Simple and Specific Electron-Capture GLC Assay for Plasma and Urine Ephedrine Concentrations following Single Doses

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Abstract □ An electron-capture GLC procedure for determination of plasma ephedrine concentrations is described. The procedure is capable of determining 2 ng/ml of ephedrine and is adequate for following profiles after 25-mg single doses. Pentane extraction of the drug and the internal standard and formation of the *N*-pentafluorobenzoyl derivatives were followed by GLC. Plasma ephedrine concentrations following a 24-mg dose of ephedrine hydrochloride to a human volunteer are presented. Formation of *N*-trifluoroacetyl, *N*-pentafluoropropionyl, *N*-heptafluorobutryl, and *N*-pentafluorobenzoyl derivatives and their GLC–mass spectrometric identification are discussed together with comparative electron-capture sensitivities of these derivatives toward a nickel-63 detector. The detection of the *N*-pentafluorobenzoyl derivative of ephedrine is at least 100-fold greater in sensitivity than detection of the *N*-trifluoroacetyl derivative.

Keyphrases □ Ephedrine—electron-capture GLC analysis in human plasma and urine □ Electron-capture GLC—comparison of various fluoroacyl derivatives of ephedrine □ GLC, electron capture—analysis, ephedrine in plasma and urine

Ephedrine (I) is widely used in the treatment of asthma, either alone or in combination with theophylline and a barbiturate. Several GLC methods (1–4) are adequate for determining plasma and urine ephedrine concentrations following therapeutic doses but are not sensitive enough for single-dose pharmacokinetic and bioavailability studies.

GLC with flame ionization has been used to estimate ephedrine and its congeners in urine (1). Heptafluorobutyryl ephedrine derivatives following benzene extraction of basified serum were used for electron-capture analysis of blood levels at therapeutic dosages (2). Previously reported procedures have been insufficiently sensitive for clinical use (3, 4).

No details are available on a modification of an electron-capture GLC assay for pseudoephedrine and norpseudoephedrine, which may have the sensitivity required for single-dose bioavailability studies (5).

A simple and specific electron-capture GLC assay of ephedrine and norephedrine is described. This procedure has a 2-ng/ml sensitivity and is used routinely for assay of ephedrine bioavailability following a single dose of the drug either alone or in combination with theophylline and a barbiturate.

EXPERIMENTAL

Reagents—Glass-distilled *n*-pentane[1] and analytical grade amyl acetate[2] were employed. Pentafluorobenzoyl chloride[3], trifluoroacetic anhydride[3], heptafluorobutyric anhydride[3], pentafluoropropionic anhydride[3], and pyridine[3] were all GLC grade. *d,l*-Ephedrine hydrochloride[4], *d,l*-norephedrine hydrochloride[4], and 3,4-dimethoxyamphetamine hydrochloride[4] were donated. *d,l*-Ephedrine[5] free base, *p*-hydroxyephedrine[5], and *p*-hydroxynorephedrine[5] were purchased. All other chemicals were analytical reagent grade.

Stock solutions of I (100 μg/ml) and the internal standard 3,4-dimethoxyamphetamine (II) (100 μg/ml) were prepared weekly by dissolving their hydrochloride salts in water. Appropriate dilutions were made daily as required.

Plasma Level Study—Ephedrine hydrochloride (24 mg) was administered in a combination tablet[6], which also contained theophylline (130 mg) and phenobarbital (8 mg), to a healthy 67.6-kg male volunteer. Blood samples, 10 ml, were withdrawn from the cubital vein into heparinized tubes[7] at 10 appropriate time intervals. The blood samples were centrifuged, and the plasma was transferred to another tube before storage at −10°.

