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GENERAL METHOD FOR THE ANALYSIS OF PHARMACEUTICAL DOSAGE FORMS BY HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

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SUMMARY

A reliable and simple method for the routine analysis of pharmaceutical dosage forms by high-performance liquid chromatography using a C_{18} Bondapak reversed-phase column with a binary solvent system consisting of acetonitrile and 0.05 *M* potassium dihydrogen phosphate has been developed. Standardised extraction procedures for drugs in various dosage forms have been developed and successfully applied to a wide range of current pharmaceutical formulations.

INTRODUCTION

High-performance liquid chromatography (HPLC) has emerged as the preferred method for the routine analysis of pharmaceuticals, where most of the procedures are specific to individual drugs, related drugs or similar dosage forms. Baker *et al.*[1] and Law *et al.*[2] have proposed general HPLC methods for the qualitative identification of drugs of forensic interest. The work by Law *et al.*, however, was limited to 84 basic drugs structurally and pharmacologically related to amphetamine. Jane *et al.*[3] extended the scope of a general HPLC method to 462 basic drugs, many with a capacity factor, k', of less than one, using a single column and mobile phase. The authors claimed the procedure was suitable for qualitative and quantitative analysis although no data was presented in respect of the quantitative analysis of drugs in authentic pharmaceutical formulations.

Since 14% of the drugs examined by Jane *et al.* exhibited chromatographic k' values of less than 1, interference from pharmaceutical excipients, manufacturing impurities and degradation products may compromise the selectivity of the method. The development of clean-up procedures to eliminate potential interference may involve laborious and tedious extraction procedures which would be inconsistent with the objective of simplicity and speed of analysis.

Hoogewigs and Massart[4] described an improved HPLC method for basic drugs in pharmaceutical preparations using simple mobile phases as extracting media. Although this technique proved effective for extracting drugs from tablets and capsules, adjustments to the mobile phase were necessary to achieve optimum chromatographic separations.

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The present investigation has lead to the development of a general HPLC method for routine analysis of a wide range of unrelated drugs in typical pharmaceutical formulations, using standardised chromatographic parameters and extraction procedures. In summary this generalised procedure, which has been successfully applied to 111 various dosage forms, employs a single reversed-phase column, a binary solvent system and three simple extraction procedures. The potential for chromatographic interference from excipients, has been minimised by setting a minimal k' acceptance value of 1, while the peak symmetry for some drugs has been improved by minor pH adjustments to the mobile phase.

EXPERIMENTAL

Reagents and chemicals

Drug reference substances were kindly supplied by various pharmaceutical companies. Mobile phases were prepared from AnalaR potassium dihydrogen orthophosphate (BDH Chemicals, Port Fairy, Australia), HPLC grade acetonitrile and methanol (Waters Assoc., Milford, MA, U.S.A.) and water was purified with a Milli-Q reagent grade water system (Millipore ZD 20 230 74).

The potassium dihydrogen phosphate buffer solution, prepared in purified water was filtered through a 0.5-μm filter utilising a Millipore filtration assembly XX1504700. Acetonitrile was degassed using an ultrasonic bath prior to mixing with the buffer solution. Ethanol 95% (CSR, Sydney, Australia) was used for sample extraction. Phosphoric Acid, Proanalysis (May & Baker, Dangenham, U.K.) was used to acidify the mobile phase, when required.

Equipment

HPLC equipment (Waters Assoc.) comprised an M6000A reciprocating pump, WISP 710B auto-injector, 720 system controller and a model 441 fixed-wavelength UV detector fitted with either a zinc or a mercury lamp with appropriate filters for detection at 214,254 and 280 nm. A μBondapak C_{18} column (30 cm $\times$ 3.9 mm I.D.) 10 μm particle size (Part No. 27324) was used. Data reduction was performed with a Spectra-Physics model SP4270 computing integrator.

