Pergamon
0731-7085(94)00113-8

Journal of Pharmaceutical & Biomedical Analysis, Vol. 13, No. 1, pp. 1–7, 1995

0731-7085/95 $9.50 + 0.00

Analytical Survey

Advances in biopharmaceutical analysis in the People's Republic of China: 1991–1993

ZHILING QIN

Department of Pharmaceutical Analysis, School of Pharmacy, Shanghai Medical University, Shanghai, P.R. China

Abstract: The methodological studies on biopharmaceutical analysis of drugs and their metabolites by liquid and gas chromatography with various detectors have been reviewed. Research articles were selected from well known journals published in the People's Republic of China between January 1991 and March 1993. The applications of these methods in bioavailability, pharmacokinetics, therapeutic drug monitoring and metabolic studies have also been discussed.

Keywords: *Biopharmaceutical analysis; HPLC; GC; metabolites; pharmacokinetics.*

Introduction

The present review is a survey of biopharmaceutical analysis as published in articles from the leading journals edited by the colleges of pharmacy, medical universities, national medical institutes and Chinese Pharmaceutical Association. From the methodological point of view, Tables 1, 2 and 3 are listed in the order of the separating means: reversed-phase high-performance liquid chromatography (R-P HPLC) and gas chromatography (GC), and the detecting systems: UV, DAD, FLU; FID, ECD, NPD, MSD and MS, so as to elucidate the recent advance of drug analysis in biological matrices.

Reversed-phase HPLC

The chromatographic conditions of the established R-P HPLC methods were listed in Table 1. In most cases, C_{18} hydrocarbon was introduced on a support by the action of octadecylchlorosilane, ODS, i.e. a bonded phase, to serve as the stationary phase [1–28], whereas the mixtures of water and methanol in various proportions were employed as the reversed mobile phase solvent systems [9–13, 29]. In some cases, the use of acetonitrile–water mixture offered an additional degree of selectivity [1, 8, 20, 21]. In order to optimize the solvent system, methanol with phosphate buffer at certain pH were selected in many cases [2–5, 7, 11–12, 14–16, 19, 26, 27, 30].

Among the detecting systems connected with HPLC, the conventional variable ultraviolet detector was the most commonly adopted [1–20, 29–31, 32–36]. The photodiode array detector (DAD) was used in several cases to examine the purity of chromatographic peak and for the sake of accurate identification of analyte [12, 20–24, 37]. According to the chemical structure of the drugs, the fluorescence [25–27] and electro-chemical detectors (ECD) [28] were also selected.

For the evaluation of the reliability and the overall performance of the proposed R-P HPLC methods, parameters involved in linearity, limit detection, recovery and precision were considered in the majority of the published papers.

HPLC column switching technique was used in several cases [32–34, 38], (Table 2) for rapid determination of drug concentration in plasma or serum and in urine by direct injection. The column switching system was equipped with a precolumn for on-line cleanup and an analytical column for separation. The plasma or serum sample was treated with acetonitrile [32], percholoride [33] or trichloroacetic acid [34] to precipitate the protein, the supernatant to be analysed was either injected directly, treated with methanol and ultrasonated [38],

