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Review article

Advances in biopharmaceutical analysis in the People's Republic of China 1995–1997

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Abstract

The present paper is the third biannual review in succession to the author's previous publications (Z.L. Qin, Advances in biopharmaceutical analysis in the People's Republic of China: 1991–1993, J. Pharm. Biomed Anal. 13, 1995, 1–7 and Z.L. Qin, Advances in biopharmaceutical analysis in the People's Republic of China: 1993–1995, J. Pharm. Biomed. Anal. 14, 1996, 1395–1403), regarding the methodological study and progress in biopharmaceutical analysis by RP-HPLC, GC and GC-MS selected from relative journals between April 1995 and March 1997 in P.R. China. The published methods were widely adopted in pharmacokinetic and metabolic studies. Investigation on drug metabolism were conducted more deeply, both in vitro and in vivo, for searching the structure of metabolites and drug metabolic pathways. The use of high performance CZE as a new trend for the analysis of drugs and metabolites in biofluids was also reported. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Biopharmaceutical analysis; RP-HPLC; GC; GC-MS; Metabolites; Pharmacokinetics

1. Introduction

This review describes recent advances in biopharmaceutical analysis of drugs and their metabolites during the period indicated. Methodological studies are classified under two main sections: the reversed phase HPLC and the CG and GC-MS, accompanied with two tables listing the chromatographic conditions and the detecting systems. The applications of the established methods are discussed in detail.

2. Reversed-phase HPLC

From the papers published during April 1995 to March 1997, RP-HPLC with UV detector [1–14,20–52,54,55] remain the most popular techniques adopted by biopharmaceutical analysts, although DAD [15,53], FLU [16–19] and EC [71] were also used occasionally.

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In addition to the detailed chromatographic conditions such as column, mobile phase and detector listed in Table 1, internal standards, the important factor for bioanalysis, are also indicated. Applications of the RP-HPLC methods are summarized below.

Methodological studies on the determination of drug concentrations in serum or plasma were reported for finding simple, rapid, sensitive and accurate methods [3–16]. Necessary parameters for evaluation and validation of the designed methods were presented in most papers.

Pharmacokinetic studies [17–38] were developed rapidly during the reviewed period. In depth research work in human or animal were carried out to elucidate the absorption, distribution, metabolism and excretion of drug in the body. The pharmacokinetic parameters were used in clinical treatments to optimize dosage regime in different patients to ensure safety and efficacy of drugs. For instance, in the case of adriamycin, intra-arterial infusion was found to be more effective and less toxic than the intravenous infusion [18]; in renal failure patients with very slow excretion, cefizoxime was given in smaller dose or longer interval between administrations [25]. Pharmacokinetics studies on sustained release tablets [24,26] were also reported.

Bioavailability and bioequivalent studies [39–47] were made on drugs in various dosage forms or from diverse origins. The pharmacokinetic parameters obtained from blood concentration-time curve were compared to show the relative bioavailability of certain formulations.

Metabolic studies [48–55] on the determination of major and active metabolites of drugs [48–50] in human or rabbit serum and plasma were reported for use in drug monitoring or pharmacokinetic studies. Besides the isolation and analysis of drug metabolites further studies on metabolism were discussed [51–55]. Structures of metabolites were identified and confirmed by means of UV, IR, MS or NMR to elucidate the pathway of biotransformation [52,54]. The incubation of rat liver microsomes in vitro was used to study the metabolic transformation of 6-chlorobutyl phthalide (CBP) [53], and the major metabolites of CBP were identified.

3. GC and GC-MS

Methodological studies on GC and GC-MS techniques [56–70] selected from research papers published in the past 2 years were displayed in Table 2, listing biosamples, internal standards, capillary columns with length and inner diameter, detectors and applications in the following aspects.

3.1. Pharmacokinetic and bioavailability studies

GC-ECD [56,57] were used for analysis of atenolol [56] and bromhexine HCl capsules [57]. GC-MS/SIM methods [64–66] were applied to study pharmacokinetic parameters of morphine [64] controlled release tablets, buspirone [65] and pravastatin [66].

