Sulfur-Containing Derivatives of Amphetamine: Thioureas, Methanesulfonamides, and Trifluoromethanesulfonamides

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Abstract □ *N*-Methylthiourea, methanesulfonamide, and trifluoromethanesulfonamide derivatives of amphetamine, 4-nitroamphetamine, and 4-aminoamphetamine were synthesized. The *N*-methylthiourea derivative of amphetamine, as well as the triethylammonium salt of the dithiocarbamate, produced significant depressor effects in normotensive dogs. *N,N'*-Bis(methanesulfonyl)-1-methyl-2-(4-aminophenyl)ethylamine and *N*-trifluoromethanesulfonyl-1-methyl-2-phenylethylamine, but not *N*-methanesulfonyl-1-methyl-2-phenylethylamine and *N*-trifluoroacetyl-1-methyl-2-(4-trifluoromethanesulfonamidophenyl)ethylamine, showed significant antiobesity effects in rats.

Keyphrases □ Amphetamine analogs—various sulfur-containing derivatives synthesized, evaluated for central stimulant and anorexic effects, rats □ 2-Phenylethylamines, substituted—various sulfur-containing amphetamine derivatives synthesized, evaluated for central stimulant and anorexic effects, rats □ Stimulant activity—various sulfur-containing amphetamine derivatives evaluated □ Anorexic activity—various sulfur-containing amphetamine derivatives evaluated □ Structure–activity relationships—various sulfur-containing amphetamine derivatives evaluated for central stimulant and anorexic activity

Conversion of the amino group of the 2-phenylethylamine structure to dithiocarbamate and thiourea groups, with the intention of providing copper-binding ligands to inhibit dopamine β-hydroxylase, resulted in compounds with blood pressure lowering effects (1). Similarly, conversion of the 2-phenylethylamine structure to methanesulfonamides, both of the aliphatic nitrogen and in the *para*-position of the ring, also gave compounds that lowered blood pressure in hypertensive rats and dogs (2). The methanesulfonamide of dextroamphetamine produced a similar result (2). Previously, inclusion of the alkanesulfonamide group in the aromatic ring of phenylethanolamines was shown to confer either adrenergic stimulant or blocking activity, the latter generally in conjunction with an isopropyl or larger group on the aliphatic nitrogen (3, 4).

To investigate further the effect of converting the aliphatic amino group of 2-phenylethylamines, particularly the amphetamine structure, to an acidic function, methanesulfonamido, trifluoromethanesulfonamido, and trifluoroacetyl derivatives of amphetamine, 4-nitroamphetamine, and 4-aminoamphetamine were prepared. Thiourea derivatives also were prepared, since a number of thiourea derivatives have shown inhibitory activity against dopamine β-hydroxylase (5) and the aliphatic amino is converted to an acidic function. Several corresponding derivatives of 2-phenylethylamine also were obtained.

Since both tyramine and the 4-hydroxy derivative of amphetamine are better substrates for dopamine β-hydroxylase than the nonhydroxylated compounds (6), the inclusion of the *para*-substituents in the amphetamine structure should provide compounds with potential for activity as inhibitors of dopamine β-hydroxylase. Larsen and Lish (7) pointed out that methanesulfonamides may be considered bioisosteres of the phenolic function.

The possibility exists that by conversion of the basic nitrogen of the amphetamine structure to an acidic function or by introduction of an essentially acidic function into the *para*-position of amphetamine, some of the characteristic pharmacological effects of amphetamine might be lost and others retained. Some ring substitutions in 2-phenylethylamine dithiocarbamates resulted in a loss of behavioral effects (8). Several pharmacological activities to be expected from amphetamine, including blood pressure effects, central nervous system (CNS) stimulation, behavioral effects, and antiobesity effects, have been observed in animals on treatment with these compounds.