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

Drug (metabolites)	Biological fluids	Chromatographic conditions			Ref. no.
		Column	Mobile phase	Detector	
Ciprofloxacin	Serum, urine	Ultrasphere-ODS (5 μm) (250 × 4.6 mm)	Ac-buffer pH 3.0 MeCN–DMF–TEBNH$_4$OH (88:6.5:5:0.5)	$UV_{\lambda=276nm}$	1, 27
Vesnarinone	Plasma (dogs)	Shimpack CLC ODS* (150 × 6.0 mm)	MeOH–1 mmol l^{-1} HAc (55:45)	$UV_{\lambda=271nm}$	2
Hydroxyphenytoin	Urine	Ultrasphere-ODS (5 μm) (25 cm × 4.6 mm)	MeOH–PO$_4$ buffer pH 6.0 (35:65)	$UV_{\lambda=240nm}$	3
Famotidine	Plasma, urine	YWG-C$_{18}$ (5 μm) (5 × 150 mm)	MeCN–H$_2$O–H$_3$PO$_4$–Et$_2$NH 1:9:0.013:0.017 (v/v, pH 3.5)	$UV_{\lambda=266nm}$	4, 31
Pseudouridine	Urine	YWG-C$_{18}$ (10 μm) (4 × 250 mm)	MeOH–PO$_4$ buffer pH 3.45	$UV_{\lambda=254nm}$	5
Berberine	Plasma	Nova-PakC$_{18}$ (4 μm) (15 cm × 3.9 mm)	DL–Camphor-10–sulphonic acid–Et$_2$NH–HAc (20:80:0.464:0.5:0.7) (pH 4.8)	$UV_{\lambda=345nm}$	6
Propafenone (5-hydroxy-,N-depropyl-)	Serum	Ultraspherre ODS-C$_{18}$ (5 μm) (4.6 × 250 mm)	PO$_4$ buffer pH 2.7–57% MeOH	$UV_{\lambda=254nm}$	7
Amitriptyline, amipramine, doxepin (nortriptyline, despramine)	Serum	Nucleosil-C$_{18}$ (7 μm) (250 × 4.6 mm)	MeOH–MeCN–H$_2$O (13:35:52)	$UV_{\lambda=254nm}$	8
Procaine (p-ABA)	Plasma	μ-Bondapak-C$_{18}$ (10 μm) (25 × 0.48 cm)	Modified MeOH	$UV_{\lambda=254nm}$	9
Methandienone	Urine	Varian ODS-C$_{18}$ (10 μm) (15 cm × 4.6 mm)	MeOH-H$_2$O (100:40, v/v)	$UV_{\lambda=254nm}$	10
Di-subst-tetra-hydroisoquinoline	Plasma (rabbit)	LiChrosorb-C$_{18}$ (5 μm) (15 cm × 4.6 mm)	MeOH–H$_2$O–TEA–H$_5$PO$_4$ (63:37:1:0.8, v/v)	$UV_{\lambda=230nm}$	11
Bepridil	Plasma	YWG-C$_{18}$ (10 μm) (15 cm × 5 mm i.d.)	MeOH–H$_2$O–TEA–H$_3$PO$_4$ (pH 3.3) (74:16:10)	$UV_{\lambda=254nm}$	12
Lidocaine	Saliva, serum	Shimpack CLC-C$_{18}$ (5 μm) (0.15 m × 6.0ϕ)	MeOH–H$_2$O (70:25)	$UV_{\lambda=214nm}$	13
m-Nifedipine	Plasma (rabbit)	YWG-C$_{18}$ (10 μm) (4 × 250 mm)	MeOH–PO$_4$ buffer (pH 6.1) (70:30, v/v)	$UV_{\lambda=237nm}$	14
Epostane	Serum (rabbit)	μ-Bondpak-C$_{18}$* (4.5 × 45 mm)	MeOH–PO$_4$ buffer (pH 7.0) (50:50, v/v)	$UV_{\lambda=285nm}$	15
Diltiazem	Plasma (rabbit)	YWG-C$_{18}$ (10 μm) (ϕ5 × 200 mm)	MeOH–PO$_4$ buffer (pH 6.5) (84:16)	$UV_{\lambda=237nm}$	16