3.2. Toxicological analysis and emergent intoxicated cases

Solid phase extraction [58–62] connected with GC using different detectors were employed to isolate and analyse groups of drugs in biofluids and tissues: GC-NPD for 5 tricyclic anti-depressant drugs (TCAs) [58], GC-FID for screening 24 sedative, hypnotic and anticonvulsant drugs [59], and for eight acidic and basic drugs [60], GC-FID and GC-MS for 34 basic drugs [61] and seven barbiturates [62]; GC-MS, for secobarbital and its four metabolites [63].

3.3. Study of drug metabolism in vitro and vivo by GC-MS

Six metabolites of penbutolol [67] were isolated from human urine, and the predicted possible structures were confirmed by MS data. The metabolism of n-butylphthalide (NBP) [68] was investigated. NBP and its four oxidative metabolites were determined in rat urine. The metabolic pathway of NBP in vivo was found to be agreeable with the results obtained in vitro. Metabolic study on biotransformation (in vitro) of 6-methoxy butyl phthalide (MBP) [69] was carried out by GC-MS and GC-MS with TMS derivatization using phenobarbital induced rat liver micro-

Table 1
RP-HPLC determination of drugs and their metabolites in biofluids and tissues

Drugs (metabolites) (biofluids)	Internal standard	Chromatographic conditions		Detector	Reference
		Column	Mobile phase		
Metronidazole (serum)	Theophylline	YWG C_{18} (10 μm) (250 × 4.6 mm)	H_2O–MeOH (73:27)	$UV_{\lambda 254nm}$	[3]
Estazolam triazolam (serum)	Diazepam	Resolve C_{18} (5 μm) (150 × 4.6 mm)	MeOH–H_2O–MeCN–TMEDA (54.5:36.5:9:0.6)–HAc	$UV_{\lambda 254nm}$	[4]
Phenobarbital, phenytoin carbamazepine (serum)	Methaqualone	YWG C_{18} (10 μm) (150 × 3.9 mm)	MeOH–H_2O–TMEDA–HAc (55:45:0.44:0.352)	$UV_{\lambda variable}$	[5]
Meclobemide (serum)	Methaqualone	YWG C_{18} (10 μm) (150 × 4.0 mm)	MeOH–H_2O–HAc–TMEDA (70:30:0.35:0.44)	$UV_{\lambda 254nm}$	[6]
Dextro methorphan hydrobromide (plasma)	Ledocain	YWG C_{18} (5 μm) (150 × 0.5 mm)	MeCN–H_2O–HAc (50:49:1)–Et_3N (pH 4.3)	$UV_{\lambda 278nm}$	[7]
Midazolam (plasma)	Diazepam	μ-Bondapak C_{18} (300 × 3.9 mm)[a]	MeOH–MeCN–H_2O (47:15:38)	$UV_{\lambda 220nm}$	[8]
Diclofenac sodium (plasma)	Diphenylamine	Spherisorb C_{18} (10 μm) (200 × 4.6 mm)	MeOH–NaAc buffer (pH 4.2) (68:32 v/v)	$UV_{\lambda 274nm}$	[9]
Tenoxicam (plasma)	Piroxicam	YWG C_{18} (150 × 4.5 mm)[a]	MeOH–PO_4 buffer (pH 6.8)–Et_3N (30:69.8:0.2)	$UV_{\lambda 254nm}$	[10]
Erythromycin (plasma)		μ-Bondapak (10 μm) (150 × 0.5 mm)	0.2 mol l^{-1} NH_4Ac–H_2O–MeCN (10:65:25) 0.05 mol l^{-1} H_3PO_4, 2 mol l^{-1} NaOH (pH 6.8)	$UV_{\lambda 235nm}$	[11]
Pentoprazole (rat plasma)	Lansoprazol	Spherisorb C_{18} (5 μm) (200 × 4.6 mm)	MeOH–H_2O–Et_3N (61:38:1)	$UV_{\lambda 290nm}$	[12]
Ipriflavone (dog plasma)	7-Ethyloxyl-isoflavone	Shimpack-CLC-ODS (150 × 4.6 mm)[a]	MeOH:H_2O (78.5:21.5)	$UV_{\lambda 248nm}$	[13]
Naftopidal (rat plasma) (urine and tissue)	Metoprolol	YWG C_{18} (10 μm) (300 × 4.6 mm)	MeOH–MeCN–H_2O-0.2 mol l^{-1} HAc-0.2 mol l^{-1} NaAc (50:45:5:0.9:0.1) (pH 4.2)	$UV_{\lambda 232nm}$	[14]
Carbamazepine		Spherisorb C_{18} (5 μm) (150 × 2.0 mm)	MeOH-0.5 mol l^{-1} Et_3N-0.5 mol l^{-1} glacial HAc (90:10 v/v) (pH 7.5)	DAD	[15]
Clozepine Doxepine Amitriptyine (Plasma)				$UV_{\lambda 261 \pm 4}$ $UV_{\lambda 261 \pm 4}$ $UV_{\lambda 257 \pm 4}$ $UV_{\lambda 245 \pm 4}$	
Tramadol (serum)		Zorbax CN (250 × 4.6 mm)[a]	MeOH–H_2O–H_3PO_4 (90:10:0.35)	FLU, $EX_{\lambda 275nm}$, $Em_{\lambda 302nm}$	[16]
Bisoprolol (plasma)		TMS (7 μm) (150 × 4.6 mm)	MeCN–$(NH_4)_3PO_4$ buffer (1 mol l^{-1} pH 4)–H_2O (18:5:77)	FLU, $EX_{\lambda 275nm}$, $Em_{\lambda 305nm}$	[17]
Adriamycin (plasma)	Zhengding-mycin	μ-Bondapak C_{18} (300 × 3.9 mm)[a]	MeOH–MeCN–$(CH_3)_2$CHOH-5 μ mol l^{-1} H_3PO_4 (10:10:35:45) (pH 2.9)	FLU, $EX_{\lambda 450nm}$, $Em_{\lambda 350nm}$	[18]

