GLC Determination of Methotrimeprazine and Its Sulfoxide in Plasma

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Abstract ☐ A GLC method, based on flame-ionization detection, was developed for the assay of methotrimeprazine and its sulfoxide in plasma. For a 6-ml aliquot, the sensitivity was 2–3 ng/ml for the unchanged drug and 4–5 ng/ml for the sulfoxide. The coefficient of variation, calculated from duplicate analyses of plasma samples, was 8–15% for concentrations between 10 and 100 ng/ml. Patients treated with orally administered methotrimeprazine had higher plasma levels of the sulfoxide than of unmetabolized drug. The method also was applied to the analysis of promazine and chlorpromazine in patient plasma.

Keyphrases ☐ Methotrimeprazine—base and sulfoxide, GLC analysis, plasma ☐ GLC—analysis, methotrimeprazine base and sulfoxide, plasma ☐ Analgesic agents—methotrimeprazine base and sulfoxide, GLC analysis in plasma

Methotrimeprazine[1] (I) has been widely used in Europe as a neuroleptic for the past 15 years. It is usually administered orally as tablets or syrup but occasionally is given intramuscularly. In the United States, the drug is mainly used as an analgesic and only is recognized for intramuscular use. The molecular formula resembles that of chlorpromazine (III), but unmetabolized methotrimeprazine has no electron-capturing groups or positions suitable for introduction of such groups. No sufficiently sensitive and specific assay for the drug in plasma is available, and information about the biological half-life and plasma levels was lacking when this study was undertaken.

Three metabolites have been identified and quantitated in urine from psychiatric patients after oral doses of methotrimeprazine: methotrimeprazine sulfoxide (II), monodesmethyl methotrimeprazine, and monodesmethyl methotrimeprazine sulfoxide (1). The urine contained II in considerably higher concentrations than the other two metabolites.

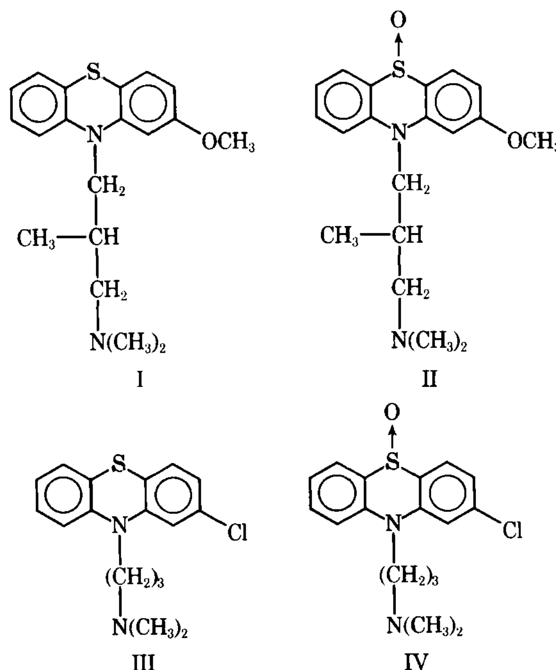
The pharmacological effects of methotrimeprazine are similar to those of chlorpromazine. A fall in the sitting systolic and diastolic blood pressure produced by chlorpromazine has been correlated with the plasma drug level (2). Sedation and orthostatic hypotension are the most important side effects of methotrimeprazine (3, 4). A method for analysis of this drug in plasma provides an opportunity to examine whether these and other adverse reactions are related to plasma drug concentrations and perhaps to establish a more rational dosage scheme.

[1] Known as levomepromazine in Europe.

A sensitive and specific method for quantitation of chlorpromazine and some of its metabolites in plasma was reported by Curry (5) and has since been modified to improve its sensitivity and accuracy (6–9). The method is based on GLC with electron-capture detection, which permits quantitation of absolute amounts down to 2 ng of chlorpromazine/sample. The method described in this report is based on a modification of the extraction procedure described by Curry (5). By a more extensive purification and concentration of the extract, absolute amounts down to 10–15 ng of methotrimeprazine and 20–25 ng of its sulfoxide/sample can be quantitated by GLC with flame-ionization detection.