DISCUSSION

Chemistry—Ammonium (+)-1-methyl-2-phenylethyldithiocarbamate was prepared previously and showed behavioral effects somewhat different from those of amphetamine (8). Since the compound was rather unstable, the triethylammonium salt was obtained to provide a product of greater stability. Nitration of amphetamine was carried out by the procedure of Holland *et al.* (9), in which the *para*-isomer was separated by fractional crystallization of the trifluoroacetyl derivative. Hydrogenation of the *para*-nitro group was achieved with either the *N*-trifluoroacetyl derivative (9) or 4-nitroamphetamine obtained by hydrolysis of the *N*-trifluoroacetyl derivative, using platinum oxide as the catalyst.

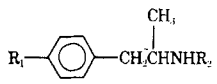
The methanesulfonamide and trifluoroacetamide derivatives were readily obtained from methanesulfonyl chloride and trifluoroacetic anhydride. Preparation of the trifluoromethanesulfonamides proved to be more difficult, but they were obtained by use of trifluoromethanesulfonic anhydride in dry ether. Vacuum distillation of the resulting liquids generally gave low melting solids. Methylthiourea derivatives were obtained from methyl isothiocyanate; many of these products were extremely hygroscopic and had to be stored under dry nitrogen and *in vacuo*.

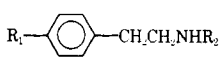
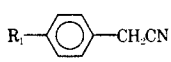
Attempts also were made to obtain 4-trifluoroacetamido-2-phenylethylamine, 4-trifluoromethanesulfonamido-2-phenylethylamine, and 4-methanesulfonamido-2-phenylethylamine from the respective benzyl cyanide derivatives; catalytic hydrogenation with various catalysts and such reducing agents as lithium aluminum hydride, diborane, and sodium borohydride failed to provide pure products. The compounds prepared are listed in Table I.

Biological Results[1]—Behavioral effects in rats were observed continuously for 6 hr and daily for 7 days after dosing with *N,N'*-bis(methanesulfonyl)-1-methyl-2-(4-aminophenyl)ethylamine (XI). An oral dose of 25 mg/kg in three rats caused low body posture (2/3), moderately decreased spontaneous motor activity (2/3), and slight (1/3) or moderate

[1] The behavioral observations and antiobesity tests were carried out at Smith Kline & French Laboratories. Results were made available through the courtesy of Dr. J. W. Wilson.

Table I—Derivatives of Amphetamine and Related Compounds



Compound	R_1	R_2	Formula	Yield, %	Melting Point	Analysis, % Calc.	Found
I(+)	H	$CS_2^-(C_2H_5)_3NH^+$	$C_{16}H_{28}N_2S_2$	46	—	C 61.54	61.3
						H 8.87	9.0
						N 8.97	8.3
						S 20.51	20.2
II(±)	H	$C(=S)NHCH_3$	$C_{11}H_{16}N_2S$	65	—	C 63.46	63.7
						H 7.69	7.8
						N 13.46	13.4
III(+)	H	SO_2CF_3	$C_{10}H_{12}F_3NO_2S$	40	75–78°	C 44.94	44.8
						H 4.49	4.46
						N 5.24	5.22
						S 11.98	12.36
IV(±)	NO_2	$C(=S)NHCH_3$	$C_{11}H_{15}N_3O_2S$	69	41–43°	C 52.17	52.0
						H 5.93	6.1
						N 16.60	16.3
V(+)	NO_2	SO_2CF_3	$C_{10}H_{11}F_3N_2O_4S$	25	42–45°	C 38.46	38.7
						H 3.53	3.8
						N 8.97	9.2
						S 10.26	10.3
VI(+)	NO_2	SO_2CH_3	$C_{10}H_{14}N_2O_4S$	79	95–98°	C 46.51	46.53
						H 5.43	5.41
						N 10.81	10.65
						S 12.40	12.32
VII(±)	CF_3CONH	$C(=S)NHCH_3$	$C_{13}H_{16}F_3N_3OS$	66	147–149°	C 48.90	49.2
						H 5.02	5.1
						N 13.17	12.7
						S 10.03	9.8
VIII(±)	CF_3CONH	$COCF_3$	$C_{13}H_{12}F_6N_2O_2$	76	173–176°	C 45.61	45.34
						H 3.51	3.72
						F 33.33	32.9
						N 8.19	7.98
IX(±)	CF_3SO_2NH	$COCF_3$	$C_{12}H_{12}F_6N_2O_3S$	37	121–123°	C 38.10	38.22
						H 3.17	3.24
						N 7.41	7.50
X(±)	$CH_3NHC(=S)NH$	$C(=S)NHCH_3$	$C_{13}H_{20}N_4S_2$	67	99–102°	C 52.70	52.62
						H 6.76	7.21
						N 18.92	18.90
XI(±)	CH_3SO_2NH	SO_2CH_3	$C_{11}H_{18}N_2O_4S_2$	50	105–108°	C 43.14	42.7
						H 5.88	5.5
						N 9.15	8.8
XII(±)	CF_3CONH	SO_2CH_3	$C_{12}H_{15}F_3N_2O_3S$	20	157–160°	C 44.44	44.7
						H 4.63	4.7
						N 8.64	8.8
XIII(±)	CH_3SO_2NH	$C(=S)NHCH_3$	$C_{12}H_{19}N_3O_2S_2$	—	45–50°	C 47.84	48.3
						H 6.31	6.4
						N 13.95	13.6
XIV(+)	CF_3CONH	SO_2CF_3	$C_{12}H_{12}F_6N_2O_3S$	26	143–145°	C 38.10	38.2
						H 3.17	3.2
						N 7.41	7.7
						S 8.47	8.1
							