Table 1 (continued)

Drugs (metabolites) (biofluids)	Internal standard	Chromatographic conditions		Detector	Reference
		Column	Mobile phase		
Salbutamol (rabbit plasma)		Nucleosic–$N(CH_3)_2$ (5 μm) (150×4 mm)	MeCN–MeOH (0.2% HAc) (2:1)	FLU, $EX_{\lambda 285nm}$, $Em_{\lambda 335nm}$	[19]
Nimodipine (plasma)	Nitrendipine methyltestosterone	Spherisorb ODS (10 μm) (250×4.6 mm)	MeOH–H_2O–n-$C_4H_9NH_2$ (65:35:0.001)	$UV_{\lambda 238nm}$	[20]
Huperzine (plasma)		Spherisorb C_{18} (5 μm) (150×5 mm)	MeOH–H_2O (45:55)	$UV_{\lambda 313nm}$	[21]
Acyclovir (plasma)	Adrenaline	Alltech C_{18} (5 μm) (260×4.6 mm)	0.04 mol l^{-1} NaCl–MeOH–IPR–B7 (100:15:0.6)	$UV_{\lambda 254nm}$	[22]
Ciprofloxacin (serum, urine)		Shim-pack CLC-ODS (5 μm) (150×6 mm)	MeOH-0.05 mol l^{-1} NH_4Ac (pH 3) (20:80)	$UV_{\lambda 276nm}$	[23]
Pseudo ephedrine (plasma)		Lichrosorb 100CN (5 μm) (250×4.0 mm)	MeCN–MeOH–KH_2PO_4 –$C_7H_{15}SO_3Na$-H_2O (50 ml:8 ml:4 g:1 g:400 ml)	$UV_{\lambda 210nm}$	[24]
Ceftizoxine (plasma, urine)		YWG-C_{18} (5μm) (150×5 mm)	MeCN–H_2O–H_3PO_4–Et_2NH (1:9:0.2:25 v/v) (pH 3)	$UV_{\lambda 254nm}$ (plasma) $UV_{\lambda 290nm}$ (urine)	[25]
Verapamil (plasma)		Zorbax silica (5 μm) (250×4.6 mm)	0.05 mol l^{-1} $NH_4H_2PO_4$–MeCN–MeOH–Et_3N (50:25:25:0.25 v/v) 85% H_3PO_4 (pH 6.0)	$UV_{\lambda 232nm}$	[26]
Verapamil (its major metabolite-norverapamil) (plasma)	Ethmosine	YWG C_{18} (10 μm) (200×4.0 mm)	MeOH–H_2O–Et_3N (67:33:0.4 v/v/v) Glacial HAc (pH 6.7)	$UV_{\lambda 279nm}$	[27,48]
Timidazole (saliva)	Metronidazole	Ultrasphere ODS C_{18} (5 μm) (250×4.6 mm)	MeOH–H_2O (23:77 v/v)	$UV_{\lambda 310nm}$	[28]
Norfloxacin (rabbit serum)	Diffluxacin	Shim-pack ODS C_{18} [a,b]	MeCN–H_2O TEBNOH–H_3PO_4 (40:360:2:0.05)	$UV_{\lambda 340nm}$	[29]
Z-47* (rabbit plasma)	Diazepam	μ-Bondapak C_{18} (10 μm) (300×4 mm)	MeOH $NH_4H_2PO_4$ buffer (3:2 v/v) pH 4	$UV_{\lambda 290nm}$	[30,51]
m-Nifedipine (rabbit serum)		Spherisorb C_{18} (3 μm) (100×4.6 mm)	MeOH–H_2O (45:20 v/v)	$UV_{\lambda 350nm}$	[31]
Ferulic acid (rabbit serum)	Coumaline	Zorbax C_{18} (5 μm) (250×4.6 mm)	MeCN-0.1 mol l^{-1} H_3PO_4 (3:7 v/v) (pH 2.5)	$UV_{\lambda 320nm}$	[32]
Crocin-I (rat plasma, urine, tissues)		Novapak C_{18} (4 μm) (150×3.9 mm)	MeOH-0.5% HAc (50:50)	$UV_{\lambda 440nm}$	[33]
N-demethyldiazepam (its metabolite: oxazepam) (human and rat plasma)	Diazepam	Shandon ODS (3 μm) (75×4.6 mm)	MeCN-0.01 mol l^{-1} NaAc buffer (pH 3.8) (33.3:66.6 v/v)	$UV_{\lambda 240nm}$	[34]
Lilopriston (rat serum)	RU486	μ-Bondapak C_{18} (10 μm) (300×3.9 mm)	MeOH–CH_2Cl_2-10 mmol l^{-1} PO_4 buffer (pH 4.0) (67:5:28 v/v)	$UV_{\lambda 302nm}$	[35]

Table 1 (continued)