By a check on whether other phenothiazines could interfere with the analysis, it became apparent that the method could be used for chlorpromazine and its sulfoxide (IV) in plasma and, by a slight reduction of the column temperature, for promazine (V) in plasma.

Sulfoxidation and N-demethylation are two of the known pathways of promazine metabolism in humans (10, 11). Peak concentrations of unchanged promazine in blood shortly after an intravenous injection were measured by a spectrophotometric method (12), but the



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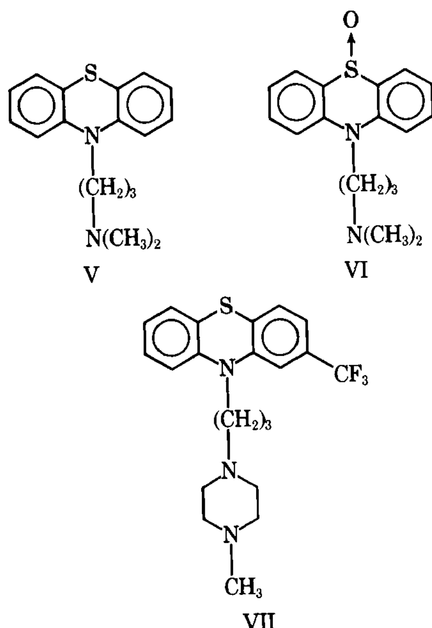

method lacks satisfactory sensitivity and precision for a pharmacokinetic study.

EXPERIMENTAL

Glassware—The glassware was cleaned by standing overnight in chromic acid, 5% NaOH, and ethanol on consecutive nights and was rinsed with water after each cleaning step. It then was silylated with 5% dichlorodimethylsilane in toluene and rinsed with toluene.

Small pointed test tubes for evaporation of samples were made from Pasteur pipets by melting off the capillary at the neck of the pipet. The 14- and 20-ml centrifuge tubes used for extractions were tapered (4 mm i.d. near the bottom) to allow the complete aspiration of the lower aqueous phase without losing any of the upper organic layer.

Reagents and Standard Solutions—Heptane, analyzed grade[2], toluene[3], and isoamyl alcohol[4] were used without prior distillation. Hydrochloric acid[4] was diluted to 0.05 *N* and washed once with heptane containing 1.5% isoamyl alcohol and once with toluene containing 15% isoamyl alcohol. Analyzed grade sodium hydroxide, 50%[2], was diluted to 5 or 1%, washed twice with heptane containing 1.5% isoamyl alcohol, and kept in bottles[5]. Concentrated ammonium hydroxide[4] was diluted to 3 *N* and washed twice with toluene containing 15% isoamyl alcohol. The aqueous solutions were diluted with distilled water and washed by shaking for 10 min with a 20% volume of organic solvent.

The following reference compounds[6] were used: mono- and didesmethyl chlorpromazine, chlorpromazine sulfoxide, monodesmethyl chlorpromazine sulfoxide, trifluoperazine (VII), mono- and didesmethyl methotrimeprazine, monodesmethyl methotrimeprazine sulfoxide, didesmethyl promazine, promazine sulfoxide (VI), monodesmethyl promazine sulfoxide, chlorpromazine hydrochloride, methotrimeprazine hydrochloride, methotrimeprazine sulfoxide, promazine hydrochloride, monodesmethyl promazine, and chlorpromazine base.