Extraction of Ephedrine—To 1 ml of plasma or 0.1 ml of urine diluted to 1 ml with distilled water, in a 15-ml glass round-bottom tube[8], were added 1 ml of aqueous solution of II (100 ng/ml) and 0.5 ml of 10 *N* NaOH. The sample was mixed[9] for 30 sec, and 7.0 ml of glass-distilled pentane[1] was added before mixing[10] for 10 min followed by centrifugation[11] (5 min at 0° at 6000 rpm). The clear organic extract was transferred by Pasteur pipet to an 8-ml polytef[12]-lined, screw-capped, round-bottom tube[13].

Pentafluorobenzoyl chloride[3], 0.1% in pentane (200 μl), was added to the extract. The tube was tightly stoppered and incubated[14] at 65° for 90 min. Then the tube was allowed to reach room temperature, and a small antibumping granule[2] was added. The sample was evaporated[14] at 65° without nitrogen until just dry.

To the dried reaction mixture, 0.5 ml of 0.1 *N* NH_4OH was added and the sample was mixed[9] for 30 sec. Amyl acetate[2] (50 μl) was added, and the sample was mixed[9] for 30 sec and centrifuged[15] for 2 min at 2500 rpm. Approximately 25 μl of the amyl acetate solution was transferred to a 1-ml disposable screw-capped vial[13]. About 2–3 μl of the sample was injected into the gas chromatograph.

GLC—The gas chromatograph[16] was equipped with a ^{63}Ni electron-capture detector. The column was a spiral glass tube[17], 0.9 m long × 2.0 mm i.d., packed with 3% phenyl cyanopropyl methyl silicone[18] coated by fluidization on acid-washed, dimethylchlorosilane-treated, 100–120-mesh, high-performance, flux-calcined diatomite support[19].

The column was conditioned at 245° for 48 hr with low nitrogen flow. For plasma analysis, the injection port, outlet, and oven temperatures were 250, 260, and 235°, respectively. Argon–methane (95:5) as a carrier gas was maintained at 93 ml/min. The ^{63}Ni detector was operated at 325° with a standing current of 3.0 namp.

For determination of the response of various ephedrine derivatives, the column was operated from 170 to 230°. The detector was operated at a standing current of 2.0 namp.

Calculations—Peak height ratios were calculated by dividing the peak height from the *N*-pentafluorobenzoyl derivative of I (1.40 min) by that of the *N*-pentafluorobenzoyl derivative of II (3.82 min). Calibration

[1] Caledon Laboratories Ltd., Georgetown, Ontario, Canada.
[2] British Drug House, Toronto, Ontario, Canada.
[3] Pierce Chemical Co., Rockford Ill.
[4] Dr. Keith Bailey, Drug Identification Division, Drug Research Laboratories, Health Protection Branch, Ottawa, Ontario, Canada.
[5] Aldrich Chemical Co., Milwaukee, Wis.
[6] Tedral, Warner-Chilcott Laboratories Co., Toronto, Ontario, Canada.
[7] Vacutainers, Becton Dickinson and Co., Mississauga, Ontario, Canada.
[8] Corex, Sorvall Inc., Newtown, Conn.
[9] Vortex Genie, Fisher Scientific Co., Montreal, Quebec, Canada.
[10] Evapo-Mix, Fisher Scientific Co., Montreal, Quebec, Canada.
[11] RC2-B centrifuge, Sorvall Inc., Newtown, Conn.
[12] Teflon, du Pont.
[13] Fisher Scientific Co., Montreal, Quebec, Canada.
[14] Thermolyne Dri-Bath, Fisher Scientific Co., Montreal, Quebec, Canada.
[15] HNS, Fisher Scientific Co., Montreal, Quebec, Canada.
[16] Model 3920, Perkin-Elmer, Montreal, Quebec, Canada.
[17] Chromatographic Specialties, Brockville, Ontario, Canada.
[18] OV-225, Chromatographic Specialties, Brockville, Ontario, Canada.
[19] Chromosorb W, Chromatographic Specialties, Brockville, Ontario, Canada.