Chromatographic conditions

Retention data of reference drugs was determined at a temperature of 25 $\pm$ 1°C, however, temperature control was unnecessary for the analysis of dosage forms which was performed under ambient conditions. The mobile phases 1, 2, 3 and 4 contained 15, 30, 45 and 70% (v/v) acetonitrile in 0.05 M potassium dihydrogen orthophosphate respectively. An injection volume of 20 μl and a flow-rate of 2 ml/min was used throughout. The detection wavelength used depended on the molar absorptivity of the drug concerned, however, when more than one wavelength was suitable the preferred order was 254 > 214 > 280 nm.

The k' values of drugs were calculated using the formula $k' = (t_R - t_0)/t_0$ where t_R is the retention time of a particular drug and t_0 is the retention time of a non-retained peak determined as uracil.

Preparation of samples and standards

The choice of extraction solvent depended upon the solubility of each drug and was limited to one of the following: 0.05 *M* dihydrogen orthosphosphate; ethanol 95%; mobile phase. Reference materials were dissolved in the same solvent and diluted to a final concentration comparable to the final sample concentration. The sample extraction procedures employed to extract a drug from various dosage forms are detailed below.

Capsules. Contents of twenty capsules were emptied and bulked. Aliquots of the contents were extracted in one of the above solvents. Where ethanol was chosen as the extraction solvent, further dilutions were made with the appropriate mobile phase to achieve the desired concentration.

Creams, ointments and suppositories. The preparations were extracted using ethanol, warming where necessary. The extract was cooled in ice cold water to precipitate excipients and the solution filtered. A 1:10 or 1:5 dilution using the appropriate mobile phase was normally sufficient to achieve the desired concentration.

Elixirs and syrups. The preparations were diluted with the appropriate mobile phase to the desired concentration. An extraction clean up procedure with an organic solvent was necessary for some formulations. Examples of these procedures are given at the beginning of Table IV.

Eyedrops and injections (Aqueous). The preparations were either injected directly or diluted with the mobile phase to the desired concentration.

Tablets. The drug content was determined on a sample of 10 single tablets collectively. Where ethanol was used as an extraction solvent, the tablets were initially disintegrated in a volume of water equivalent to 10% of the volume of ethanol used and a 1:10 dilution was made with the appropriate mobile phase to achieve the desired concentration. In certain tablet formulations where the solubility of the active drug in 10 tablets was limited in the chosen extraction solvent, the content was determined by assaying two aliquots of 20 powdered tablets.

In all instances, the resulting sample solutions were filtered through a 0.45 μm filter prior to analysis.

Method development

The following criteria were established for the development of the analytical procedure: (1) use of the smallest number of mobile phases to analyse the maximum number of drugs preferably achieved by varying the ratios of a binary solvent system; (2) restriction of k' values to between 1 and 5 for all drugs to minimise interference; (3) the mobile phase should allow the detection at low wavelengths of a drug with a weak chromophore; (4) ionisation and any potential interaction between drug molecule and residual silanol groups on the surface of silica should be suppressed.

Following consideration of these criteria 0.05 *M* potassium dihydrogen phosphate and acetonitrile were selected as the components of the mobile phase. Ratios of organic modifier to buffer were selected by examining the retention behaviour of 147 randomly selected reference materials using a mobile phase of acetonitrile–0.05 *M* potassium dihydrogen phosphate (40:60). The substances were then grouped according to k' values; 0, 0–1, 1–5 and above 5 for group I, II, III and IV respectively.

The k' values of the drugs in each group were then determined in two additional mobile phases (Table I). The composition of the mobile phases for each group

of drugs were calculated from the equation cited by Snyder *et al.*[5] to yield k' values of about 4 and 2 respectively.

$$\log k' = \log k_W - S\alpha$$

where k_W = capacity factor of a solute using water as mobile phase. The value of this term was determined from the data in the first experiment using acetonitrile–0.05 *M* potassium dihydrogen phosphate (40:60) mobile phase; α = the percentage of organic component in the mobile phase; S = a constant dependent on both an organic modifier and a solute. The quoted value of this constant is 3 for acetonitrile.

