microspheres of ≥8 μm were mechanically filtered and retained in the lungs, while smaller spheres cleared the lungs and localized in the liver and spleen. Although the effect of physicochemical surface properties on distribution has been recently reported (15), the possible long-term effects associated with retention of particulate matter in the body tissues have not been studied.

Emulsifying agents have been found to affect the fractional removal rate of lipid emulsions from the blood stream (16, 17). Since emulsifying agents appear to play a major role in the removal of lipid substances from the blood stream, it was anticipated that adsorbed surfactants also influence the clearance of polymethyl methacrylate nanoparticles from the blood. Other workers have demonstrated the significance of plasma components with respect to the uptake of particulate polymeric matter by cells of the reticuloendothelial system and, accordingly, in the clearance from the blood and subsequent organ distribution (18, 19). Distribution in various organs has been reported to be influenced by the surface charge of the particles. Microspheres with adsorbed positively charged proteins (18) and nonionic surfactant (15) show a decreased uptake by the liver.

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