Drugs (metabolites) (biofluids)	Internal standard	Chromatographic conditions		Detector	Reference
		Column	Mobile phase		
GP-7* (rat plasma)	GP-1	Zorbax-ODS (5 μm) (150×4.6 mm)	MeOH–H_2O–glacial HAc (59:41:0.6)	$UV_{\lambda 285nm}$	[36]
Triptonide (rat plasma, urine, tissues)		Spherisorb C_{18} (5 μm) (150×4.6 mm)	MeCN–H_2O (35:65)	$UV_{\lambda 218nm}$	[37]
Cifotamixe (rat plasma)	β-NSA	KYWG–C_{18}[a,b]	15 mmol l^{-1} NaH_2PO_4–MeOH (83:17 v/v) (pH 4.8)	$UV_{\lambda 254nm}$	[38]
Flunarizine (plasma)		MicroPac MCH-5 (10 μm) (300×4.0 mm)	MeOH–H_2O (65:35 v/v) 0.02 mol l^{-1} TEBNBr, H_3PO_4 (pH 3.0)	$UV_{\lambda 254nm}$	[39]
Tamoxifen (plasma)		Micro Pak-ODS (10 μm) (300×4.6 mm)	MeOH–H_2O–Et_2NH (90:10:0.1 v/v/v)	$UV_{\lambda 254nm}$	[40]
Lorcainide HCl (serum)	Diltiazem	YWG C_{18} (5 μm) (200×5.0 mm)	MeOH–H_2O-0 625 mol l^{-1} NH_4Ac (86:13:1 v/v) NH_4OH (pH 8.0)	$UV_{\lambda 226nm}$	[41]
Captopril (plasma)	4-Chloro-2-nitroaniline	Spherisorb C_{18} (10 μm) (250×4.6 mm)	MeCN–H_2O–glacial HAc (45:55:0.2)	$UV_{\lambda 260nm}$	[42]
Gliclazide (plasma)	Tolbutamide	Zorbax C_8 (250×4.6 mm)[a]	MeOH–0.2% glacial HAc (62:38)	$UV_{\lambda 229nm}$	[43]
Glipizide (plasma)		Spherisorb C_{18} (5 μm) (150×4.6 mm)	MeOH–PO_4 buffer (0.01 mol l^{-1} $NH_4H_2PO_4$) (25:75 v/v)	$UV_{\lambda 225nm}$	[44]
Tranilast (plasma)	Nitro diazepam	YWG-C_{18} (10 μm)[b]	0.02 mmol l^{-1} KH_2PO_4–MeOH (40:60 v/v)	$UV_{\lambda 333nm}$	[45]
Cyclosporin (plasma)	Cyclosporin-D	Spherisorb C_8 (7 μm) (250×4.6 mm)	MeCN–MeOH–H_2O-$(CH_3)_2$-CHOH (56:18:26:1 v/v)	$UV_{\lambda 208nm}$	[46]
4-Methylamino-antipyrine (plasma)	Isopropylamino-antipyrine	YWG C_{18} (10 μm) (150×5 mm)	PO_4 buffer (pH 5.5)–MeOH (68:32)	$UV_{\lambda 254nm}$	[47,48] see [27]