The log of k' values obtained for each drug in the specified phases was graphed against α. A grid of ordinate lines at α increments of 5% and an abscissa grid consisting of two lines at k' values of 1 and 5 were drawn, Fig. 1 (α increments of 10% are drawn for clarity in Fig. 1). The minimum number of ordinate grid lines which intersected all of the bounded segments ($1 < k' < 5$) of the f(α) curves for the drugs were found from the graph. These values of α, four in total, determined the acetonitrile content of the final mobile phases for the general HPLC scheme.

A number of drugs exhibited skewed peaks when chromatographed in the optimised mobile phases. Peak distortion was minimised by lowering the pH of the mobile phase to around 2.5. Consequently, an acidified version of each of the optimised mobile phases was included in the scheme. For simplicity these acidified variants were produced by adding 1 ml of phosphoric acid to each 500 ml of a particular mobile phase. Fig. 2 depicts the improvement in the shape of a chlorpheniramine peak achieved by lowering the pH of the mobile phase.

RESULTS AND DISCUSSION

Reference drugs atenolol and pholcodine exhibited a k' value of 0.4 when chromatographed in the mobile phase of category 1 and naphazoline hydrochloride exhibited a k' value of 0.5 when chromatographed in the acidified mobile phase of category 2. Antazoline sulphate, which is usually present with naphazoline as an eye drop preparation, produced a k' value of 1.7 under similar experimental conditions. Although these values of k', except for antazoline, are below the minimum defined

TABLE I

MOBILE PHASE COMPOSITION FOR EACH DRUG GROUP

Group	*Additional phases acetonitrile–0.05 M potassium dihydrogen phosphate*
I	10:90
	15:85
II	20:80
	30:70
III	30:70
	40:60
IV	50:50
	60:40

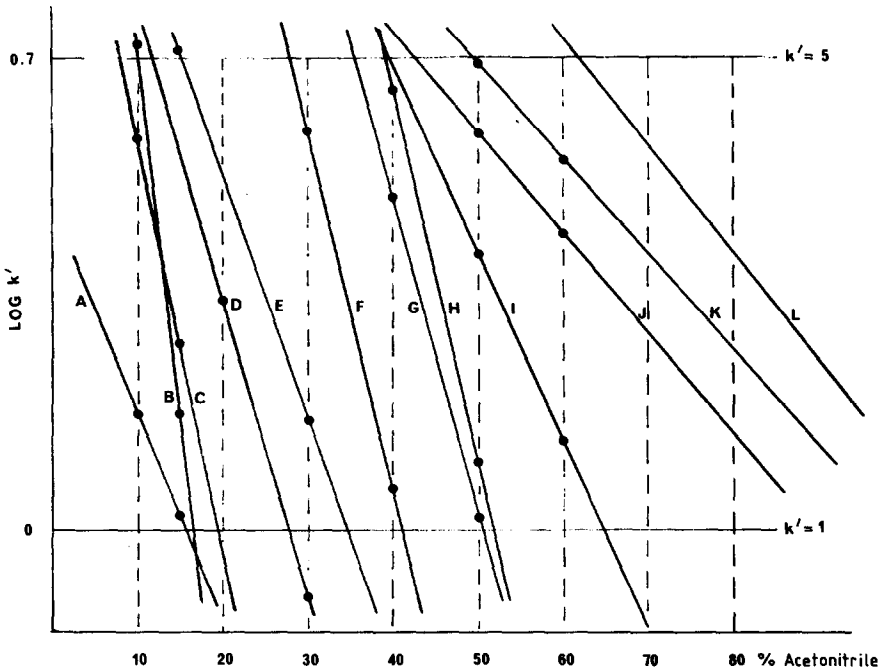

Fig. 1. Relationship between % (v/v) acetonitrile in the mobile phase (acetonitrile–0.05 *M* potassium dihydrogen phosphate) and log *k'* for a number of reference drugs examined in this study. The drugs plotted are, from left to right, metronidazole (A), codeine (B), neostigmine (C), metoprolol (D), oxprenolol (E), flurazepam (F), temazepam (G), bendrofluazide (H), warfarin (I), phenylbutazone (J), medazepam (K) and econazole (L). The horizontal lines at log $k' = 0$ and 0.7 are the boundaries enclosing the preferred retention region ($1 < k' < 5$). The composition of the final mobile phase was predicted from the intersection of the plot of log *k'* *vs.* α, and the vertical dashed lines (% acetonitrile) within this region.