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Table I—Electron-Capture Sensitivity and Retention Times of Ephedrine Derivatives

Derivative	Response, coulombs × 10^3/mole	Retention Time, min	Column[a] Temperature
Pentafluorobenzoyl	14.303	1.42	230°
Heptafluorobutyryl	0.971	1.04	170°
Pentafluoropropionyl	0.812	1.28	170°
Trifluoroacetyl	0.013	1.46	170°

[a] Chromatographed on OV-225.

curves were constructed by plotting the spiked control plasma peak height ratios against the concentrations of I (nanograms per milliliter of plasma).

Electron-Capture Response of Various Ephedrine Derivatives—*Stock Solution of* d,l-*Ephedrine*—A solution of *d,l*-ephedrine free base (1000 μg/ml) in glass-distilled pentane was prepared.

N-*Trifluoroacetyl,* N-*Heptafluorobutyryl, and* N-*Pentafluoropropionyl Derivatives*—To 1 ml of I stock solution (1000 μg) in an 8-ml polytef-lined, screw-capped, round-bottom tube[13] were added either 0.5 ml of trifluoroacetic anhydride[3] or 200 μl of heptafluorobutyric[3] or pentafluoropropionic anhydride[3] and 20 μl of pyridine[3]. The tubes were tightly stoppered and incubated for 60 min at 45° for trifluoroacylation or for 90 min at 65° for other derivatives. The tubes were cooled to room temperature, a small antibumping granule was added to each, and excess anhydride was removed by evaporation without nitrogen until just dry at 45° for trifluoroacetic anhydride and at 65° for other anhydrides. Then 1 ml of 1 *N* NaOH and 0.5 ml of amyl acetate[2] were added, and the contents of the tube were mixed for 5 min and centrifuged for 2 min at 2500 rpm. Appropriate dilutions of each derivative were made with amyl acetate to yield final concentrations of 13.33 ng/μl for the *N*-trifluoroacetyl derivative and 6.66 ng/μl for the other two derivatives.

N-*Pentafluorobenzoyl Derivative*—The reaction was the same as described for the other *N*-acyl derivatives. In this case, dilution of 10 μl of pentyl acetate to 15 ml yielded a final concentration of 0.67 ng/μl. Flame-ionization GLC analysis of the three undiluted reaction mixtures described previously showed that at least 95% of I was present as the corresponding *N*-monoacyl derivative.

Di-Derivatives of Ephedrine with Trifluoroacetic Anhydride, Heptafluorobutyric Anhydride, and Pentafluoropropionic Anhydride—The reactions for the di-derivatives of I were the same as described for each reagent, except that the derivative was back-extracted following the addition of 1 ml of 0.1 *N* NH_4OH instead of 1 ml of 1 *N* NaOH.

Measurement of Electron-Capture Response—The electron-capture response of the ephedrine amide derivatives was determined by mixing the pentafluorobenzoyl derivative with each derivative separately at a ratio of exactly 1:1 (v/v). This step was necessary because the former three derivatives did not separate completely under the chromatographic conditions employed. No change in the response of the *N*-pentafluorobenzoyl derivative was observed when it was chromatographed separately or as a mixture with any of the three derivatives. The response of the other three derivatives was calculated using the *N*-pentafluorobenzoyl derivative as a reference.

Each fluoroacyl derivative gave a sharp symmetrical peak when chromatographed under the conditions described. The response of each derivative was expressed in 10^3 coulombs/mole and was calculated for each derivative from its peak area (width of the peak at half height × peak height) by converting the area to coulombs from the chart speed and the current for full-scale deflection.

RESULTS AND DISCUSSION

N-Pentafluorobenzoyl derivatives of I, norephedrine, and the internal standard (II) gave sharp peaks (a, b, and c, Fig. 1B) with retention times of 1.40, 2.38, and 3.82 min, respectively. The presence of these *N*-pentafluorobenzoyl derivatives was established by GLC–mass spectrometry[20].