XV	H	SO_2CF_3	$C_9H_{10}F_3NO_2S$	35	35–38°	C 42.29	42.06
						H 3.95	3.87
						N 5.54	5.34
						S 13.00	12.85
XVI	CF_3CONH	$COCF_3$	$C_{12}H_{10}F_6N_2O_2$	51	210–212°	C 43.90	44.06
						H 3.05	2.96
						N 8.54	8.53
XVII	CF_3SO_2NH	SO_2CF_3	$C_{10}H_{10}F_6N_2O_4S_2$	33	143–145°	C 30.00	30.2
						H 2.50	2.6
						N 7.00	6.8
							
XVIII	CF_3CONH	—	$C_{10}H_7F_3N_2O$	70	153–156°	C 52.63	52.56
						H 3.07	3.27
						N 12.28	12.20
XIX	CF_3SO_2NH	—	$C_9H_7F_3N_2O_2S$	18	105–108°	C 40.91	40.8
						H 2.65	2.7
						N 10.61	10.5
						S 12.12	12.1

(1/3) hypothermia. The bis(trifluoroacetyl) derivative (VIII), however, showed most of the behavioral effects of amphetamine, whereas IX had no overt effects at the same dose level.

In antiobesity tests, oral administration of 25 mg/kg of the same compound to rats daily for 5 days significantly reduced 1-hr food consumption as well as 5-hr food consumption over the 5-day period. There was also a significant change in body weight gain compared to controls during the 5-day test period.

Oral administration of 25 mg/kg of III to rats in the antiobesity test significantly reduced both 1- and 5-hr food consumptions over the 5-day period. There was also a significant change in body weight gain compared to controls during this period. However, oral administration of 25 mg/kg of *N*-methanesulfonyl-1-methyl-2-phenylethylamine, previously prepared (2), to rats significantly reduced 1-hr food consumption only on Day 4 and failed to reduce 5-hr food consumption significantly. There was no significant change in body weight gain for this compound compared to controls over the 5-day period. Oral administration of 25 mg/kg of *N*-trifluoroacetyl-1-methyl-2-(4-trifluoromethanesulfonamidophenyl)ethylamine (IX) to rats failed to produce a significant reduction in either 1- or 5-hr food consumption. There was, however, a significant reduction in body weight compared to controls over the 5-day test period.