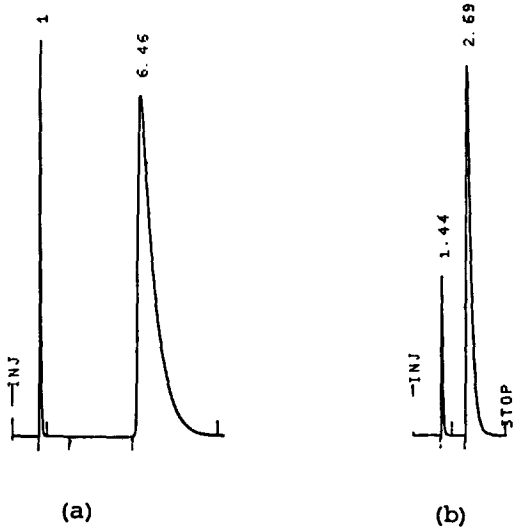

Fig. 2. (a) Chlorpheniramine maleate chromatographed in acetonitrile–0.05 *M* potassium dihydrogen phosphate (30:70); (b) chlorpheniramine maleate chromatographed in acidified acetonitrile–0.05 *M* potassium dihydrogen phosphate (30:70).

TABLE II

EXPERIMENTAL CONDITIONS

Abbreviations: d = drops (eye); n = linctus; t = tablets; 4E = extract with chloroform, evaporate to dryness and dissolve in mobile phase; – = undiluted sample.

Drug	*Formulation*	*Mobile phase*	*Final concn. (mg/ml)*	*Detector wavelength (nm)*	*Extraction method*
Antazoline and naphazoline hydrochloride	d	2*	5.00 0.20	280	–
Atenolol	t	1	1.00	254	2
Pholcodine	n	1	0.10	254	4E

* Acidified mobile phase.

TABLE III

CAPACITY FACTORS, k', AND CATEGORIES OF PURE DRUG REFERENCE SUBSTANCES

The mobile phases of categories 1, 2, 3 and 4 contain 15, 30, 45 and 70% (v/v) acetonitrile in 0.05 *M* potassium dihydrogen phosphate.

Drug name	*Mobile phase category*	k'	*Drug name*	*Mobile phase category*	k'
Acetohexamide	3	1.7	Chlorpromazine hydrochloride	3	2.3
Alcuronium chloride	2*	2.3	Chlorthalidone	2	1.0
Alprenolol hydrochloride	2	2.3	Clemizole hydrochloride	3	1.7
Ambenonium chloride	2*	1.0	Clidinium bromide	2	1.7
Amethocaine hydrochloride	3	1.0	Clonazepam	3	1.7
Amiloride hydrochloride	1	1.0	Clonidine hydrochloride	1	1.7
Amitriptyline hydrochloride	3	2.3	Clorexolone	3	1.7
Amodiaquine hydrochloride	1	3.0	Clotrimazole	4	1.7
Antazoline hydrochloride	2*	1.7	Codeine phosphate	1	1.0
Atropine methonitrate	1	3.7	Colchicine	2	1.7
Atropine sulphate	1	3.7	Cyclopenthiazide	3	2.3
Azatadine maleate	2	2.3	Cyproheptadine hydrochloride	3	3.0
Baclofen	1	1.0	Debrisoquine sulphate	1	3.0
Bendrofluazide	3	2.3	Desipramine hydrochloride	3	1.0
Benzhexol hydrochloride	3	1.7	Dextromoramide tartrate	3	1.7
Benztropine mesylate	2	1.7	Diazepam	4	1.7
Biperiden hydrochloride	3	1.0	Difenoxin hydrochloride	3	1.0
Bisacodyl	3	3.7	Diltiazem hydrochloride	3*	1.0
Bromazepam	2	2.3	Dimethindene maleate	3	1.0
Bromocriptine mesylate	3	5.0	Diphenhydramine hydrochloride	4	3.0
Bromopheniramine	2*	3.0	Diphenylpyraline hydrochloride	3	1.7
Bupivacaine hydrochloride	2	2.3	Dipivefrine hydrochloride	3	1.7
Carbamazepine	3	1.0	Dipyridamole	3	1.0
Carbimazole	2	1.0	Econazole nitrate	4	2.3
Chlordiazepoxide hydrochloride	3	1.0	Enalapril maleate	2	1.7
Chloroquine phosphate	1	1.7	Ethacrynic acid	2	3.0
Chlorothiazide	1	1.7	Fenoterol hydrobromide	1	2.3
Chlorpheniramine maleate	2*	1.7	Flunitrazepam	3	2.3

