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Review

Advances in biopharmaceutical analysis in the People's Republic of China: 1993–1995

Zhi-ling Qin[1]

Department of Pharmaceutical Analysis, School of Pharmacy, Shanghai Medical University, Shanghai 200032, People's Republic of China

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Abstract

Progress in biopharmaceutical analysis of drugs and their metabolites by liquid and gas chromatography between April 1993 and March 1995 has been reviewed. The evaluation and validation of these methods, as well as their applications in pharmacokinetics and metabolic studies, are also discussed.

Keywords: Biopharmaceutical analysis; GC; HPLC; Metabolites; Pharmacokinetics

1. Introduction

The present review is a continuation of the author's previous publication on the same topic (1991–1993) [1]. Research articles were selected from leading journals published in the People's Republic of China during the period April 1993–March 1995 and are classified under sections dealing with reversed-phase high performance liquid chromatography (RP-HPLC) and gas chromatography (GC). Detailed chromatographic conditions and various detecting systems are summarized in appropriate tables. As evident from the research conducted during the period reviewed, the tendency for metabolite determination of parent drugs in biological fluids was to use GC-MS methods as the first choice.

2. RP-HPLC

In the period 1993–1995, RP-HPLC was still the most widely-used technique in biopharmaceutical analysis [2–41]. Table 1 summarizes the chromatographic conditions in detail, including the stationary phase used, the size of column particles, the length and inner diameter of the column as well as the composition of the solvent systems and the pH of any buffer used in the mobile phase.

Table 1 is arranged in order of the detection systems used in conjunction with HPLC. According to the molecular structure of the drugs, UV was the predominant choice for detection [2–34]

[1]Address for correspondance: Room 6, House 2, 1664 Xie Tu Road, Shanghai 200032, People's Republic of China.

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Table 1
RP-HPLC determination of drugs and their metabolites in biological fluids

Drug (metabolites)	Biological fluids	Chromatographic conditions			Ref.
		Column	Mobile phase	Detector	
Diclofenac	Serum	Hypersil C18 (5μm) (100 mm × 4.6 mm)	MeOH–MeCN–PO_4 buffer pH 6.0 (25:20:55)	$UV_{\lambda\ 280\ nm}$	2
Propranolol	Plasma	Spherisorb 5 ODS C18[a] (150 mm × 4.6 mm)	MeOH–H_2O–0.2 mol l^{-1} KH_2PO_4 (100:15:1)	$UV_{\lambda\ 232\ nm}$	3
Fluoroquinolones	Plasma	Spherisorb C18 (5 μm) (250 mm × 4.6 mm)	MeOH–0.008 mol l^{-1} PO_4 buffer–0.5 mol l^{-1} $TBNH_4Br$ (16:75:1.4, pH 2.6)	$UV_{\lambda\ 280\ nm}$	4
Omeprazole	Plasma	Ultrasphere ODS (5 μm) (250 mm × 4.6 mm)	MeOH–PO_4 buffer pH 7.6 (60:40)	$UV_{\lambda\ 308\ nm}$	5
Tricyclic anti-depressant drugs	Serum	YWG C18[a] (150 mm × 4.6 mm)	MeOH–H_2O–TMEDA (70:30:1)–HAc(pH 6.4)	$UV_{\lambda\ 254\ nm}$	6
8-CL-CAMP	Serum (human, rabbit)	Kesheng ODS C18 (10μm) (250 mm × 4.6 mm)	MeOH–0.02 mol l^{-1} KH_2PO_4 (8:92)	$UV_{\lambda\ 259\ nm}$	7
Ondansetron	Plasma	Zorbax Silica (5 μm) (250 mm × 4.6 mm)	MeCN–0.025 mol l^{-1} NaAc (40:60)–HAc (pH 4.2)	$UV_{\lambda\ 310\ nm}$	8
Acyclovir	Plasma	YWG C18 (10 μm) (300 mm × 3.9 mm)	5% MeOH–H_2O	$UV_{\lambda\ 254\ nm}$	9
Ephedrines	Urine	Lichrosphere RP-18 (5 μm) (125 mm × 4 mm)	(A) 0.05 mol l^{-1} KH_2PO_4–Et_3N (pH 5.5) (B) MeOH	$UV_{\lambda\ 210\ nm}$	10
Diclofenac	Transdermal fluid	Hypersil C18 (5 μm) (100 mm × 4.6 mm)	MeOH–0.05 mol l^{-1} PO_4 buffer (pH 7.0) (56:44)	$UV_{\lambda\ 280\ nm}$	11
Tretinoin	Transdermal fluid	YWG C18 (10 μm) (150 mm × 4.6 mm)	MeOH–NH_4Ae buffer (pH 6.0) (85:15)	$UV_{\lambda\ 348\ nm}$	12
Timolol	Transdermal fluid	Zorbax ODS (5 μm) (250 mm × 4.6 mm)	MeCN–H_2O–Et_3N–H_3PO_4 (22:78:10:1)	$UV_{\lambda\ 294\ nm}$	13
Phenyltoin (DPH) (P-OHD)	Plasma (rabbit)	Zorbax C8[a] (250 mm × 4.6 mm)	MeOH–MeCN–H_2O (40:10:50)	$UV_{\lambda\ 203\ nm}$	14
Cotrimexazole (Ac-SMZ)	Serum (rabbit)	Spherisorb ODS C18 (5 μm) (250 mm × 4.6 mm)	MeOH 0.067 mol l^{-1}–KH_2PO_4 buffer (pH 4.6) (35:65)	$UV_{\lambda\ 225\ nm}$	15
Malotilate (main metabolite)	Serum	μ-Bondapak C18 (10 μm) (300 mm × 3.6 mm)	MeOH–H_2O–36% HAc (80:19.2:0.8)	$UV_{\lambda\ 362\ nm}$	16