Piroxicam	Serum	YWG-C_{18} (10 μm) (150 × 5 mm)	MeOH–NH_4AC (pH 4.5) (1:0.9, v/v)	$UV_{\lambda=360nm}$	17
Clomipramine	Serum	CLC-ODS* (15 × 0.6 cm)	MeOH–H_2O–TEMED–HAc (67:33:0.4:0.32)	$UV_{\lambda=254nm}$	18
Ibuprofen	Plasma	Zorbax-C_8 (5 μm) (2.5 × 4.6)†	MeOH–Ac buffer (pH 4.7)–H_3PO_4 (135:35:30)	$UV_{\lambda=225nm}$	19
1-Hexylcarbamoyl-5-fluoro-uracil	Serum (rats)	Shimpack CLC-ODS* (150 mm × 6 mm)	H_2O	$UV_{\lambda=254nm}$	41
Ofloxacin	Plasma	Spherisorb-C_{18} (5 μm) (200 mm × 4.6 mm)	MeOH–PO_4 buffer–$TBNH_4Br$ (35:65:4, pH 2.50)	$UV_{\lambda=294nm}$	30
Carbamazepine	Plasma, saliva	YWG-C_{18} (10 μm) (250 × 4.0 mm)	MeOH–H_2O (59:41)	$UV_{\lambda=245nm}$	29
Rifandin	Urine	Shimpack-CLC-TMS (5 μm) (150 × 4.6 mm)	0.01 M KH_2PO_4–MeCN (50:50)	$UV_{\lambda=316nm}$	20
Homoharringtonine	Liver microsomes (rats, rabbits)	Lichrosorb C_{18} (10 μm) (250 × 4.6 mm)	MeOH–H_2O (MeOH 20–80%)	DAD $UV_{\lambda=29;254,320nm}$	37
Dieuretics, probenecid, caffeine, pemoline	Urine	Lichrosorb C_{18} (5 μm) (200 × 4.6 mm)	PO_4 buffer pH 3 MeCN	DAD $UV_{\lambda=276,230,275nm}$	21
Ceftazidime	Serum	ODS-Hypersil microbore (5 μm) (2.1 × 100 mm)	NH_4Ac (pH 3.5)–MeOH (9:1)	DAD $UV_{\lambda=254nm}$	22
D-Catechin	Plasma (rabbit)	YWG-C_{18} (10 μm) (150 × 5 mm)	MeOH–Citric buffer pH 4.7 (16:84, v/v)	DAD $UV_{\lambda=280nm}$	23
Diltiazem (desacetyl-)	Plasma	(μ-Bondapak-C_{18} (10 μm) (300 × 3.9 mm)	MeOH–TEMED (pH 5.4) (60:40, v/v)	DAD $UV_{\lambda=238nm}$	24
Amiloride	Plasma, urine	Nucleosil-C_{18} (7 μm) (250 × 4.6 mm)	45% MeOH 0.1 mol l^{-1} $HClO_4$	Flu. $Ex_{\lambda=286nm}$; $Ex_{\lambda=418nm}$	25
Puerarine	Plasma (rats, rabbits, dogs)	YWG-C_{18} (10 μm) (4.6 × 250 mm)	MeOH–H_2O PO_4 (pH 7.4) (450:522.5:27.5, v/v)	Flu. $Ex_{\lambda=350nm}$; $Em_{\lambda=470nm}$	26
Ciprofloxacin	Serum	KYWG-C_{18} (10 μm) (4.6 × 250 mm)	MeOH–MeCN–0.05 mmol l^{-1} KH_2PO_4 (33:11:56)	Flu. $Em_{\lambda=280nm}$; $Em_{\lambda=455nm}$	1, 27
Furosemide	Serum, urine	8MB-C_{18} (10 μm) (10 cm × 8 mm)	EtOH-$(Bu_4N)_3PO_4$(pH 7.5)	ED 0.90V	28

*No particle size indicated in the original paper.
†No unit indicated.