TABLE III (*continued*)

Drug name	*Mobile phase category*	*k'*	*Drug name*	*Mobile phase category*	*k'*
Fluphenazine hydrochloride	3	3.0	Pheniramine maleate	2	1.7
Flurazepam dihydrochloride	2	2.3	Phensuximide	3	1.0
Frusemide	2	1.0	Phenylbutazone	4	1.0
Gliclazide	3	3.0	Phenytoin sodium	3	1.0
Guanabenz acetate	2	3.0	Pilocarpine hydrochloride	1	1.0
Haloperidol	3	2.3	Pindolol	1	1.7
Homatropine hydrobromide	1	1.7	Pizotifen maleate	3	1.7
Hydrochlorothiazide	1	2.3	Prazosin hydrochloride	2	1.0
Hydroxychloroquine sulphate	1	1.0	Prilocaine hydrochloride	1	1.7
Ibuprofen	4	1.0	Primaquine phosphate	3	1.0
Imipramine hydrochloride	3	1.7	Probenecid	3	1.0
Indomethacin	3	1.7	Prochlorperazine	3	4.3
Isocarboxazid	3	1.0	Procyclidine hydrochloride	3	1.0
Labetalol hydrochloride	2	2.3	Proguanil hydrochloride	2	2.3
Levamisole hydrochloride	1	1.7	Promethazine hydrochloride	2	1.7
Lignocaine hydrochloride	1	1.7	Propantheline bromide	3	1.7
Liothyronine sodium	2	4.3	Propranolol hydrochloride	2	2.3
Loperamide hydrochloride	4	1.0	Protriptyline hydrochloride	3	1.0
Lorazepam	3	1.0	Quinethazone	1	3.0
Mebhydrolin Napadisylate	3	2.3	Quinidine bisulphate	2	2.3
Medazepam	4	1.7	Quinine dihydrochloride	2	2.3
Mefruside	3	1.7	Quinine sulphate	2	2.3
Mepivacaine hydrochloride	1	1.7	Spironolactone	4	1.0
Methylclothiazide	3	1.0	Sulindac	4	1.0
Metoclopramide hydrochloride	2	1.0	Sulphacetamide sodium	1	1.0
Metolazone	3	1.0	Sulphadimidine	2	1.0
Metoprolol tartrate	1	3.0	Sulphafurazole	2	1.0
Metronidazole	1	1.7	Sulphamethizole	1	1.0
Miaserine hydrochloride	3	1.0	Sulphamethoxazole	3	1.0
Minoxidil	1	2.3	Sulphasalazine	2	1.0
Naloxone hydrochloride	1	1.0	Sulphinpyrazone	2	2.3
Naphazoline hydrochloride	2*	0.5	Temazepam	3	1.0
Naproxen	3	1.7	Thiabendazole	2	1.7
Neostigmine bromide	1	1.0	Thioridazine	4	1.0
Nifedipine	3	2.3	Thyroxine sodium	3	1.0
Nitrazepam	3	1.0	Timolol maleate	1	1.0
Nomifensine maleate	2	1.0	Triamterene	1	3.0
Nortriptyline hydrochloride	3	1.0	Trifluoperazine hydrochloride	4	1.7
Opipramol hydrochloride	2	4.3	Trimethoprim	1	2.3
Orphenadrine hydrochloride	3	1.0	Trimipramine maleate	3	2.3
Oxazepam	3	1.7	Trioxysalen	4	1.0
Oxprenonol hydrochloride	2	1.0	Triprolidine hydrochloride	2	3.0
Oxyclozanide	4	1.0	Verapamil hydrochloride	3	1.7
Pethidine hydrochloride	3	1.0	Warfarin sodium	3	2.0

* Acidified mobile phase.