Table 1 (continued)

Drug (metabolites)	Biological fluids	Chromatographic conditions			Ref.
		Column	Mobile phase	Detector	
Moricizine (Mor–SO, Mor–SO_2)	Plasma, urine	YWG C18 (10 μm) (200 mm × 4.6 mm)	MeOH–MeCN–H_2O–Et_3N (15:45:40:0.5, pH 5.4)	$UV_{\lambda\ 254\ nm}$	17, 18
Benorylate (active metabolites)	Plasma	YWG C18 (10 μm) (250 mm × 5 mm)	MeOH–PO_4 buffer (pH 2.1) (60:50)	$UV_{\lambda\ 238\ nm}$	19
Alprazolam, doxepin	Plasma	Spheri-5RP 18 (5 μm) (220 mm × 4.6 mm)	MeOH 0.05 mol l^{-1} NH_4Ac buffer (1% Et_3N, pH 5.0) (60:40)	$UV_{\lambda\ 254\ nm}$	20
Gliclazide	Plasma	Hitachi Gel ODS (5 μm) (150 mm × 5 mm)	MeCN–MeOH–H_2O (30:25:45)–H_3PO_4(pH 3.5)	$UV_{\lambda\ 228\ nm}$	21
Oxiracetam	Serum, urine	Bondapak NH_2 (10 μm) (30 mm × 4.6 mm)	MeCN–H_2O (80:20)	$UV_{\lambda\ 210\ nm}$	22
Tetramethyl pyrazine	Serum (rat)	Shim-pak CLC-ODS (5 μm) (150 mm × 6 mm)	MeOH–H_2O (72:28)	$UV_{\lambda\ 280\ nm}$	23
Rifapentine	Serum	YWG-C18 (10 μm) (250 mm × 4.6 mm)	MeOH–0.01 mol l^{-1} PO_4 buffer (pH 5.5) (70:30)	$UV_{\lambda\ 336\ nm}$	24
Ethmozine	Plasma	Spherisorb C18 (5 μm) (250 mm × 4.6 mm)	MeOH–H_2O–Et_3N (70:30:0.4) HAc (pH 6.5)	$UV_{\lambda\ 268\ nm}$	25
Thioridazine	Serum	YWG-C18[a] (150 mm × 4.6 mm)	MeOH–H_2O–TEMED (85:15:0.5)–HAc (pH 6.0)	$UV_{\lambda\ 263\ nm}$	26
Lomefloxacine	Plasma	Nucleosil-C18 (7 μm) (250 mm × 4.6 mm)	MeOH–0.008 mol l^{-1} PO_4 buffer–0.05 mol l^{-1} TEBNBr (30:75:4)	$UV_{\lambda\ 288\ nm}$	27, 28
Diclofenac	Serum	Spherisorb-C18 (5 μm) (250 mm × 4.0 mm)	MeOH–0.25 mol l^{-1} NaAc buffer (pH 3.6) (36:64)	$UV_{\lambda\ 282\ nm}$	29
1-Tetrahydro palmatine	Plasma	YWG-C18 (10 μm) (250 mm × 4.0 mm)	MeOH–H_2O (70:30)	$UV_{\lambda\ 281\ nm}$	30
