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Review

UPLC System for the Analysis of Active Substances from Various Biological Materials

Natalia Hetman [1], Iwona Dymek [1], Małgorzata Starek [1], Przemysław Dorożyński [1], Przemysław Talik [2], Mariia Data [1] and Monika Dąbrowska [1,*]

[1] Department of Inorganic Chemistry and Pharmaceutical Analytics, Faculty of Pharmacy, Jagiellonian University Medical College, 9 Medyczna St, 30-688 Kraków, Poland; nhetman9@gmail.com (N.H.); iwona.dymek9@gmail.com (I.D.); m.starek@uj.edu.pl (M.S.); przemyslaw.dorozynski@uj.edu.pl (P.D.); mariia.data@student.uj.edu.pl (M.D.)

[2] Faculty of Chemistry, University of Opole, 48 Oleska St, 45-052 Opole, Poland; przemyslaw.talik@uni.opole.pl

* Correspondence: monika.1.dabrowska@uj.edu.pl

Abstract

Ultra-performance liquid chromatography (UPLC) is a type of liquid chromatography characterized, compared to other chromatographic methods, by shorter analysis times, resulting from factors such as the use of columns with smaller particle sizes. It has been used in many scientific studies, including pharmaceutical and medical research. This paper compiles information from various publications on the use of UPLC for the determination of compounds in biological materials. The following biological materials of human and animal origin were taken into account: hair, nails, blood (whole blood and plasma), urine, tissues, saliva and gastric fluids, cerebrospinal fluids, feces and seminal plasma. The characteristics of each biological material were discussed, together with the appropriate processing procedures required for subsequent testing. The substances analyzed included compounds from the group of drugs, hormones, biomarkers, proteins, enzymes, metabolites, lipids and toxic substances. In addition, the collected data also included information on the type and parameters of the UPLC column, mobile phase composition, flow rate, detection method, total run time and values of the LOD (Limit of detection) and LOQ (Limit of quantitation) parameters. The collected data can aid analysts in a broad range of laboratory research, enabling the monitoring of active ingredient concentrations in biological materials, which is crucial, especially in the context of therapy and human health.

Keywords: UPLC; blood; urine; tissues; hair; nails; saliva; gastric fluid; cerebrospinal fluid; feces; seminal plasma

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1. Introduction

UPLC and Ultra-High-Performance Liquid Chromatography (UHPLC) are both liquid chromatography techniques that use columns with particle sizes of less than 2 micrometers in order to achieve high-resolution separation, but there are few differences between them. UHPLC is a more general term for advanced liquid chromatography systems, whereas UPLC is a specific brand developed by Waters Corporation. These techniques differ in terms of system design, column characteristics, separation rate and versatility. The aforementioned liquid chromatography techniques are characterized by short analysis times; specifically, the analysis time for UPLC can be up to 10 times shorter, while for UHPLC it is typically 3 to 5 times shorter, compared to conventional high-performance liquid chromatography (HPLC) techniques. Unlike HPLC, where particles can range in size from 2.5 to 10 µm,

UPLC allows the use of particles less than 2 µm (usually 1.7 µm) and 1.7 to 2.5 µm in UHPLC columns [1]. This particle size requires higher pressures, so UPLC system operate in the 6000 to 15,000 psi range [2]. In addition, by using higher temperatures, the viscosity of the mobile phase will decrease and thus the flow rate will increase. In this way, even higher efficiency can also be achieved [3].

These methods use columns with smaller solid grains, which allows analysis to be carried out at lower solvent flows. Thus, the volume of consumed solvent is much lower than with HPLC, helping to reduce the amount of chemical waste generated by the process. UHPLC is characterized by shorter analysis times compared to HPLC. Shorter times mean that the chromatography process is less energy intensive and requires less electricity. In addition, due to the smaller solid grains in UPLC columns, it features higher resolution, leading to better separation of sample components. This greater separation efficiency translates into fewer repeat analyses and reduced waste generated by the process. These factors contribute to a reduction in chemical waste, energy consumption and overall environmental impact [1]. In this publication, most of the analyzed sources are based on UPLC rather than UHPLC; therefore, only the term 'UPLC' will be used.

Two separation techniques can be used in UPLC: Hydrophilic Interaction Chromatography (HILIC) and Reversed-Phase Chromatography (RP/RPLC). HILIC is used for the separation of highly polar compounds: amino acids, sugars, small peptides, organic acids and metabolites. RP, on the other hand, is used to separate non-polar, hydrophobic and moderately polar compounds (e.g., most small-molecule drugs, impurities, fat-soluble vitamins). Regardless of the method chosen: HILIC or RP, UPLC technology enables significantly narrower peaks and better separation of multi-component mixtures than traditional HPLC, at higher operating pressure. HILIC in UPLC system, combined with mass spectrometry, delivers satisfactory results in metabolomic analysis. UPLC with an RP column, on the other hand, is the standard for the qualitative and quantitative analysis of pharmaceuticals [4].

Despite its numerous advantages, the UPLC method also has disadvantages that should be considered when selecting a method. The main disadvantage is faster column wear due to the use of higher pressures [1].

Due to its high throughput, UPLC is currently used in many studies, and in combination with tandem mass spectrometry, it is widely used in drug metabolite identification, pharmacokinetics, toxicology, bioanalysis and bioequivalence studies, contributing to the development of medical science [5].