Sulindac (and its metabolites) (serum)	Indomethacin	Spherisorb C_{18} (5 μm) (200×4.6 mm)	MeCN–4% glacial HAc (50:50, 5 min), MeCN–4% glacial HAc (80:20, 15 min)	$UV_{\lambda 328nm}$	[49]
Analgin (and its main metabolites, rabbit plasma)	β-Naphthalene sulfonate	Shim-pack CLC-ODS (150×6.0 mm)[a]	MeOH–H_2O-0.5 mol l^{-1} NaH_2PO_4–Et_3N (35:63:2:0.01) H_3PO_4 (pH 6.0 ± 0.5)	$UV_{\lambda 260nm}$	[50]
Major metabolites of Z-47* (rabbit urine)		1. μ-Bondapak C_{18} (10 μm) (300×4 mm)	1. MeOH–$NH_4H_2PO_4$ buffer (1:1)	$UV_{\lambda 290nm}$	[30,51]
		2. Nucleosil C_{18} (7 μm) (250×4.6 mm)	2. MeOH–$NH_2H_2PO_4$ buffer (2:3)	$UV_{\lambda 270nm}$	
Metabolite of 5-ethyl-5-(*para*-fluorobenzoyl propyl) barbituric acid (rabbit urine)		YWG C_{18} (10 μm) (300×4 mm)	MeOH–H_2) (1:1)	$UV_{\lambda 254nm}$	[52]
Metabolism of 6-chlorobutylphthalide (rat liver microsomes)		Lichrosorb C_{18} (10 μm) (250×4.6 mm)	MeOH–H_2O gradient elution (MeOH 20%→80%)	DAD, $UV_{\lambda 220/4nm/}$ 287/4nm, $Ref_{\lambda 550/}$ 100nm	[53]

Table 1 (continued)

Drugs (metabolites) (biofluids)	Internal standard	Chromatographic conditions		Detector	Reference
		Column	Mobile phase		
Metabolites of tetramethyl pyrazine (rabbit serum)		YWG C_{18} (10 μm) (300 × 4 mm)	$MeOH-H_2O$ (55:45)	$UV_{\lambda 280nm}$	[54]
Major metabolite of etofesalamide (rabbit urine)		1. Nucleosil C_{18} (7 μm) (250 × 4.6 mm)	1. $MeOH-H_2O$ glacial HAc (55:50:0.6)	$UV_{\lambda 290nm}$	[55]
		2. μ-Bondapak C_{18} (10 μm) (250 × 4.0 mm)	2. $MeOH-H_2O$ (1:1) NH_4OH (pH 7)	$UV_{\lambda 270nm}$	

[a] No particle size indicated in the original paper.
[b] No column id and length indicated.
* Z-47; (3H-1, 2-dihydro-2-(4-methyl-phenyl amino) methyl-1-pyrolizinone). See Ref. [30]
* GP-7; 4-[4″-(2″,2″,6″,6″-tetra methyl-1″-piperidinyloxy)amino]-4′-demethylepipodophyllotoxin.