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

Drugs (biological fluids)	Pre-column	Eluent	Anal. column	Mobile phase	Detector	Ref. no.
Quinidine (plasma, serum)	Spheriosorb-C_{18} 5 μm 45 × 4.6 mm	MeOH–H_2O 75:25	Sphereiosorb-C_{18} 5 μm 250 × 4.6 mm	MeOH–H_2O–HAc–N–Et$(CH_2)_2NH_2$ 75:25:0.04:0.04	$UV_{\lambda=332nm}$	32
Captopril (plasma, urine)	μ-Bondapak-C_{18} 37–50 μm 5 × 0.5 cm	0.2% HAc	YWG-C_{18} 10 μm 15 × 0.5 cm	MeCN–H_2O–HAc 35:65:0.4	$UV_{\lambda=260nm}$	33
Gliquidone (plasma)	Lichroprep RP2 25–40 μm 3 cm × 4.6 mm	H_2O	Shimpack CLC-ODS 5 μm 15 cm × 6 mm	MeOH–$(CH_3)_2CHOH$–0.2 mol l^{-1} NH_4Ac 61:5:34	$UV_{\lambda=310nm}$	34
Difloxacin (plasma) (dog)	YWG-C_{18} 10 μm 5 cm × 4.6 mm	0.2 mol l^{-1} HAc	Shimpack CLC-ODS 5 μm 15 cm × 6 m	38% MeOH/0.2 mol l^{-1} NH_4Ac	$UV_{\lambda=290nm}$	35
Cifixime (plasma,* urine†)	μ-Bondapak-C_{18} 37–50 μm, 5.0 cm × 5 mm	0.01 mol l^{-1} H_3PO_4–0.1 mol l^{-1} KH_3PO_4–H_2O 21:1:79, pH 2.5	Hitachi GEL 3056 ODS 5 μm 15 cm × 5 mm	MeCN–0.01 mol l^{-1} H_3PO_4–0.1 mol l^{-1} KH_3PO_4–H_2O 13:20:1:66, pH 2.5	$UV_{\lambda=286nm}$* $UV_{\lambda=314nm}$†	36
Mitoxantrone (plasma)	YWG-CN 10 μm 5 cm × 4.6 mm	H_2O	Shimpack CLC-ODS 5 μm 15 cm × 6 mm	48% MeOH/0.2 mol l^{-1} NH_4Ac pH 1.9	$Vis_{\lambda=658nm}$	38

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

Drugs (metabolite)	Biological fluids	Column	Detector	Ref. no.
Oxysophocarpine	Plasma (rabbit)		FID	42
Isoniazide (acetylhydrazine)	Plasma (rats)		FID	43
p-(3,3-Dimethyl-1-triazneo) Benzoic acid	Plasma (mouse)	Capillary	FID	44
Nifedipine	Plasma	Capillary	ECD	14, 45
Timolol, butofilolol (their metabolites)	Urine		MSD	46
Codeine (metabolits)	Urine	Capillary	MSD	47
Nitrendipine	Plasma	Capillary	MSD	56
Oxprenolol, proprenolol, alprenolol (their metabolites)	Urine	Capillary	NPD, MSD	49
Anileridine, levorphanol, nalbuphine, ethanmivan (their metabolites)	Urine	Capillary	NPP, MSD	57
Beta-blockers (their metabolites)	Urine	Capillary	MSD	48
Dehydro-chloromethyl-testosterone (metabolites)	Urine	Capillary	MS	50
Boldenone (metabolites)	Urine	Capillary	MS	51
Norethandrolone (metabolites)	Urine	Capillary	MS	52
Metandienone (metabolites)	Urine	Capillary	MS	53
Anabolic steroids (their metabolites)	Urine	Capillary	MS	54
Testosterone and epi-testosterone	Urine	Capillary	MS	58

or simply diluted with acetic acid [34] or water [36] and injected directly onto HPLC precolumn.

The use of micellar HPLC — the direct plasma injection technique was established [39].

The internal surface reversed-phase (ISRP) for HPLC analysis in the presence of protein was successfully applied to determine drug concentration in body fluid [40].

The applications of R-P HPLC methods listed in Table 1 and 2 for the simultaneous determination of drugs and their active or major metabolites were reported [7–10, 24]. A method for screening the metabolites from the microsomal incubation system was used to study the metabolism of homoharringtonine *in vitro* (25).

Most of the R-P HPLC methods were widely applied to therapeutic drug monitoring, clinical pharmacological research [7–9, 29] as well as bioavailability [4, 20, 25, 31] and pharmacokinetic studies [7, 9, 11, 12, 14–19, 23, 25, 26, 29–31, 39–41]. The related parameters were reported in several papers [1–16, 23, 26, 31].