The GLC–mass spectra of the *N*-pentafluorobenzoyl derivative of I and norephedrine did not give molecular ions, but diagnostic ions for the derivative of I were at *m/e* 252, 253, 234, 195, 167, 107, 105, 79, and 77. For the derivative of norephedrine, they were at *m/e* 238, 239, 195, 167, 107, 105, 79, and 77. The GLC–mass spectrum of the *N*-pentafluorobenzoyl derivative of II gave a molecular ion at *m/e* 389 and other characteristic ions at *m/e* 238, 178, 151, 121, 195, 167, 91, and 77. These mass spectra indicate that peaks a, b, and c (Fig. 1) were due to *N*-monoacyl derivatives.

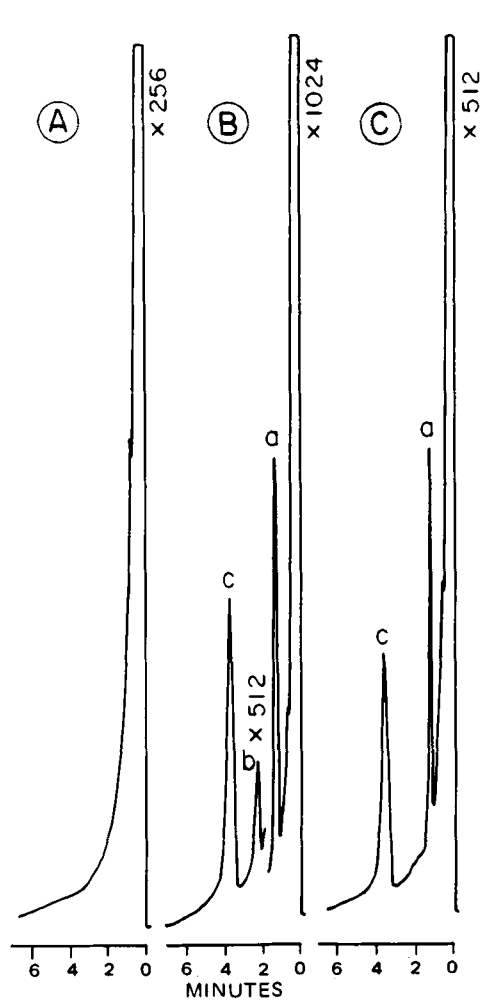

Figure 1—*Typical chromatograms of human plasma. Key: A, blank control plasma; B, spiked plasma containing 100 ng of ephedrine, 100 ng of norephedrine, and 100 ng of 3,4-dimethoxyamphetamine; C, plasma (0.5-hr sample) from a dosed volunteer who received a combination tablet (containing 24 mg of ephedrine hydrochloride) containing 57.14 ng of ephedrine and 100 ng of 3,4-dimethoxyamphetamine; peak a,* N-*pentafluorobenzamide of ephedrine; peak b,* N-*pentafluorobenzamide of norephedrine; and peak c,* N-*pentafluorobenzamide of 3,4-dimethoxyamphetamine.*

Derivatization of I and norephedrine with pentafluorobenzoyl chloride followed by GLC did not give any peaks other than for *N*-monoacyl derivatives, which suggested that the β-hydroxy group did not undergo acylation. However, on increasing the reaction time to 7 hr with subsequent GLC examination, a small peak (5% by peak area) eluted (retention time of 0.5 min) just before peak a. The GLC–mass spectrum of this peak gave a base peak at *m/e* 195 and other diagnostic ions at *m/e* 342, 341, 252, 238, 208, 168, 167, 105, and 77. The absence of ions at *m/e* 253 and 107 is diagnostic for the formation of the *O*-pentafluorobenzoyl derivative[21].