The reference compounds were dissolved in heptane containing 1.5% isoamyl alcohol, for direct injection into the gas chromatograph, or in water, for addition to blank plasma to obtain standard curves. An amount equivalent to 10 mg of free base was dissolved in 10 ml and diluted further to 0.5 ng/μl. Aqueous solutions of reference compounds obtained as free bases were made by dissolving in 0.05 *N* HCl and diluting with distilled water. Organic solutions of compounds obtained as water-soluble salts were made by extraction from 0.5 ml of 5% NaOH into 10 ml of heptane–isoamyl alcohol.

Standard solutions were stored in the dark at 5° in silylated screw-capped glass counting vials. The aqueous solutions were stable for 3–4 months under these conditions, while the organic standard solutions remained unchanged for more than 1 year.

Preparation of Samples—Blood samples of 5–10 ml were collected in heparinized polyethylene tubes. After immediate centrifugation, the plasma was divided into two aliquots and stored at −24°. The two aliquots from each sample were analyzed on different days within 6 weeks after sampling.

Extraction Procedure—All extractions were performed with a mechanical shaker[7] at its maximum speed. The samples were centrifuged at 500×*g*[8].

A 1–6-ml aliquot of plasma was transferred to a 20-ml glass-stoppered centrifuge tube, and 100 μl of a 10-ng/μl aqueous solution of trifluoperazine hydrochloride was added as the internal standard. The plasma was made alkaline with a 20% volume of 5% NaOH and shaken for 60 min with 10 ml of heptane containing 1.5% isoamyl alcohol. The sample was centrifuged for 5 min, and the aqueous phase was removed by suction.

To the heptane phase was added 1 ml of 1% NaOH. The sample was shaken for 10 min, and the aqueous phase was aspirated before the tube was centrifuged for 2 min. The heptane phase was then transferred with a glass pipet to a 14-ml glass-stoppered centrifuge tube and shaken for 15 min with 1.5 ml of 0.05 *N* HCl. After 2 min of centrifugation, the heptane phase was discarded and 2.5 ml of heptane with 1.5% isoamyl alcohol was added. The sample was shaken for 10 min and centrifuged for 2 min, and the heptane phase was discarded.

The aqueous phase was made alkaline with 0.1 ml of 3 *N* NH_4OH, and the sample was extracted into 0.25 ml of toluene with 15% isoamyl alcohol by shaking for 15 min. Following 2 min of centrifugation, the aqueous phase was carefully removed with a Pasteur pipet, and the organic phase was transferred from the tip of the tube to a tapered 45-mm glass tube (5 mm i.d.).

The organic phase was evaporated to dryness at 45° under a stream of nitrogen, and the tubes were kept in a vacuum desiccator at room temperature, protected from light, until the GLC runs were made—usually on the following day but sometimes as much as 3 days later.

GLC—A gas chromatograph[9], equipped with two flame-ionization detectors and 180-cm glass columns (2 mm i.d.), was used. The columns were packed with 3% OV-17 on 80–100-mesh Supelcoport[10] and conditioned overnight at 315°. Purified nitrogen, 25 ml/min, was used as carrier gas. The injector and detector temperatures were 270°, and the column temperature was 245 or 255°.

At the beginning of each day, the columns were conditioned by an injection of 20 μl of a silylating reagent[11] and then saturated by an injection of 2 μg of each substance to be analyzed during the day.

Ten microliters of heptane containing 20% isoamyl alcohol was added to the small test tubes with evaporated samples. The opening of the tube was covered with aluminum foil, and the tube was stirred for 1 min on a mixer[12]. From 10–20% of the solvent evaporated during the stirring, and the residual 8–9 μl was injected into the gas chromatograph in two aliquots.

Standard Curves and Analysis of Samples—Standard curves for each drug and its sulfoxide were obtained by adding 50–300 μl of aqueous standard solutions (0.5 or 5.0 ng/μl) to 2.5 ml of blank plasma. The internal standard was added after 15 min of incubation, and the extraction and GLC were performed as already described. The ratio of the peak heights of the analyzed compound and the internal standard was determined for the drug and for the sulfoxide and used as a measure of the amount in the samples.