A highly sensitive, simple, rapid and reproducible R-P HPLC method for the detection of drug both in plasma and saliva was introduced [29]. The correlation betwen the drug concentration in serum and saliva and their corresponding pharmacokinetic parameters were studied and compared [13].

A R-P HPLC screening procedure for the rapid determination of drugs (belonging to different pharmacological groups) was developed. The urinary excretion–time curves of some drugs were reported [37].

In some cases, R-P HPLC method was found to be much simpler and less expensive than that of GC–MS [10].

Gas chromatography and gas chromatography–mass spectrometry

The reviewed papers of GC–FID, GC–ECD, GC–MSD, GC–NPD/MSD and GC–MS methods for biopharmaceutical analysis were collected in Table 3. GC–FID [42, 43], capillary GC–FID [44] and GC–ECD [45] methods for the determination of drugs and metabolites in plasma (rabbit, rat and mouse) were applied to study their pharmacokinetics in detail. Parameters were also reported.

GC–MSD [46–48] and GC–NPD/MSD [49] methods for analysis of beta-blockers and their metabolites in urine were estabilished. The procedure of the extraction and derivatization were suitable for screening and confirmation of beta-blockers in dopine control. The method [49] had also been accepted by the International Olympic Committee to test the urine samples of athletes.

GC–MS methods for the analysis of steroids and their metabolites in human urine were investigated [50–54]. The structure of metabolites were elucidated [50, 52] and the metabolic pathway of steroids [50, 54] were proposed on the basis of GC–MS feature of their metabolites.

In addition to R-P HPLC and GC analysis, a simple radioreceptor assay for drugs in serum was introduced [55]. The assay is sensitive to a concentration as low as 5 ng ml^{-1} and the method had been employed to determine the serum concentration–time profile after i.v. administration of the drug to mice.

Acknowledgement — I would like to thank my dear wife, Weiyu Chen, for her help in the completion of the present review.