Similarly, reactions of I and norephedrine with heptafluorobutyric anhydride, pentafluoropropionic anhydride, and trifluoroacetic anhydride as checked by GLC–mass spectrometry yielded *N,O*-diacyl derivatives as the main products equal to 95% peak area compared to *N*-monoacyl derivatives. *N,O*-Diacyl derivatives of I were not hydrolyzed with 0.1 *N* NH_4OH. Shaking of diacyl derivatives with 1 *N* NaOH gave *N*-monoacyl derivatives, showing that the *O*-acyl, and not the *N*-acyl, functions of these derivatives are hydrolyzed with 1 *N* NaOH.

N-Pentafluorobenzoyl derivatives of phenylalkylamines have great

[20] GC–MS-data system model HP5985, Hewlett-Packard Corp., Ottawa, Ontario, Canada.

[21] K. K. Midha, J. W. Hubbard, J. K. Cooper, and D. Gagné, to be published.

electron-capturing affinity (1, 6). In the present study, the electron-capturing affinity of the *N*-pentafluorobenzoyl derivative of I was nearly 15 times that of the *N*-heptafluorobutyryl derivative, 18 times that of the *N*-pentafluoropropionyl derivative, and 1100 that of the *N*-trifluoroacetyl derivative of I (Table I).

Figure 1 shows a typical chromatogram obtained by processing control blank plasma without the internal standard. No extraneous peaks are observed. Similar chromatograms of urine extracts were as clean as those from plasma. A chromatogram obtained when the method was applied to spiked human plasma containing 100 ng each of I, norephedrine, and II is also shown in Fig. 1.

Figure 1 also shows a chromatogram of the plasma sample (1 ml) from blood withdrawn from a male volunteer (67.6 kg) at 0.5 hr after administration of 24 mg of I in a combination tablet[6] containing theophylline and phenobarbital. Analysis time was 6 min, and a 57.14-ng/ml level of I was found in this 0.5-hr sample.

Ether was the solvent of choice for the extraction of ephedrines from biological fluids in several studies (3, 4, 7, 8). Recently, degradation of I during extraction with ether was observed (9, 10). In the present study, ether was tried as a solvent for the extraction of I and II from plasma at different pH values. The extraction from plasma with ether at pH 12 and subsequent derivatization of I and II with pentafluorobenzoyl chloride yielded chromatograms with many endogenous interfering peaks and irreproducible peak height ratios (I to II). Back-extracting the ethereal extract of plasma containing I and II into aqueous acid, basifying the aqueous layer to pH 12, extracting with ether, and derivatizing with pentafluorobenzoyl chloride did not eliminate all interfering peaks. Raising the pH to 14 and extracting with pentane eliminated all interfering peaks, which may have been from phenolic substances that would not be extracted into a nonpolar solvent such as pentane at pH 14.

When two known phenolic metabolites of I, *p*-hydroxyephedrine and *p*-hydroxynorephedrine, were carried through the extraction and derivatization procedures, neither was observed by GLC. However, peaks for the *N*-pentafluorobenzoyl derivatives of these metabolites were observed when they were not carried through the extraction but were derivatized directly[22].

After extraction and derivatization of I and II with pentafluorobenzoyl chloride, the excess reagent was hydrolyzed with 0.1 *N* NH_4OH, and the derivatives of I and II were extracted with amyl acetate. The pentyl acetate extract had to be removed from contact with the ammonium hydroxide within 20 min or slow hydrolysis of the derivatives occurred, as shown by a decrease in peak heights. Once the amyl acetate was removed from contact with the ammonia layer, these derivatives were stable for several months.

Nitrogen evaporation of pentane extracts of derivatized or underivatized drug caused perceptible loss of derivative and even greater loss of free drug. Even after reaction and evaporation to dryness without nitrogen, the derivative was lost if the samples were left too long in the bath. Thus, the samples were evaporated without the use of nitrogen and removed immediately when dry.