TABLE IV

LIST OF PHARMACEUTICAL DOSAGE FORMS ANALYSED USING THE GENERAL HPLC METHOD DESCRIBED

Abbreviations: A = 0.7% (v/v) hydrochloric acid–acetonitrile; B = extract from an aqueous basic solution with chloroform, dissolve and dilute the residue to final concentration with mobile phase; C = acidify sample and wash with chloroform, basify and extract with chloroform, evaporate to dryness and dissolve the residue in mobile phase; D = 1% ethanolic ammonia; F = extract from ether solution with water, dilute with the phosphate buffer; G = extract powdered tablets with dimethylformamide, dilute with mobile phase; H = 0.1 *M* sodium hydroxide; P = powdered tablets; a = oral solution; b = rectal solution; c = capsules; d = drops; e = elixir; f = expectorant; g = suppositories; h = solution; i = injection; k = suspension; l = lotion; n = linctus; o = ointment; s = syrup; t = tablets; – = undiluted sample.

Drug	*Formulation*	*Mobile phase*	*Final concn. (mg/ml)*	*Dectector wavelength (nm)*	*Extraction method*
Alcuronium chloride	i	2	1.00	280	3
Ambenonium chloride	t	2*	0.50	214	1
Amiloride hydrochloride	t	1	0.20	254	3
Amitriptyline hydrochloride	i	3	0.10	254	3
Atenolol and chlorthalidone	t	1	1.00	254	4A
			0.25		
Atropine methonitrate	a, t, d	1	0.10	214	3
Atropine sulphate	d, i, t	1	0.06	214	3
Azatadine maleate	t	2	0.1	280	3
Benztropine mesylate	i	3	0.1	214	3
Benzhexol hydrochloride	t	3	0.04	214	3
Bisacodyl	b	3	0.50	254	4B
Bromopheniramine	s, t	2*	0.40	254	4C
Carbamazepine	s, t	3	0.10	280	2
Chloroquine phosphate	i,	1	0.25	254	3
	t	1	0.25	254	2
Chlorpheniramine maleate	t	2*	0.40	254	3
Chlorpromazine hydrochloride	e, i, g	3	0.10	254	3
	t	3	0.10	254	2
Clonidine hydrochloride	i, t	1	0.10	214	3
Clotrimazole	l	4	1.00	214	3
Cyproheptadine hydrochloride	t	3	0.20	254	3
Debrisoquine	t	1	0.10	214	2
Diazepam	i, t	4	0.10	254	3
Diltiazem hydrochloride	t	3*	0.30	254	1
Diphenhydramine hydrochloride	c, f	3*	0.50	214	3
Diphenylpyraline hydrochloride	s, t	3	0.15	214	3
Dipivefrin hydrochloride	d	3	0.10	214	3
Dipyridamole	t	3	0.5	214	2
Enalapril maleate	t	2	0.50	214	1
Fenoterol hydrobromide	t,	1	0.25	254	2
	e	1	0.25	254	3
Flurazepam hydrochloride	c	2	0.60	254	1
Frusemide	i,	2	0.10	254	3
	t	2	0.10	254	2
Gliclazide	t	3	0.80	254	2P
Guanabenz acetate	t	2	0.10	254	2
Haloperidol	i, t	3	0.10	254	3

TABLE IV (*continued*)