References

[1] Y.P. Qin and D.R. Liang, Determination of ciprofloxacin in human serum and urine by R-P HPLC, *J. West China Univ. Med. Sci.* **24**, 104–107 (1993).
[2] S.C. Wu and C.Y. Wu, Solid phase clean-up and determination of vesnarinone in plasma by HPLC, *J. West China Univ. Med. Sci.* **23**, 106–109 (1992).
[3] J.Z. Zeng, D.Y. Liu and Y.G. Zou, HPLC determination of hydroxyphenytoin in human urine, *J. West China Univ. Med. Sci.* **23**, 321–324 (1992).
[4] S. Gau, G.L. Liu and S.X. Wang, Determination of famotidin in plasma and urine by HPLC, *Chinese J. Pharm. Anal.* **11**, 329–332 (1991).
[5] K. Wang, C.H. Yi, P. Liu, S.Y. Yang and G.B. Xie, Rapid determination of human urinary pseudouridine by HPLC, *Chinese J. Chromatogr.* **10**, 48–50 (1992).
[6] C. Yu, Y.C. Hong and H. Zhung, DL-Camphor-10-sulfonic acid as an ion-pair reagent for determination of berberine in plasma by R-P HPLC, *Chinese J. Chromatogr.* **10**, 167–168 (1992).
[7] W.L. Zhang and Y.N. Tang, Simultaneous determination of propafenone and its active metabolites in serum by HPLC, *Acta Pharm. Sinica* **27**, 552–555 (1992).
[8] B. Lu and X.W. Wang, R-P HPLC simultaneous determination of tricyclic antidepressants and their major metabolites in serum, *Chinese J. Pharm. Anal.* **12**, 4–8 (1992).
[9] L.M. Jiang, Y.Y. Li, J.L. Ma and D.H. Zhou, Determination of Procaine and its metabolites para-aminobenzoic acid in human plasma by HPLC, *Chinese J. Pharm. Anal.* **12**, 21–25 (1992).
[10] X.R. Liu, R.J. Wu, M. Lin and Z. Yan, Determination of methandinone and its metabolites in human urine by HPLC, *J. China Pharm. Univ.* **22**, 83–85 (1991).
[11] X.Y. Xie, W.B. Cheng, Z.S. Zhou and Z.L. Qin, R-P HPLC determination of 1-(p-methylphenyl-2-(2-piperidinoacetyl-1,2,3,4-tetrahydroisoquinoline hydrochloride in rabbit plasma and its pharmacokinetic parameters, *Acta Pharm. Sinica* **26**, 593–597 (1991).
[12] J. Wang, W.B. Cheng, D.L. Liu, Z.S. Zhou and Z.L. Qin, R-P HPLC determination of Bepridil in human plasma and its pharmacokinetic parameters, *Acta Academ. Med. Shanghai* **20**, 289–293 (1993).
[13] L.K. Ye, G.X. Li, H.R. Yu, H. Xue, B. Ye, B.W. Quan and Y.Q. Wu, The correlations of saliva and serum concentrations and the clinical pharmacokinetics on subcutaneous injection of lidocain in healthy volunteers defatted, *J. Shenyang Coll. Pharm.* **9**, 114–119 (1992).
[14] Y.B. Liang, X.Y. Ma, G.J. Wu, L.F. Wang, D.K. Liu, J.F. Xing and G.S. Zhao, Determination of m-nifedipine and its pharmacokinetic study in rabbits by HPLC, *Acta Pharmacol. Sinica* **13**, 163–166 (1992).
[15] C.G. Liu, Z.Y. Wu, W.K. Li, X.M. Bai, X.Y. Wu, T. Xue and Z.M. Lin, Pharmacokinetics of epostane in rabbits by HPLC method, *Acta Pharmacol. Sinica* **13**, 467–470 (1992).
[16] K. Li, Y.S. Yuan, H.G. Wang and J.C. Li, R-P HPLC determination of diltiazem in plasma and its pharmacokinetic parameters, *Chinese J. Pharm. Anal.* **121**, 12–15 (1992).
[17] X.G. Jiang, S.D. Ge, X.J. Wang and N.Z. Xi, An HPLC method for determining peroxicam in body fluids, *Acta Pharmacol. Sinica* **12**, 381–384 (1991).
[18] X.H. Yan, H.D. Li, S.W. Xu and J.P. Zhao, Determination of the blood concentration of clomipramine by R-P HPLC, *Chinese J. Pharm. Anal.* **13**, 8–11 (1993).
[19] X. Tang, E.G. He and Y.M. Cai, An analytical HPLC method for determining ibuprofen level in human plasma and its pharmacokinetics in human volunteers, *J. Shenyang Coll. Pharm.* **9**, 1–3 (1992).
[20] Z.G. He, X. Tang and Y.M. Cai, HPLC determination of rifandin content in urine and its bioavailability, *J. Shenyang Coll. Pharm.* **9**, 4–14 (1992).
[21] X. Jin, Z.H. Zhou, X.F. He, X.H. Zhang and M.Z. Wang, Solid phase extraction and R-P HPLC screening procedure for diuretics, probenecid, caffeine and pemoline in urine, *Acta Pharm. Sinica.* **27**, 875–880 (1992).
[22] Y. Zhang and M.F. Xu, Determination of ceftazidine in serum by HPLC, *Chinese J. Pharm. Anal.* **12**, 131–134 (1992).
[23] H.Y. Pan, D.L. Liu, P.P. Xu and M.L. Lu, Determination of D-catechin plasma concentration and pharmacokinetic parameters using HPLC method, *Acta Pharm. Sinica.* **26**, 371–374 (1991).
[24] Z.C. Zheng, M.Z. Wu, A.H. Wang and M.L. Lu, An improvement of the determination of diltiazem and desacetyldiltiazem by HPLC in biological fluid, *Acta Academ. Med. Shanghai* **19**, 381–385 (1992).
[25] D.K. Xu, J.H. Zhou, Y.S. Yuan, X.Q. Liu and S.K. Huang, HPLC analysis of amiloride in plasma and urine, *Chinese J. Pharm. Anal.* **11**, 210–214 (1991).
[26] X.L. Jin and X.Y. Zhu, Pharmacokinetics of puerarin in rats, rabbits and dogs, *Acta Pharmacol. Sinica.* **13**, 284–288 (1992).
[27] B. Yao and H. Yu, Determination of content of ciprofloxacin in human serum by HPLC, *Chinese J. Pharm. Anal.* **12**, 270–272 (1992).
[28] H.Z. Li, H.A. Kubo, Y.S. Kobayashi and T.S. Kinoshita, *Acta Pharm. Sinica.* **26**, 923–927 (1991).
[29] X.Y. Ma, Y.B. Liang and G.J. Wu, HPLC deter-