Different GLC stationary phases such as phenyl methyl dimethyl silicone[23] and phenyl methyl (50:50) silicone[24] were tried but were not suitable for quantitation. The drug and internal standard were poorly resolved with the former, and broad peaks were obtained with the latter. A column of methyl phenyl silicone containing about 75% phenyl silicone[25] gave sharp peaks for I and the internal standard. However, norephedrine, the major metabolite of I (which was extracted in the procedure) could not be separated from I. A liquid phase of phenyl cyanopropyl and methyl silicone[17], however, separated the *N*-pentafluorobenzamide derivatives of I and norephedrine.

After repeated injections into the gas chromatograph, a noisy baseline was occasionally observed, and the ratios of I to II became irreproducible. This result was initially considered to be due to detector contamination. However, baking the detector at 350° over 24 hr did not remedy the problem. When the glass liner in the injection port of the gas chromatograph was examined, a white coating of small particles was observed on the inside. After cleaning the glass liner by soaking it in a chromic acid solution in an ultrasonic bath overnight, reproducible ratios of I to II were obtained. The irreproducible ratios may have been caused by buildup of endogenous materials contained in derivatized plasma extracts and/or by septum particles. By changing the glass liner in the injection port either weekly or after approximately 500 injections, the problem of irreproducible ratios was overcome.

Table II—Calibration Curve of Ephedrine Extracted from Plasma [a]

Nanograms per Milliliter	*n*	Mean	±*SD*	±*CV*, %
5	8	0.113	0.0046	4.09
10	7	0.216	0.0089	4.13
20	8	0.445	0.0169	3.77
30	9	0.659	0.0190	2.89
50	11	1.092	0.0436	3.98
100	9	2.128	0.0755	3.55

[a] Mean *CV* = 3.74%, slope = 0.0215 ± 0.0002, and correlation = 0.9986.

Table III—Recovery of Ephedrine and 3,4-Dimethoxyamphetamine from Plasma

Nanograms Added to 1 ml of Plasma	*n*	Mean Nanograms Recovered	Percent Recovery, mean ± *SD*
	Recovery of Ephedrine		
20	4	19.51	97.56 ± 1.16
100	4	96.94	96.94 ± 1.18
Mean			97.25 ± 1.13
	Recovery of 3,4-Dimethoxyamphetamine		
100	4	51.74	51.74 ± 0.85

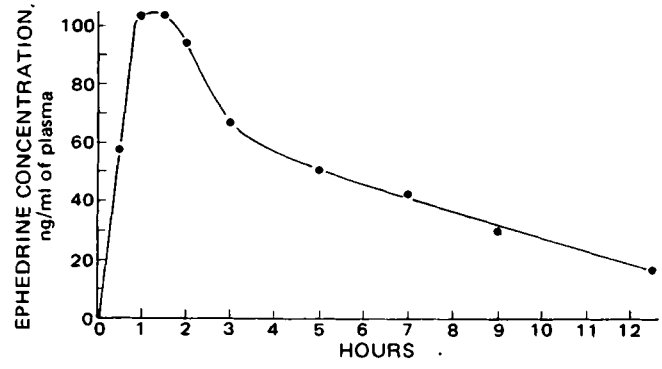

Figure 2—*Ephedrine concentrations in the plasma of a human volunteer (67.6 kg) following a single 24-mg dose of ephedrine hydrochloride in a combination tablet.*

The accuracy and precision of the GLC assay are demonstrated in Table II. Results are based on at least seven determinations of each concentration of I, ranging from 5.0 to 100.0 ng/ml. The overall coefficient of variation was 3.98%. The calibration curve obtained by plotting the peak height ratio of the *N*-pentafluorobenzoyl derivatives of I:II *versus* the I concentration was linear ($y = mx$) over the 5.0–100.0-ng of I/ml of plasma range. A mean slope value of 0.0215 ± 0.0002 ($r^2 = 0.999$) was obtained.