Standard curves of peak height ratios as a function of the amount of compound added were determined from four or five samples each time patient plasma was analyzed. The least-squares regression line of the standard curve was calculated using reciprocal weighting.

[2] J. T. Baker Chemicals N.V., Deventer, Holland.
[3] Fluka AG, Buchs, Switzerland.
[4] E. Merck, 61 Darmstadt, West Germany.
[5] Teflon (du Pont).
[6] All reference compounds were obtained from one of the following companies: Pharma Rhodia, Birkerod, Denmark; Société des Usines Chimiques Rhône-Poulenc, 94, Vitry-sur-Seine, France; AB Mekos, Helsingborg, Sweden; A/S Ferrosan, Copenhagen, Denmark; or May & Baker Ltd., Dagenham, England.
[7] C. Desaga, GmbH, Heidelberg, West Germany.
[8] IEC model UV centrifuge, International Equipment, Needham Heights, Mass.
[9] Varian model 2100, Varian-Aerograph, Walnut Creek, Calif.
[10] Supelco Inc., Bellefonte, PA 16823
[11] Silyl-8, Pierce Chemical Co., Rockford, IL 61105
[12] Vortex-Genie model K-550-GE, Scientific Industries Inc., Springfield, MA 01103

Table I—Absolute Recovery of Added Reference Compounds after Extraction from Plasma, Evaporation, and Solution in 10 μl of Organic Solvent

Compound	Recovery, %							
	Nanograms Added							
	25	50	100	250	500	1000	1500	Mean ± *SD*
I	—	67 (5)[a]	68 (6)	63 (5)	62 (5)	65 (6)	65 (3)	65 ± 7 (30)
II	—	63 (5)	67 (6)	72 (6)	63 (4)	72 (5)	73 (5)	68 ± 6 (31)
III	70 (1)	66 (4)	58 (4)	65 (5)	68 (5)	65 (2)	64 (2)	65 ± 11 (24)
IV	87 (4)	82 (5)	81 (4)	90 (4)	89 (4)	—	—	86 ± 8 (21)
V	53 (1)	76 (4)	74 (5)	64 (3)	76 (5)	65 (3)	67 (3)	71 ± 12 (24)
VI	30 (1)	35 (1)	32 (2)	26 (3)	32 (3)	27 (1)	26 (1)	30 ± 4 (12)

[a] Number in parentheses is the number of determinations.

RESULTS

Extraction Procedure—The absolute recoveries of compounds added to blank plasma (Table I) were calculated from the peak heights after extraction and GLC *versus* the peak heights obtained when known amounts were injected from organic standard solutions. The recoveries varied considerably from sample to sample but were generally 60–70%, except for promazine sulfoxide where the recovery was as low as 30%.

The recovery was also determined by the addition of 250 ng of ^{35}S-labeled chlorpromazine[13] to blank plasma samples. After extraction, evaporation, and solution in 10 μl of heptane–isoamyl alcohol, the recovery in six samples was 68 ± 7%.

GLC—Figure 1 shows a chromatogram of a patient plasma sample containing I and II in concentrations close to the lower detection limit of the method. The sample was taken, 36 hr after administration of the last dose of methotrimeprazine, from a patient who had received 25 mg orally twice daily for 21 days.

Absolute amounts down to 10–15 ng/sample of I, III, and V and 20–25 ng of the sulfoxides gave measurable peaks in the chromatograms. Since as much as 6 ml of plasma could be used without the appearance of interfering peaks from plasma constituents, concentrations down to 2–3 ng/ml of I, III, and V and 4–5 ng/ml of the sulfoxides could be measured.