mination of carbamazepine in human plasma and saliva, *Chinese J. Pharm. Anal.* **11**, 257–263 (1991).
[30] D.K. Xu, A.Z. Ding, Y.S. Yuan and Y. Diao, Determination of oflozacin in human plasma and studies on its pharmacokinetics using HPLC method, *Acta Pharm. Sinica.* **27**, 462–466 (1992).
[31] S. Gao, G.L. Liu, S.Y. Wang and X.H. Gao, Pharmacokinetics and bioavailability of famotidine in 10 healthy Chinese volunteers, *Acta Pharmacol. Sinica.* **12**, 195–198 (1991).
[32] L.C. Guo and Y.Q. Hu, Fast determination of the blood concentration of quinidine with column-switching HPLC, *Chinese J. Pharm. Anal.* **13**, 12–15 (1993).
[33] W.R. Tian, S. Gao and S.X. Wang, Determination of captopril in plasma and urine by HPLC with column switching, *Acta Pharm. Sinica.* **27**, 613–617 (1992).
[34] P. Guo, Z.W. Li, C.H. Chen, S.P. Deng and S.G. Tang, Direct injection of plasma to determine gliquidone in plasma using HPLC column switching technique, *Acta Pharm. Sinica.* **27**, 452–455 (1992).
[35] P. Guo, Z.W. Li and T.S. Wu, Determination of difloxacin in plasma using HPLC column switching technique, *Chinese J. Pharm. Anal.* **12**, 1–4 (1992).
[36] G.L. Liu, R.G. Sha, S. Gao, Y.X. Shen and S.X. Wang, Determination of cefixime in human plasma and urine using HPLC column switching technique, *Acta Pharm. Sinica.* **28**, 216–221 (1993).
[37] Y.Y. Cui and M.Z. Wang, The metabolism of homoharringtonine by liver microsomes of rats and rabbits, *Acta Pharm. Sinica* **26**, 274–279 (1991).
[38] P. Guo, L.M. Ye, C.Y. Wu, Z.W. Li and T.S. Wu, Determination of antitumour drug mitoxantrone in plasma using HPLC column switching technique, *Acta Pharm. Sinica.* **26**, 367–370 (1991).
[39] P. Ma and C.Y. Wu, Studies on the determination of plasma level and pharmacokinetic parameters of anisodamine by micellar liquid chromatography, *Acta Pharm. Sinica.* **27**, 763–767 (1992).
[40] Z.Y. Wu and S.A. Matlin, The application of internal surface reversed-phase (ISRP) to drug analysis of body fluids, *Chinese J. Chromatogr.* **10**, 357–358 (1992).
[41] Y.Y. Zhu, Y.S. Gao, Y.Q. Zheng and J.Q. Qu, R-P HPLC determination of 1-hexylcarbamoyl-5-fluorouracil and its pharmacokientic study in rats serum, *Chinese J. Pharm. Anal.* **12**, 142–145 (1992).
[42] H. Lu, S.K. Huang, X.H. Wang, Y. Li and P.H. Yu, GC determination of oxysophocarpine in rabbit plasma and its pharmacokinetics, *J. China Pharm. Univ.* **22**, 36–38 (1991).
[43] R.L. Zhang, Z.Y. Wang, D. Li and W.B. Cheng, Effects of rifapicin on pharmacokinetics of isoniazid and its metabolite acetylhydrazone in rats, *Acta Pharmacol. Sinica.* **13**, 494–496 (1992).