Epostane	Plasma, tissues (rats)	YWG-C18 (10 μm) (150 mm × 4.6 mm)	MeOH–0.5% TMEDA (80:20) (pH 7.5)	$UV_{\lambda\ 254\ nm}$	31, 32
Glibenclamide	Serum	Shimpak-CLC-ODS[a] (150 mm × 6.0 mm)	MeCN–H_2O (55:45) (pH 4.7)	$UV_{\lambda\ 230\ nm}$	33
Ribavirin	Plasma	Micropak ODS (5 μm) (200 mm × 5.0 mm)	10 mmol L^{-1} $NH_4H_2PO_4$ buffer–85% H_3PO_4 (pH 2.5)	$UV_{\lambda\ 207\ nm}$	34
N,N-di(*n*-butyl) doxorubicin-14-valerate (its metabolites)	Urine (rats)	Nova-pak C18 (4 μm) (100 mm × 5 mm)	(A) 0.05 mol l^{-1} $HCOONH_4$ buffer (pH 4.0) (B) MeCN	FLU $E_{x\lambda\ 482\ nm}$ $E_{m\lambda\ 550\ nm}$	35

Table 1 (continued)

Drug (metabolites)	Biological fluids	Chromatographic conditions			Ref.
		Column	Mobile phase	Detector	
Adriamycin	Plasma, liver tissue	μ-Bondapak C18[a] (300 mm × 5.0 mm)	MeOH–0.01 mol l^{-1} $NH_4H_2PO_4$–HAc (70:30:0.5)	FLU $E_{x\lambda 450\,nm}$ $E_{m\lambda 530\,nm}$	36
Metoprolol, α-hydroxymetoprolol	Urine	Spherisorb C18 (5 μm) (250 mm × 4.6 mm)	(A) MeOH (B) H_2O–HAc–Et_3N (1000 ml:1.8 ml:150μl) (A):(B) 50:50, (pH 3.4)	FLU $E_{x\lambda 277\,nm}$ $E_{m\lambda 299\,nm}$	37
Ciprofloxacin	Serum (human, rabbit)	Nucleosil C18[a] (250 mm × 4.6 mm)	MeCN–10 mmol l^{-1} PO_4 buffer–5 mmol l^{-1} $TEBNHSO_4$ (pH 2.7) (18:82)	FLU $E_{x\lambda 274\,nm}$ $E_{m\lambda 418\,nm}$	38
Harringtonine	Serum (rabbit)	Shim-Pak CLC-ODS (5 μm) (150 mm × 6 mm)	MeOH–0.1 mol l^{-1} $HCOONH_4$ buffer (65:35)	FLU $E_{x\lambda 290\,nm}$ $E_{m\lambda 325\,nm}$	39
Ofloxacin	Serum	Hypersil C18 (5 μm) (100 mm × 4.6mm)	0.05 mol l^{-1} citric acid–0.5 mol l^{-1} NH_4Ac–MeCN–1% H_3PO_4–Et_2NH (75:1:22:2:0.15)	FLU $E_{x\lambda 295\,nm}$ $E_{m\lambda 505\,nm}$	40
S-(-) and *R*-(+)-ofloxacin	Urine	Shimadzu ODS (10 μm) (150 mm × 6.3 mm)	MeOH–CMPA (14:86)	FLU $E_{x\lambda 330\,nm}$ $E_{m\lambda 505\,nm}$	41