Table 2
GC and GC-MS determination of drugs and their metabolites in biofluids and tissues

Drugs (metabolites) (biofluids, tissues)	Internal standard	Capillary column	Detector	Application	Ref.
Atenolol (plasma)	Metoprolol	HP-1 (0.33 μm) (12 m × 0.2 mm)	ECD	Pharmacokinetics, bioavailability	[56]
Bromhexine HCl (plasma)	2-amino-5-chlorobenzophenone	(5% SE-30) (2 m × 3 mm)	ECD	Pharmacokinetics, bioavailability	[57]
Amitriptyline, trimipramine, imipramine, doxepine, clomipramine (whole blood, liver)	SKF 525A	I. OB-17 (25 m × 0.22 mm) II. BP-10	NPD	Solid-phase extraction used in toxicological analysis	[58]
24 Sedative, hypnotic, anticonvulsant drugs (plasma)	SKF 525A	SE-54 (25 m × 0.25 mm)	FID	Solid-phase extraction used in toxicological analysis	[59]
Eight acidic and basic drugs (plasma)	SKF 525A	SE-54 (25 m × 0.25 mm)	FID	Solid-phase extraction used in toxicological analysis	[60]
34 Basic drugs (plasma)	SKF 525A	SE-54 (25 m × 0.25 mm), BP-5 (25 m × 0.25 mm)	FID, MS	Solid-phase extraction used in toxicological analysis	[61]
Seven barbiturate drugs (plasma)	SKF 525A	SE-54 (25 m × 0.25 mm), SE-54 (10 m × 0.25 mm)	FID, MS	Solid-phase extraction used in toxicological analysis	[62]
Secobarbital (and its metabolites) (blood, urine, gastric juice)		HP-5 (12 m × 0.2 mm)	MS	Analysis for intoxicated cases	[63]
Morphine (plasma)	Codeine phosphate	PH-1 (0.33 μm) (12 m × 0.2 mm)	MS/SIM	Pharmacokinetics	[64]
Buspirone (plasma)		PH-1 (0.33 μm) (12 m × 0.2 mm)	MS/SIM	Clinical pharmacokinetic study	[65]
Pravastatin (plasma)		pH-1 (0.32 μm) (12 m × 0.2 mm)	MS/SIM	Pharmacokinetics	[66]
Penbutolol (its metabolite) (plasma, urine)	Nadolol	See ACTA Pharm Sin. 30 (9) (1995) 702–705	MSD	Study on metabolic pathway	[67]
Metabolism of n-butyl-phthalide (NBP) (urine)		Ref. Chin. Chem. Lett. 6 (1995) 55	MS	Metabolic pathway in vivo	[68]
Metabolism of 6-methoxy butyl phthalide (MBP) (rat liver microsomes)		DB-5 (0.25 μm) (30 m × 0.25 mm)	MS	Biotransformation of MBP in vitro	[69]
Metabolism of 6-methoxy n-butyl phthalide (MBP) (rat urine)		Ref. Chin. Chem. Lett., 6 (1995) 55	MS	Metabolism of MBP in vivo	[70]

somes, where as the study on MBP in vivo [70] was done by hydrolysis of rat urine sample with β-glucuronidase. The results of metabolic biotransformation of MBP in vivo well coincided with those in vitro, and the main metabolic pathway of MBP in vivo was discussed in detail.

High performance capillary zone electrophoresis (HPCZE) were used as new techniques in biopharmaceutical analysis recently. A direct assay of cephalexin [72] in human plasma without any pretreatment was reported. A method for separation of warfarin enantiomers in serum was established [73]. Through the metabolic transformation of the racemic warfarin in vivo the clearance of S(−) warfarin was faster than that of R(+) warfarin, thus the peak heights of S(−) and R(+) warfarin could be identified.

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