Column temperatures and retention times are given in Table II. To obtain satisfactory separation from the solvent peak, it was necessary to analyze V at a column temperature 10° lower than for I and III. The monodesmethyl analogs of Compounds I–VI had 20–27% longer retention times, and the didemethylated analogs of I, III, and V had 37, 31, and 26% longer retention times, respectively. The peaks of desmethyl methotrimeprazine, didesmethyl methotrimeprazine, and didesmethyl chlorpromazine overlapped partially with the peak of the internal standard.

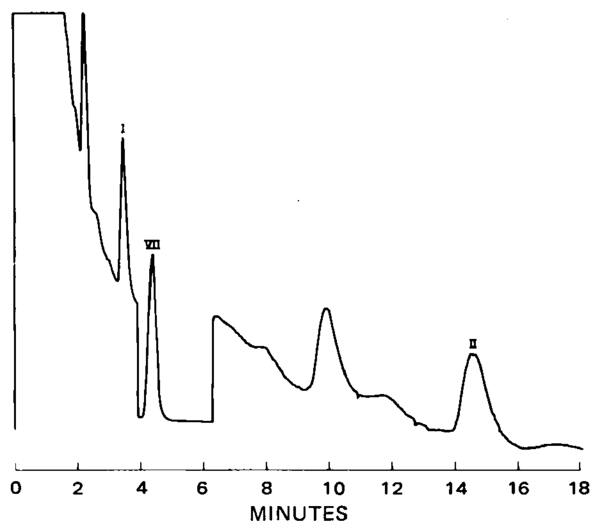

Figure 1—*Gas chromatogram from 6 ml of patient plasma containing I, 4.4 ng/ml, and II, 8 ng/ml. Trifluoperazine (VII) was the internal standard. Electrometer settings were: range, 10^{-12} for all peaks; and attenuation, 16 for I, 128 for VII, and 4 for II.*

[13] Radiochemical Centre, Amersham, England.

Standard Curves—Each standard curve was determined from two GLC runs of four or five known samples. The standard curves were linear within the range indicated in Table I, and the intersections with the y-axis were not significantly different from the origin.

The slopes of the standard curves showed some variation from column to column and sometimes also during the lifespan of each column (Table III). The relative standard deviation of the slope of the regression line for each standard curve was an average of 2–3% for I, III, and V and 3–5% for the sulfoxides (Table III).

Patient Plasma Samples—Figure 2 shows plasma concentration curves for three male patients following oral maintenance doses of either methotrimeprazine, chlorpromazine, or promazine. The biological half-lives (in hours), determined from the regression line through the points at 12–36 hr, were: 22.5 (I), 16.6 (II), 11.8 (III), 12.2 (IV), and 8.0 (V). The patient treated with methotrimeprazine showed plasma concentrations of the sulfoxide approximately double those of the unmetabolized drug. About the same ratio was found in plasma from two other male patients who had been treated for several months with methotrimeprazine tablets, 125 mg/day. Before the morning dose was given, plasma concentrations of I were 46 and 56 ng/ml, and the concentrations of II were 4.1 and 1.7 times higher, respectively.

The method has since been used to analyze plasma from five patients after single and multiple doses of methotrimeprazine (13). Chromatograms from blank plasma, taken before administration of the first dose, never contained peaks showing retention times similar to I–VII; all samples taken 2–12 hr after the first oral dose gave peaks with the same retention times as I and II.

The coefficients of variation of the overall method, calculated from duplicate analyses of patient plasma samples, are given in Table IV. Duplicate analyses were performed on different days, within 6 weeks after sampling. For methotrimeprazine in concentrations of 10–100 ng/ml, the coefficient of variation was 10–15%.

DISCUSSION

Endogenous substances with partitioning properties similar to the phenothiazines might theoretically interfere in this analysis, because of the general response of the flame-ionization detector to organic compounds. However, no interfering peaks were seen in chromatograms of blank plasma from healthy volunteers or of plasma taken from psychiatric patients who had received no drugs for 4 weeks or longer.