[44] Y. Li, P.H. Yu, H. Lu and S.K. Huang, Determination of p-(3,3-dimethyl-1-triazneo) benzoic acid by capillary gas chromatographic method, *J. China Pharm. Univ.* **22**, 207–209 (1991).
[45] W. Lu, L. Wang, J.M. Zhang, X. Chen, Y. Yan and A.Q. Zou, Determination of plasma nifedipine by GC method, *Chinese J. Pharm. Anal.* **12**, 67–70 (1992).
[46] C.H. You and H.J. Fang, Studies on analysis of β-blockers III. Analysis of metabolites of timolol and butofilolol, *Chinese J. Pharm. Anal.* **12**, 264–268 (1992).
[47] H.J. Hong, Y.Q. Xu, H.J. Duan, Y.X. Xu, Y. Wu and H. Chi, Studies on the analysis of codeine and its metabolites in urine, *Chinese J. Chromatogr.* **10**, 63–66 (1992).
[48] H.J. Duan, H.J. Fang, Y. Wu, T.H. Zhou, Y.Q. Xu, Y.X. Xu and H. Chi, Analysis of β-blockers in dopine control, *Chinese J. Pharm. Anal.* **11**, 272–275 (1991).
[49] Y.X. Xu, H.J. Fang, Y.Q. Xu, Y. Wu and H.J. Duan, Studies on the analysis of beta-blockers and their metabolites in urine by GC I. Analysis of Alprenolol, oxprenolol, propranolol and their metabolites by GC/NPD and GC/MSD, *Chinese J. Chromatogr.* **10**, 7–9 (1992).
[50] C.S. Liu, J. Zhang and T.H. Zhou, Investigation on the metabolism of dehydro-chloromethyltestosterone in man, *Acta Pharm. Sinica.* **26**, 682–687 (1991).
[51] J. Zhang, C.S. Liu and T.H. Zhou, GC/MS analysis of boldenone urinary metabolites in man, *Acta Pharm. Sinica.* **26**, 362–366 (1991).
[52] C.S. Liu, J. Zhang and T.H. Zhou, GC–MS analysis of norethandrolone and its metabolites in man, *Acta Pharm. Sinica.* **26**, 777–781 (1991).
[53] Y.W. Yang, R.J. Wu, Z.L. Wang and J.Y. Ren, GC–MS method for determination of metandienone and its metabolites in urine, *J. China Pharm. Univ.* **22**, 282–285 (1991).
[54] J. Zhang, C.S. Liu, H.G. Bi, Y.Z. Zhang, L. Ye and T.H. Zhou, The chromatographic–mass spectrometric analysis and detection of anabolic steroids in human urine and metabolic study, *Acta Pharm. Sinica.* **26**, 598–605 (1991).
[55] M. Chang, A sensitive radioreceptor assay for enpiperate in serum, *J. Beijing Medical Univ.* **24**, 106–108 (1992).
[56] X.J. Yang, L.L. Yang, Z.Y. Zhu and F.F. Mao, Determination of nitrendipine in human plasma by GC with a mass selected detector (GC–MSD), *Chinese J. Chromatogr.* **10**, 35–37 (1992).
[57] Y.Q. Xu, H.J. Fang, Y.X. Xu, H.J. Duan and Y. Wu, Studies on the analysis of anileridine, levorphanol, nalbuphine and ethamivan in urine, *Acta Pharm. Sinica.* **26**, 606–610 (1991).
[58] Y.W. Yang and R.J. Wu, Trimethylsilylation of testosterone, epitestosterone and determination of their ratio in urine by GC–MS, *Acta Pharm. Sinica.* **27**, 758–762 (1992).