[a] No particle size indicated in the original paper.

and fluorescence (FLU) was also employed in some cases for drugs with fluorescent characteristics [35–41]. The wavelengths applied for UV and FLU (excitation and emmision) are given.

Table 1 also lists biological fluids analyzed, such as plasma, serum and urine, along with tissues of humans or animals. Some papers reported the use of transdermal fluids of drugs [11–13].

Evaluation and validation of the established RP-HPLC methods were reported in most research papers, including the reliability and overall performance [2–12,14,16,20–27,29–31,36,37,40,42–47].

Together with the parent drugs, the active or major metabolites were analyzed simultaneously in several papers as follows: phenyltoin (DPH) and P-OHD [14], cotrimexazole and AC-SMZ [15], malotinate and its main metabolite [16], moracizine (Mor) and its two metabolites (Mor–SO and Mor-SO_2 [17,18]), benorylate and its active metabolites (paracetamol and salicylic acid [19]), and *N*,*N*-di(*n*-butyl) doxorubicine-14-valerate and its eight urinary metabolites [35].

In the majority of published RP-HPLC UV or FLU methods, emphasis was placed on methodological study to choose the optimized chromatographic conditions for use in biopharmaceutical analysis. However, actual applications of the established methods were reported for the study of metabolic profiles, bioavailability [13,19,28,33,34,-44], clinical pharmacological research and therapeutic drug monitoring [17,18,20–25,30,38]. The pharmacokinetic behaviors were discussed [13,16,-26–29,31–34,39,44].

Table 2
Column-switching RP-HPLC determination of drugs in biological fluids

Drugs (Biological fluids)	Pre-column	Eluent	Anal. column	Mobile phase	Detector	Ref.
Ciprofloxacin (plasma)	Lichroprep RP_2 25–40 μm 3 cm × 4 mm	H_2O	Shimpack CLC-ODS 5 μm 15 cm × 6 mm	MeOH–0.2 mol l^{-1} NH_4Ac (pH 2.7) (32:68)	$UV_{\lambda\ 280\ nm}$	42
Norfloxacin (plasma, tissue) (guinea pig)	μ-Bondapak-C18 37–50 μm 5 cm × 5 mm	0.008 mol l^{-1} PO_4 buffer	YWG-C18 10 μm 15 cm × 5 mm	MeOH–0.008 mol l^{-1} PO_4 buffer–0.05 mol l^{-1} $TBNH_4Br$ (25:75:4)	$UV_{\lambda\ 280\ nm}$	43
Fluconazole (plasma)	Lichroprep RP_2 25–45 μm 3 cm × 4.6 mm	H_2O	Shimpack CLC-ODS 5 μm 15 cm × 6 mm	MeOH–0.2 mol l^{-1} NH_4Ac (pH 2.7) (50:50)	$UV_{\lambda\ 260\ nm}$	44
Norethindron-α,β-poly-(3-hydroxypropyl)-DL-asparamide conjugate (serum) (rabbit)	ODS 9–11 μm 5 cm × 4 mm	H_2O	Shimpack CLC-ODS 4 μm 15 cm × 4 mm	MeOH–H_2O (7:3)	$UV_{\lambda\ 240\ nm}$	45
Adriamycin (plasma)	μ-Bondapak-C18 37–50 μm 5 cm × 5 mm	25 mmol l^{-1} $NH_4H_2PO_4$–0.03 mol l^{-1} H_3PO_4 buffer	YWG-C18 10 μm 15 cm × 5 mm	MeOH–MeCN–25 mmol l^{-1} $NH_4H_2PO_4$–0.03 mol l^{-1} H_3PO_4 buffer (50:10:40)	FLU $E_{x\lambda\ 495\ nm}$ $E_{m\lambda\ 560\ nm}$	46
Dextrorphan (plasma)	μ-Bondapak-C18 37–50 μm 3 cm × 5 mm	0.2% HAc	YWG-C18 5 μm 15 cm × 5 mm	MeCN–H_2O–HAc–Et_3N–CH_2Cl_2 (17:82:1:0.05:0.025)	FLU $E_{x\lambda\ 290\ nm}$ $E_{m\lambda\ 315\ nm}$	47