The recovery by extraction from plasma, evaporation to dryness, and solution in 10 μl of heptane–isoamyl alcohol was variable, but

Table II—Column Temperature and Retention Times

Compound	Column Temperature	Retention Time, min
I	255°	3.50
II	255°	14.50
III	255°	3.25
IV	255°	11.75
VII	255°	4.50
V	245°	2.75
VI	245°	11.50
VII	245°	6.30

Table III—Range of Slopes and Average Standard Deviation of Each Slope for Standard Curves Obtained on Different Days from Four or Five Known Samples Each Day

Compound	Number of Standard Curves	Slope of Regression Lines: Range	Average SD^a
I	8	$1.40–1.70 \times 10^{-3}$	0.03×10^{-3}
II	7	$2.75–3.80 \times 10^{-4}$	0.09×10^{-4}
III	5	$1.40–1.50 \times 10^{-3}$	0.03×10^{-3}
IV	6	$4.20–4.90 \times 10^{-4}$	0.16×10^{-4}
V	3	$2.75–3.25 \times 10^{-3}$	0.08×10^{-3}
VI	2	$2.50–2.75 \times 10^{-4}$	0.12×10^{-4}

[a] Calculated by the formula $\sqrt{\Sigma_{i=1}^{n} s_i^2/n}$, where s_i is the standard deviation of the slope of the regression line for the ith standard curve, and n is the number of standard curves.

these variations were generally not reflected in the ratio of the peak heights of the analyzed compound and the internal standard, which had very similar chemical properties. Christoph *et al.* (7) reported that a significant and irreproducible portion of ^{35}S-labeled chlorpromazine was lost when the sample was evaporated to dryness, presumably by adsorption to the glass walls. As indicated by the overall precision (Tables III and IV), this problem was overcome by the present method.

Adsorption to the GLC column was previously a problem, especially with nanogram amounts of the sulfoxides. However, on-column silylation improved the column performance sufficiently to quantitate injected amounts down to about 10 ng. Even with this treatment, adsorption to the column seemed to be the main source of variation in analysis of samples containing less than 100 ng; triplicate analyses of each sample might have improved the accuracy.

The plasma samples were sufficiently purified by the extraction procedure to permit the injection of the whole sample into the gas chromatograph, which is one reason for the relatively high sensitivity of the method, considering that flame-ionization detection was used. To obtain maximum sensitivity, the GLC conditions were adjusted so that the peaks of I, III, and V came at the base of the solvent peak and could be detected at 1/16 of the maximum sensitivity of the instrument. Because of the relatively long retention times of the sulfoxides, the baseline was usually sufficiently stable to run the gas chromatograph at one-fourth of its maximum sensitivity when they eluted from the column.

Contamination from the glassware could disturb the analysis of samples containing less than 100 ng, and great care in washing and

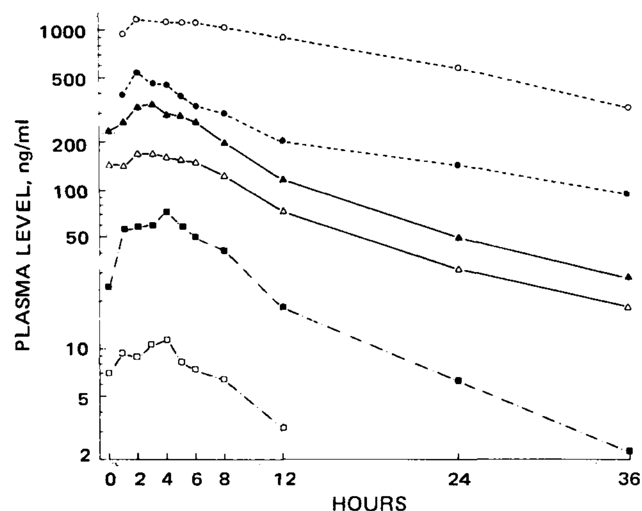

Figure 2—*Plasma concentrations in three adult male patients who had been treated for at least 4 weeks with oral doses of I (2 × 300 mg), III (4 × 400 mg), or V (2 × 150 mg). Each patient received only one drug. The usual morning dose was given at time 0 hr, and no medication was given during the 36 hr when the blood samples were drawn. Each point represents the mean value of two determinations, except for VI which was only determined once. Key: ●, I; ○, II; ▲, III; △, IV; ■, V; and □, VI.*