The following cardiovascular effects were observed[2]. The triethylammonium salt of the dithiocarbamate of amphetamine (I) and the *N*-methylthiourea of amphetamine (II) both produced significant depressor effects at doses of 4 mg/kg in normotensive dogs anesthetized with urethan–chloralose, with I being the most potent (10). Both compounds caused CNS stimulation, significantly reduced the effects of ephedrine in rats, and reduced hexobarbital sleeping time in mice. In addition, the typical stereotyped behavior of amphetamine was observed in mice, along with increased motor activity and mydriasis.

Whereas the dithiocarbamate and methylthiourea of amphetamine retained much of the behavioral pattern of amphetamine, the more negatively *N*-substituted bis(methanesulfonyl) derivative (XI) lost most of these behavioral effects while retaining the ability to suppress appetite. Conversion of the nitrogen of amphetamine to a negatively substituted amide was not the sole requirement for this combination of effects, however, since the *N*-methanesulfonyl derivative of amphetamine (2) and IX showed no significant appetite suppressant effects.

EXPERIMENTAL[3]

The following procedures are representative.

Triethylammonium (+)-1-Methyl-2-phenylethyldithiocarbamate (I)—To a cooled solution of 5.44 g (0.04 mole) of dextroamphetamine in 25 ml of absolute ethanol was added, with stirring, 6.06 g (0.06 mole) of triethylamine. To this solution was added dropwise 4.56 g (0.06 mole) of carbon disulfide. Stirring was continued for 24 hr, and the dark-yellow liquid was evaporated in a rotary evaporator, leaving a sticky, yellow residue. This residue was washed with dry ether and dried *in vacuo*, giving 5.8 g (46%) of yellow oil; IR (film): 3220 (NH), 2620 (NH^+), 1300 (C=S), and 970 (C=S) cm^{-1}; $[\alpha]_D^{29}$ +32.1° (c = 1, ethyl acetate); n_D^{22} 1.6011.

Anal.—Calc. for $C_{16}H_{28}N_2S_2$: C, 61.54; H, 8.97; N, 8.97; S, 20.51. Found: C, 61.3; H, 9.0; N, 8.5; S, 20.2.

(±)-1-Methyl-3-(1-methyl-2-phenylethyl)thiourea (II)—To a solution of 2.72 g (0.02 mole) of dextroamphetamine in 25 ml of absolute ethanol was added dropwise, with stirring, 1.125 g (0.025 mole) of methyl isothiocyanate in 10 ml of absolute ethanol. The mixture was refluxed for 12 hr and was allowed to cool, and the solvent was removed in a rotary evaporator. The sticky residue was washed with petroleum ether and dried *in vacuo*. A 65% yield of brown oil was obtained; IR (film): 3220 (NH), 1250 (C=S), and 970 (C=S) cm^{-1}; n_D^{22} 1.6042.

Anal.—Calc. for $C_{11}H_{16}N_2S$: C, 63.46; H, 7.69; N, 13.46. Found: C, 63.7; H, 7.8; N, 13.4.

(+) - *N* - Trifluoromethanesulfonyl-1-methyl-2-phenylethylamine (III)—To a cooled solution of 2.72 g (0.02 mole) of dextroamphetamine in 25 ml of ether was added, with stirring, 7.05 g (0.025 mole) of trifluoromethanesulfonic anhydride (8) in 25 ml of ether. The mixture was stirred for 3 hr, refrigerated overnight, and filtered; the solvent was removed in a rotary evaporator. The white solid was recrystallized from petroleum ether (bp 30–60°), giving 2.1 g (40%), mp 75–78°; IR (potassium bromide): 3300 (NH), 1600 (NH), and 1175–1225 (SO_2) cm^{-1}; $[\alpha]_D^{29}$ +21.0° (c = 1, ethyl acetate).

Anal.—Calc. for $C_{10}H_{12}F_3NO_2S$: C, 44.94; H, 4.49; N, 5.24; S, 11.98. Found: C, 44.8; H, 4.46; N, 5.22; S, 12.36.