Table 3
GC and GC–MS determination of drugs and their metabolites in biological fluids

Drugs (Metabolite)	Biological fluids	Column	Detector	Ref.
Central nervous system sedatives	Blood	Capillary	FID	48
Hypnotic and sedative drugs	Blood	Capillary	FID, NPD	49
Mephenytoin	Urine	Capillary (chiral)	NPD	50
Betahistine	Plasma		NPD	51
Methaqualone (its metabolites)	Urine, blood	Capillary	FID, MS	52
Local anaesthetics	Plasma	Capillary	FID, MS	53
Meperidine (its metabolites)	Urine	Capillary	FID, MS	54
Soporific and sedative drugs	Blood	Capillary	FID, MS	55
Drugs of abuse (their metabolites)	Urine	Capillary	FID, MS	56
Amphetamines (their metabolites)	Urine	Capillary	NPD, MS	57
Stimulants (their metabolites)	Urine	Capillary	NPD, MSD	58
Tramadol (its metabolites)	Urine	Capillary	MSD	59
Salbutamol	Urine	Capillary	MSD	60
Trenbolone (its metabolites)	Urine	Capillary	MSD	61
Dihydroetophine hydrochloride	Blood, urine	Capillary	MS/SIM	62
Bencynonate	Plasma	Capillary	MS/SIM	63
Anadol (its metabolite)	Urine	Capillary	MS	64
Calusterone (metabolites)	Urine	Capillary	MS	65

HPLC column switching techniques are summarized in Table 2, including the on-line clean-up precolumn and the analytical column for separation. The particle sizes of both stationary phases and the lengths of both columns, as well as the composition of the eluent and the mobile phase are all given in detail. The detectors used were UV or FLU with the wavelengths indicated in each case [42–47].

3. GC and GC–MS

GC (capillary) and GC–MS methods for biopharmaceutical analysis selected from research papers published between April 1993 and March 1995 are collected in Table 3. These are listed in the order of the detectors used in conjunction with GC: FID [48], FID-NPD [49], NPD [50,51], FID-MS [52–56], NPD-MS [57,58], MSD [59–61], MS-SIM [62,63], and MS [64,65].

These methods were widely applied in the separation and analysis of groups of drugs such as central nervous system sedatives [48], hypnotic and sedative drugs [49], local anesthetics [53], drugs of abuse [56] and stimulants [58] etc., as well as individual drugs for clinical pharmacokinetic study and related bioavailability [48,63], drug monitoring in emergency treatment [52] and in addicted and poisoned cases [62].

In addition to the analysis of parent drugs, the separation and identification of the metabolites of the following drugs were reported, methaqualone [52], meperidine in free or conjugated forms [54], 26 drugs of abuse [56], amphetamines [57], 41 stimulants [58], tramalol [59], trenbolone [61], anadol [64] and calusterone [65].

As described above, the study of the metabolites seemed to be more focused than ever before on the elucidation of the metabolic pathway and the fate of the drug in the body.

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