Table IV—Mean Coefficient of Variation Calculated from Duplicate Analyses of Patient Plasma Samples

Compound	Number of Samples	Concentration Range, ng/ml	Mean Coefficient of Variation[a], %
I	15	2–10	16.1
	56	10–25	14.7
	38	25–50	10.2
	18	50–100	10.3
II	4	5–10	12.1
	18	10–25	9.9
	30	25–50	7.6
	51	50–100	8.8
III	8	200–350	3.6
IV	7	100–175	6.7
V	6	40–75	5.9

[a] Calculated by the formula $(100/n)\sqrt{2}\,\Sigma_{i=1}^{n}[|A_i - B_i|/(A_i + B_i)]$ where A_i and B_i are the results from duplicate analyses of the same plasma, and n is the number of different plasma samples.

handling was necessary. Peaks from two unidentified substances appeared in the chromatograms of plasma samples (Fig. 1), but neither overlapped with any analyzed drug or metabolite. One had a retention time of 2 min at 255° and seemed to come from the heptane. The other, with a retention time of 10 min at 255°, was not seen when a buffer solution was analyzed in the same way as plasma.

Demethylated metabolites that would overlap with the peak of the internal standard did not disturb the analysis of plasma from patients, since as much as 1 µg of internal standard was used per sample. Even with another internal standard with a longer retention time, the present method is probably less accurate for the direct quantitation of the demethylated metabolites in plasma due to a stronger tendency to column adsorption of these compounds.

Within the concentration range indicated in Fig. 2, the method was used without changing the amount of heptane solution injected into the gas chromatograph or the amount of internal standard per sample. The method was successfully applied to samples from *in vitro* studies containing several micrograms simply by increasing the amount of internal standard.

The sensitivity of the method seems to be sufficient for plasma concentrations of I–V after single or multiple therapeutic doses of the drugs. The method is less suitable for promazine sulfoxide (VI) due to the low recovery from the extraction procedure. The extraction procedure is more elaborate than the procedures previously described for chlorpromazine, while this method has the advantage of the simpler operation of the flame-ionization detector, compared to the electron-capture detector.

As is evident from Table IV, the method has been used so far mainly to analyze I and II in plasma from patients receiving I, and it is well suited for this purpose.

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Drug Release from Methyl Acrylate–Methyl Methacrylate Copolymer Matrix III: Simultaneous Release of Noninteracting Drug–Excipient Mixtures

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Abstract ☐ The simultaneous release of mixtures of noninteracting chemicals incorporated in a methyl acrylate–methyl methacrylate copolymer was studied. Different mixtures of dextrose–methapyrilene hydrochloride and sodium chloride–methapyrilene hydrochloride in the plastic were compressed into tablets, and single-surface release was obtained in 0.1 *N* HCl at 37°. The amounts of both drug and excipients released per unit surface area were linearly dependent on the square root of time. The release rate constants were analyzed in terms of the solubility, diffusion coefficient, concentration of each chemical, and porosity and tortuosity of the tablets. It was concluded that for each tablet system the individual solid–liquid boundaries of the incorporated chemicals had merged together, and the release could be explained by Higuchi's square root of time relationship.