(+)-1-Methyl-2-(4-nitrophenyl)ethylamine—A mixture of 11.0 g (0.04 mole) of (+)-*N*-trifluoroacetyl-1-methyl-2-(4-nitrophenyl)ethylamine (9) and 120 ml of 1 *N* sodium hydroxide in 180 ml of dimethoxyethane was stirred at 25° for 3 hr under nitrogen. The dimethoxyethane was removed *in vacuo*, and the aqueous portion was extracted three times with 70-ml portions of methylene chloride. The combined extracts were washed three times with 50-ml portions of water and dried over anhydrous sodium sulfate. The solvent was removed in a rotary evaporator, leaving 5 g (95%) of residual oil. This oil was converted to the hydrochloride, mp 195–199° [lit. (11) mp 197–199°]; $[\alpha]_D^{29}$ +30.0° (c = 4, ethyl acetate).

(+) - *N* - Methanesulfonyl-1-methyl-2-(4-nitrophenyl)ethylamine (VI)—To a cooled solution of 9.0 g (0.05 mole) of (+)-1-methyl-2-(4-nitrophenyl)ethylamine in 50 ml of methylene chloride were added dropwise, with stirring, 5.92 g (0.052 mole) of methanesulfonyl chloride in 40 ml of methylene chloride and 5.25 g (0.052 mole) of triethylamine in 40 ml of methylene chloride. The mixture was then allowed to reach room temperature and was stirred for 12 hr. The resulting solution was washed with 1 *N* hydrochloric acid and water, dried over anhydrous sodium sulfate, and evaporated in a rotary evaporator. The brown residue was dissolved in hot benzene, treated with charcoal, and filtered. The cooled filtrate gave 10 g (79%) of the desired product, mp 95–98°; IR (potassium bromide): 3270 (NH), 1500 (NO_2), and 1145 (SO_2) cm^{-1}; $[\alpha]_D^{29}$ +30.0° (c = 1, ethyl acetate).

Anal.—Calc. for $C_{10}H_{14}N_2O_4S$: C, 46.51; H, 5.43; N, 10.81; S, 12.40. Found: C, 46.53; H, 5.41; N, 10.65; S, 12.32.

(+)-1-Methyl-2-(4-aminophenyl)ethylamine—(+)-1-Methyl-2-(4-nitrophenyl)ethylamine (18 g, 0.1 mole) in 200 ml of tetrahydrofuran with 0.3 g of platinum dioxide was hydrogenated at 4 atm. After the theoretical amount of hydrogen had been taken up, the catalyst was filtered and the solvent was removed in a rotary evaporator. A yield of 14.2 g (95%) of compound was obtained; the dihydrochloride melted at 255–260° [lit. (12) mp 258–260°]; $[\alpha]_D^{29}$ +15.8° (c = 1, ethyl acetate).

(±)-*N,N'*-Bis(trifluoroacetyl)-1-methyl-2 - (4 - aminophenyl)ethylamine (VIII)—To a cooled solution of 2.46 g (0.01 mole) of (±)-1-methyl-2-(4-aminophenyl)ethyltrifluoroacetamide (9) in 50 ml of benzene was added 2.94 g (0.014 mole) of trifluoroacetic anhydride dropwise over 10 min. The mixture was brought to room temperature and refluxed for 3 hr. It was refrigerated overnight, and the white solid was filtered, washed with dilute hydrochloric acid and water, and dried in a vacuum desiccator. The product was recrystallized from chloroform, giving 2.6 g (76%) of white solid, mp 173–176°; IR (potassium bromide): 3300 (NH), 1700 (C=O), 1550 (amide), and 1150 (CF_3) cm^{-1}.

Anal.—Calc. for $C_{13}H_{12}F_6N_2O_2$: C, 45.61; H, 3.51; F, 33.33; N, 8.19. Found: C, 45.34; H, 3.72; F, 32.9; N, 7.98.