Drug	*Formulation*	*Mobile phase*	*Final concn. (mg/ml)*	*Dectector wavelength (nm)*	*Extraction method*
Hydrochlorothiazide	t	1	0.20	254	3
Hydrochlorothiazide and			5.00		
Amiloride	t	1	0.02	254	2
Ibuprofen	t	4	0.16	214	2
Indomethacin	c, g	3	0.10	214	3
Labetalol hydrochloride	t	2	0.5	254	2P
Lignocaine hydrochloride	i	1	1.00	254	3
Loperamide hydrochloride	c	4	0.04	214	3
Mebhydrolin napadisylate	k, t	3	0.50	254	4D
Metoclopramide hydrochloride	i, s	2	0.10	254	3
	t	2	0.10	254	2
Metronidazole	i, h, g, t	1	0.10	214	3
Minoxidil	t	1	0.10	280	2
Naloxone hydrochloride	i	1	0.40	214	–
Nifedipine	c	3	0.10	254	2
Nitrazepam	t	3	0.10	214	3
Nortriptyline hydrochloride	t, e	e	0.2	254	2
Orphenadrine hydrochloride	t.	3	0.50	214	2
Oxazepam	t	3	0.15	254	3
Oxprenolol hydrochloride	i,	2	1.00	254	1
	t	2	1.00	254	2
Pethidine hydrochloride	i	2	2.50	214	3
Pheniramine maleate	s,	2	0.60	254	3
	t	2	0.60	254	2
Phensuximide	c	3	1.00	254	3
Phenytoin sodium	i, k, t	3	0.6	254	3
Pilocarpine hydrochloride	d	1	0.10	214	3
Pindolol	t	1	0.20	254	3
Primaquine phosphate	t	3	0.15	254	1
Promethazine hydrochloride	e, i	2	0.10	254	3
	t	2	0.10	254	2
Quinidine Bisulphate	t	2	0.10	214	2P
Quinine Bisulphate	t	2	0.10	214	2P
Quinine dihydrochloride	c	2	0.10	214	2
Quinine sulphate	t	2	0.10	214	2P
Sulphacetamide sodium	d	1	0.5	254	3
Sulphadimidine	t	2	0.10	254	2
Sulphafurazole	t	2	0.10	254	2P
	o	2	0.10	254	4F
	d	2	0.10	254	3
Sulphamethizole	k, t	1	0.10	254	2
Sulphasalazine	t	2	1.00	254	4G
Temazepam	c	3	0.10	254	2
Timolol maleate	d, t	1	0.5	254	3
Thyroxine sodium	t	3	0.01	214	4H
Trimethoprim	t	1	0.10	254	2
Trimethoprim and sulphamethazole	i,	1	0.02	254	3
	t	1	0.10	254	2P
	s	1	0.10	254	3
Verapamil hydrochloride	t	3	1.00	280	1

* Acidified mobile phase.

value of 1, the dosage forms containing these drugs have been successfully analysed without interference from excipients. The conditions of analysis are detailed in Table II.

Table III provides an alphabetical list of reference drugs tested using this procedure together with their k' values (all greater than 1) in the mobile phase of the assigned category.

To assess its versatility the method was initially applied to 31 pharmaceutical dosage forms including capsules, injections, suppositories and tablets. The assay results were compared with those obtained with established procedures. Values of 0.46 and 1.11 obtained for Student t and F tests respectively were well within the theoretical value of 2.0 (for both t and F) at a 95% confidence level.

The optimum conditions for wavelength of detection, final concentration and extraction procedure are listed in Table IV for the dosage forms analysed to date using this method.

It is proposed that a drug substance not previously investigated will be chromatographed in the mobile phase of category 3 [acetonitrile–0.05 M potassium dihydrogen phosphate (45:55)], which covers about 40% of the total drugs analysed, to calculate its k' value. If the calculated value of k' does not lie within the specified range of 1 to 5, the drug substance will be chromatographed in a category with higher or lower organic modifier to obtain a value of k' within the desired range.

CONCLUSION

A simple HPLC procedure for the routine analysis of pharmaceutical preparations has been developed. The method has been successfully applied to a number of drug preparations and the assay results obtained show a good correlation with those obtained with established methods. The procedure is at present applied routinely to about 30–40% of the samples examined in our laboratory. The approach should increase the efficiency and reduce the operating cost of laboratories engaged in the quality control of pharmaceuticals by effective utilisation of automated equipment.

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