Keyphrases ☐ Methyl acrylate–methyl methacrylate copolymer—tablets, simultaneous release of noninteracting drug–excipient mixtures ☐ Copolymers—methyl acrylate–methyl methacrylate copolymer tablets, simultaneous release of noninteracting drug–excipient mixtures ☐ Drug release—from methyl acrylate–methyl methacrylate copolymer tablets, effect of water-soluble excipients ☐ Tablets—water-soluble drug in methyl acrylate–methyl methacrylate copolymer tablets, effect of water-soluble excipients ☐ Methapyrilene hydrochloride—release from methyl acrylate–methyl methacrylate copolymer tablets, effect of water-soluble excipients

It was shown previously (1) that drug release from tablets compressed directly from mixtures of a single drug and a methyl acrylate–methyl methacrylate copolymer follows the time dependency suggested by Higuchi's (2) theoretical relationship. The magnitude of the release rate constant was dependent on the solubility, diffusivity, and concentration of the drug as well as the matrix porosity and tortuosity.

BACKGROUND

Singh *et al.* (3) considered the simultaneous release of a mixture of two noninteracting drugs dispersed in an inert insoluble matrix composed of a polyethylene–polyvinyl chloride mixture. The developed relationships expressed the diffusion-controlled rate of release of both drugs as functions of solubilities, diffusivities, and concentrations of each drug in the matrix and the porosities and tortuosities of the matrix. Thus, the release of drug *a*, which had the slower moving solid–liquid boundary, was described by (2):

$$\frac{dQ_a}{d(t^{1/2})} = \left[D_a \frac{\epsilon_1}{\tau_1}(2A_a - \epsilon_1 C_a{}^s)C_a{}^s\right]^{1/2} \quad \text{(Eq. 1)}$$

where subscript 1 refers to that region of the tablet matrix bounded on one side by the solvent front and on the other side by the solid–liquid boundary of drug *a*. This part of the tablet will be described as region 1 in subsequent discussions. The release of drug *b*, with the faster moving solid–liquid boundary, was described by the following, more complex, expression:

$$\frac{dQ_b}{d(t^{1/2})} = \frac{2D_b\epsilon_1}{\tau_1 \frac{k_a}{A_a}}\left[\frac{\frac{\epsilon_2}{\tau_2}C_b{}^s}{\frac{\epsilon_2}{\tau_2} + \frac{\epsilon_1}{\tau_1}\left[\frac{\frac{k_b}{A_b} - \frac{k_a}{A_a}}{\frac{k_a}{A_a}}\right]}\right] \quad \text{(Eq. 2)}$$

where subscript 1 is the same as in Eq. 1, and subscript 2 refers to region 2 in the tablet bounded on one side by the solid–liquid boundary for drug *a* and on the other side by the solid–liquid boundary for drug *b*. Other symbols used in Eqs. 1 and 2 are defined as follows:

- Q_i = grams of drug i released per unit area of exposed tablet surface at time t
- D_i = diffusion coefficient of drug i in the release medium
- A_i = concentration of drug i in the tablet
- $C_i{}^s$ = solubility of drug i in the release medium
- ϵ_j = porosity of region j of the tablet
- τ_j = tortuosity of region j of the tablet
- k_i = slope of Q_i *versus* $t^{1/2}$ plot for release of drug i from the tablet

The methyl acrylate–methyl methacrylate copolymer has been used to control and regulate the release of highly water-soluble drugs. The purpose of this investigation was to investigate the effect of two common, highly water-soluble excipients on the release of a model of a highly water-soluble drug from matrixes of this copolymer. Methapyrilene hydrochloride was selected as the model drug. It was also proposed to determine whether the mathematical model developed by Singh *et al.* (3) and tested with salicylic and benzoic acid combinations was valid for simultaneous release of highly water-soluble noninteracting chemicals.

EXPERIMENTAL

Chemicals—The plastic used in all tablets was a powdered methyl acrylate–methyl methacrylate copolymer[1]. This polymer is insoluble and inert in aqueous media at all pH values. The drug employed was methapyrilene hydrochloride NF. Anhydrous dextrose USP and

[1] Rohm and Haas Co., Philadelphia, Pa.