(±)-*N*-Methanesulfonyl-1-methyl-2-(4 - trifluoroacetylaminophenyl)ethylamine (XII)—A solution of 2.28 g (0.01 mole) of VI in 200 ml of absolute ethanol with 0.65 g of 5% platinum-on-charcoal was hydrogenated at 3 atm. After 48 hr, the mixture was filtered and the solvent was removed *in vacuo*. The residual viscous liquid was dissolved in 250 ml of benzene, and trifluoroacetic anhydride (2.1 g, 0.015 mole) was added with stirring. The mixture was refluxed for 3 hr, allowed to cool, and refrigerated overnight. The resulting solid was filtered, washed with water, and dried *in vacuo*. It was recrystallized from ethanol–water, giving 0.5 g, mp 157–160°; IR (potassium bromide): 3270 (NH) and 1700 (C=O) cm^{-1}.

Anal.—Calc. for $C_{12}H_{15}F_3N_2O_3S$: C, 44.44; H, 4.63; N, 8.64. Found: C, 44.7; H, 4.7; N, 8.8.

(±)-1-Methyl-3-[1-methyl-2-(4-methanesulfonamidophenyl)ethyl]thiourea (XIII)—A solution of 2.28 g (0.01 mole) of VI in 200 ml of absolute ethanol with 0.65 g of 5% platinum-on-charcoal was hydrogenated at 3 atm. After 48 hr, the mixture was filtered and the solvent was removed *in vacuo*. The residual viscous liquid was dissolved in 50 ml of absolute ethanol, and 0.85 g (0.008 mole) of methyl isothiocyanate was added. The mixture was refluxed for 3 hr, the solvent was removed *in vacuo*, and the residue was washed with dry ether and dried *in vacuo*, mp 45–50°; IR (film): 3350 (NH), 1300–1335 (SO_2), and 1135–1165 (SO_2) cm^{-1}.

Anal.—Calc. for $C_{12}H_{19}N_3O_2S_2$: C, 47.84; H, 6.31; N, 13.95. Found: C, 48.2; H, 6.4; N, 13.6.

(+)-*N*-Trifluoromethanesulfonyl-1-methyl-2 - (4 - nitrophenyl)ethylamine (V)—To a cooled solution of 9.0 g (0.05 mole) of (+)-1-methyl-2-(4-nitrophenyl)ethylamine in 30 ml of anhydrous ether was added, with stirring, 14.6 g (0.052 mole) of trifluoromethanesulfonic anhydride in 20 ml of anhydrous ether. The resulting mixture was stirred

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[3] Melting points were determined in capillaries with a Mel-Temp melting-point block and are uncorrected. IR absorption spectra were obtained with a Perkin-Elmer model 137B spectrophotometer. Optical rotations were obtained with a Carl Zeiss polarimeter. NMR spectra were determined with a Varian T60 spectrometer using tetramethylsilane as the internal standard. Elemental analyses were performed by Dr. F. B. Strauss, Oxford, England, or by Dr. Carol K. Fitz of Carlisle, Mass. TLC was carried out using silica gel, and products were detected by exposure to iodine vapor. Dextroamphetamine, 4-aminobenzyl cyanide, 4-amino-2-phenylethylamine, trifluoroacetic anhydride, methyl isothiocyanate, and methanesulfonyl chloride were obtained from Aldrich Chemical Co. Trifluoromethanesulfonic acid was obtained from the 3M Co.

for 12 hr and refrigerated overnight. The precipitate was filtered and washed with dry ether, and the filtrate was evaporated *in vacuo*, leaving an oil. This oil was distilled at 165–170°/0.2 mm, giving 3.8 g (25%) of a solid, mp 42–45°; IR (potassium bromide): 3300 (NH), 1520 (NO_2), 1335–1375, and 1125–1150 (SO_2) cm^{-1}; $[\alpha]_D^{30}$ +37.0° (c = 1, ethyl acetate).