The overall recoveries of I and II from plasma were 97.25 ± 1.13 and 51.74 ± 0.85%, respectively (Table III). The procedure described has been applied to numerous plasma sample analyses. However, since II is a restricted drug in Canada, an alternative internal standard may be desirable. 3,4-Dimethoxyphenethylamine[5], a commercially available chemical, was suitable, and its *N*-pentafluorobenzoyl derivative gave a sharp symmetrical peak at 4.3 min, well separated from the peak due to the derivative of I. Recovery under the extraction conditions and the sensitivity of the procedure using this alternative internal standard were approximately equivalent to those with II.

The application of the present method to the determination of plasma I concentrations is shown in Fig. 2. A combination tablet[6] containing ephedrine hydrochloride (24 mg), theophylline, and phenobarbital was given as outlined in the *Experimental* section, and aliquots of the sampled plasma were assayed for I by GLC. Plasma concentrations over 24 hr in the subject fit a one-compartment model from which the elimination half-life was calculated (4.8 hr).

[22] Bonded Carbowax; C. R. Hastings, J. M. Augl, S. Kapila, and W. A. Aue, *J. Chromatogr.*, 87, 49 (1973).
[23] OV-7, Chromatographic Specialties, Brockville, Ontario, Canada.
[24] OV-17, Chromatographic Specialties, Brockville, Ontario, Canada.
[25] OV-25, Chromatographic Specialties, Brockville, Ontario, Canada.

REFERENCES

(1) G. R. Wilkinson and A. H. Beckett, *J. Pharmacol. Exp. Ther.*, **162**, 139 (1968).

(2) L. M. Cummins and M. J. Fourier, *Anal. Lett.*, **2**, 403 (1969).

(3) M. E. Pickup and J. W. Paterson, *J. Pharm. Pharmacol.*, **26**, 561 (1974).

(4) C. Bye, H. M. Hill, D. T. D. Hughes, and A. W. Peck, *Eur. J. Clin. Pharmacol.*, **8**, 47 (1975).

(5) E. T. Lin and L. Z. Benet, "Abstracts, APhA Academy of Pharmaceutical Sciences," 19th National Meeting, Atlanta, Ga., 1975, p. 155.

(6) S. B. Matin and M. Rowland, *J. Pharm. Sci.*, **61**, 1235 (1972).

(7) A. H. Beckett and B. Testa, *J. Pharm. Pharmacol.*, **25**, 382 (1973).

(8) P. S. Sever, L. G. Dring, and R. T. Williams, *Eur. J. Clin. Pharmacol.*, **9**, 193 (1975).

(9) A. H. Beckett and G. R. Jones, *Tetrahedron*, **33**, 3313 (1977).

(10) A. H. Beckett, G. R. Jones, and D. A. Hollingsbee, *J. Pharm. Pharmacol.*, **30**, 15 (1978).

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Effects of Amorphous Silicon Dioxides on Drug Dissolution

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Abstract □ The dissolution profiles of prednisone, digoxin, and griseofulvin in simulated GI fluids were determined after solvent deposition or ball milling with three commercially available grades of amorphous silicon dioxide. The former procedure resulted in adsorbates showing evidence of drug entrapment by the two grades with larger average pore diameters. Ball milling the drugs with the grade possessing the largest average particle diameter produced triturations with the slowest dissolution rates. A relationship between drug dissolution and extent of dilution with the amorphous silicon dioxides was shown. Particle-size measurements revealed that the ball milling procedure was more apt to broaden the size distribution as compared with the solvent-deposition method of drug incorporation.

Keyphrases □ Dissolution rate—effects of amorphous silicon dioxides on prednisone, digoxin, griseofulvin, simulated GI fluids, solvent deposition compared to ball milling □ Silicon dioxide, amorphous—effect on dissolution rates of prednisone, digoxin, griseofulvin in simulated GI fluids, solvent deposition compared to ball milling □ Dispersions, solid—effect of amorphous silicon dioxides on prednisone, digoxin, griseofulvin, simulated GI fluids, solvent deposition compared to ball milling

Various water-insoluble drugs, solvent deposited on fumed silicon dioxide, have been reported to have more rapid dissolution rates than the pure micronized drugs. Surface area of the acidified and basified silica gel adsorbents was a controlling factor for the increased dissolution rate of these adsorbate samples (1).