Anal.—Calc. for $C_{10}H_{11}F_3N_2O_4S$: C, 38.46; H, 3.53; N, 8.97; S, 10.26. Found: C, 38.7; H, 3.8; N, 9.2; S, 10.3.

(+)-*N*-Trifluoromethanesulfonyl-1-methyl-2 - (4 - trifluoroacetylaminophenyl)ethylamine (XIV)—A solution of 3.12 g (0.01 mole) of V in 150 ml of tetrahydrofuran with 0.4 g of platinum dioxide was hydrogenated at 3 atm. After 48 hr, the solution was filtered and the solvent was removed *in vacuo*. The residual viscous liquid was dissolved in 250 ml of benzene; to this solution was added, with stirring, 2.1 g (0.015 mole) of trifluoroacetic anhydride. The mixture was refluxed for 3 hr, allowed to cool, and refrigerated overnight. The resulting solid was filtered, washed with water, and dried *in vacuo*. Recrystallization from aqueous ethanol gave 0.8 g, mp 143–145°; IR (potassium bromide): 3350, 3230 (NH), 1700 (C=O), 1200, and 1150 (SO_2) cm^{-1}; $[\alpha]_D^{29}$ +20° (c = 1, ethyl acetate).

Anal.—Calc. for $C_{12}H_{12}F_6N_2O_3S$: C, 38.10; H, 3.17; N, 7.41; S, 8.47. Found: C, 38.2; H, 3.2; N, 7.7; S, 8.1.

Antiobesity Test—Rats were trained over 2 weeks to eat their daily food ration[4] in only 5 hr. After training, either vehicle (controls) or drug was administered orally by gastric intubation daily for 5 days. One hour after drug, tared food cups containing the food ration were presented. The cups were weighed after 1 hr of feeding and again after 5 hr of feeding. Water was available *ad libitum*. Rats were weighed daily before drug administration.

[4] Ground Purina Laboratory Chow.

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Release of Drugs from Ointment Bases II: *In Vitro* Release of Benzocaine from Suspension-Type Aqueous Gels

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Abstract □ The *in vitro* release of benzocaine, suspended in an aqueous gel, through silicone rubber membranes was studied to test an extension of existing mathematical models. The theoretical treatment proposed is intended for experimental systems involving release, through a nonporous membrane, of a drug whose concentration is a few times (≥3) greater than its solubility in the vehicle. For either micronized (2 μm) or macrosize (125 μm) drug, the Q (amount released) *versus* $t^{1/2}$ (time$^{1/2}$) plots were not linear until substantial time had elapsed. Excellent agreement was found between the experimental points and theoretical plots, generated by a computer fit to experimental data of an equation derived from a reported vehicle-boundary diffusion layer model. The values of the solubility and of the diffusion coefficient of benzocaine in the gel, calculated by the present mathematical treatment from release data, were in agreement with literature data. The particle size of released benzocaine did not influence the release pattern, thus confirming release in the present conditions to be diffusion rather than dissolution controlled. The present method is applicable for determining the solubility and diffusion coefficient of drugs in vehicles in cases not contemplated in current release theories.

Keyphrases □ Drug release—benzocaine from aqueous gels through silicone rubber membranes *in vitro*, mathematical models extended □ Benzocaine—release from aqueous gels through silicone rubber membranes *in vitro*, mathematical models extended □ Models, mathematical—extended to fit *in vitro* drug release system where drug concentration is greater than solubility in vehicle □ Solubility—benzocaine in aqueous gel vehicle, calculations derived from mathematical drug release models □ Diffusion coefficients—benzocaine in aqueous gel vehicle, calculations derived from mathematical drug release models

The *in vitro* release of drugs from topical vehicles, in spite of its limited correlations with *in vivo* absorption, may offer useful information on some physicochemical factors involved in the latter process. Such important parameters as the diffusion coefficient and the solubility of a drug in a vehicle can be calculated by relatively simple equations, derived from mathematical models describing the process of *in vitro* release of drugs dissolved (1–3) or