This study evaluated the effects of three commercial grades of amorphous silicon dioxide on the dissolution rates of digoxin, griseofulvin, and prednisone. The micrometer-sized, synthetic, amorphous silicon dioxides possess a unique combination of properties. Purity, nontoxicity, uniformity, chemical inertness, large surface area and porosity, controlled particle size, and a high adsorptive capacity for both oil and water characterize these versatile products. The three grades selected differ from one another in surface pH, particle size, surface area, and pore volume and diameter (Table I).

In addition to the customary procedure of solvent deposition, ball milling was used to spread each drug on the amorphous silicon dioxide surfaces. Earlier studies had shown that ball milling was superior to solvent deposition for preparing drug–lactose triturations (2, 3). Besides comparison of these two methods, the effect of pore diameter on the dissolution rate of entrapped drug molecules was studied.

EXPERIMENTAL

Materials—The following were obtained from commercial sources: amorphous silicon dioxides[1], digoxin[2] USP, griseofulvin[3] USP, prednisone[4] USP, sodium hydroxide[5] USP, monobasic sodium phosphate[6] USP, sodium chloride[7] USP, reagent grade hydrochloric acid[5], and absolute ethanol[8].

Equipment—The following were used: the USP XIX dissolution test basket assembly[9]; a constant-temperature shaker bath[10]; a grating spectrophotometer with digital display[11]; a jar mill, 10.16-cm (4-in.) diameter with 1.27-cm (0.5-in.) diameter porcelain balls[12]; a pH meter[11]; a particle-size counter[13]; a U.S. standard sieve, 60 mesh[14]; a Swinny adapter[15], 13 mm; and filter paper, 0.45-μm porosity[15].

Preparation of Drug–Amorphous Silicon Dioxide Triturations—The drug–amorphous silicon dioxide triturations were prepared in a weight ratio of 1:20. Simple blends were prepared by manual bottle tumbling for 15 min. Ball milled triturations were prepared from homogeneous simple blends. Ball milling was carried out for 48 hr in a jar mill half-filled with porcelain balls.

Solvent deposition consisted of dissolving prednisone or griseofulvin in sufficient absolute ethanol (80% ethanol was used for digoxin) and uniformly wetting the various silicas contained in a beaker. The mixture was stirred with a magnetic stirrer while the solvent was evaporated in an air stream. The residues were dried at 37° for 24 hr and passed through a 60-mesh screen to break up any agglomerates. The sieved material was bottle blended to ensure homogeneity.

[1] Syloid 63, 72, and 266, Davison Chemical Division, W. R. Grace & Co., Baltimore, Md.
[2] Roussel Corp., New York, N.Y.
[3] Ayerst Laboratories, New York, N.Y.
[4] The Upjohn Co., Kalamazoo, Mich.
[5] J. T. Baker Chemical Co., Phillipsburg, N.J.
[6] Fisher Scientific Co., Fair Lawn, N.J.
[7] Apache Chemicals, Seward, Ill.
[8] U.S. Industrial Chemicals Co., New York, N.Y.
[9] Hanson Research Corp., Northridge, Calif.
[10] Model WBR, New Brunswick Scientific Co., New Brunswick, N.J.
[11] Model DB-GT, Beckman Instruments, Fullerton, Calif.
[12] Paul O. Abbe Inc., Little Falls, N.J.
[13] Model T, Coulter Electronics Inc., Hialeah, Fla.
[14] Dual Manufacturing Co., Chicago, Ill.
[15] Millipore Corp., Bedford, Mass.

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