The aim of this narrative review is to collect data on the use of UPLC in the assay of biological active substances obtained from biological material of various origins. Publications were considered eligible if they addressed the application of UPLC or UHPLC for the analysis of biological materials and were relevant to the determination of bioactive compounds, including drugs, hormones, biomarkers, proteins, enzymes, metabolites, lipids, and toxic substances. Priority was given to original research articles providing specific information on analytical procedures and experimental results. Studies describing biological sample preparation, chromatographic conditions, detection techniques, and analytical performance parameters, such as the limit of detection (LOD) and quantification (LOQ), were considered particularly relevant. This review is intended to serve as a general introduction to the analysis of biological samples using UPLC and to facilitate decisions regarding the choice of an analytical method. However, it does not constitute a detailed protocol for conducting a specific analysis but rather provides a basis for selecting the methodology. The selected literature was analyzed narratively, with particular emphasis on biological matrices, sample preparation procedures, chromatographic column characteristics, mobile phase composition, flow rate, detection methods, analysis time, and reported LOD and LOQ values. The collected information was subsequently organized according to the type

of biological material to facilitate comparison of the analytical approaches described in the literature. The study provides a comprehensive comparison of analytical strategies used in various biological matrices, encompassing both commonly analyzed samples (plasma, serum, urine) and less frequently described materials such as saliva, hair, nails, and feces. We also emphasized the practical nature of the review, focusing on chromatographic column selection, UPLC conditions, and detection methods, which can be helpful in designing new analytical methods. A prepared analysis of the literature in terms of analytical conditions can provide valuable information to scientists, eliminating the need to re-develop the conditions for determining selected active substances in complex biological material.

Literature Search and Selection

The literature review was conducted using the bibliographic databases PubMed, Scopus, Web of Science Core Collection, and Google Scholar. Full-text articles were additionally retrieved through publisher platforms including ScienceDirect (Elsevier), SpringerLink, Wiley Online Library, Taylor & Francis Online, MDPI, and ACS Publications.

The search strategy combined keywords related to ultra-performance liquid chromatography and biological matrices using Boolean operators. Representative search strings included:

- ("UPLC" OR "UHPLC" OR "ultra-performance liquid chromatography" OR "ultra-high-performance liquid chromatography");
- AND ("MS/MS" OR "mass spectrometry" OR "tandem mass spectrometry");
- AND ("bioanalysis" OR "bioanalytical method" OR "biological matrix");
- AND ("plasma" OR "serum" OR "urine" OR "hair" OR "nails" OR "saliva" OR "cerebrospinal fluid" OR "feces" OR "tissue").

Additional articles were identified through manual screening of the reference lists of relevant publications. Publications from 2005 to 2026 were considered for inclusion, with emphasis placed on studies reporting analytical applications, method development, validation, and recent advances in UPLC/UHPLC techniques. References to current regulatory guidance documents, including FDA M10, ICH M10, and EMA Bioanalytical Method Validation Guideline, were also included where relevant. Publications written in English and available up to early 2026 were considered. Materials unrelated to the subject matter, duplicate entries across databases, studies with imprecise results, and content of low methodological quality were excluded.

2. UPLC Analysis Conditions in Various Biological Materials

2.1. Blood

Blood is a valuable source of information about a patient's health. UPLC coupled with mass spectrometry allows accurate and precise determination of many compounds present in blood. It is used to optimize treatment conditions, especially long-term ones. Long-term use of medications such as sedatives or analgesics can be associated with a high risk of addiction. To reduce this risk and ensure appropriate therapy, blood drug and metabolite concentrations are measured. In such cases, UPLC is justified due to its high sensitivity and short analysis time [6]. The reduction in the analysis time during the determination of doxazosin in plasma from 15 to 2 min compared to HPLC is an undoubted advantage of UPLC, especially in toxicological analysis [7]. This enables the testing of a larger number of compounds without compromising the quality of the analysis, as demonstrated in a study in which 9 psychoactive substances (amphetamine, methamphetamine, ephedrine, pseudoephedrine, phentermine, 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyethamphetamine (MDEA), ketamine) were determined in less than 3 min [8]. Monitoring drug concentra-

tions in the body is crucial, especially for drugs requiring precise dosing and administered to children, pregnant women, and the elderly. Patient plasma samples were analyzed to determine the concentrations of cefuroxime, meropenem, and amoxicillin/clavulanic acid [9]. Another antibiotic tested was linezolid, the use of which may cause side effects in the circulatory system. Wang et al. measured plasma concentrations of linezolid and heme using UPLC-MS-MS to determine the hematological toxicity of this drug [10]. There are several detection methods that can be coupled with UPLC, such as mass spectrometry (MS), UV and fluorescence; however, tandem mass spectrometry (MS-MS) detection is the best choice due to its superior sensitivity and selectivity. However, the software and equipment required for MS analysis are significantly more expensive than the other options [11]. Lidocaine and its metabolite concentrations were also analyzed in plasma samples from pregnant women with gestational diabetes, which is extremely important because diabetes can interfere with the metabolism of many drugs [12]. In the pharmacokinetics study of diclofenac sodium, a mixture of acetonitrile and aqueous ammonium hydroxide solution was used as the mobile phase [13]. A UPLC-MS-MS method was developed for the determination of 22 antiepileptic drugs in plasma. It is characterized by a short analysis time (approximately 10 min) and can be used to monitor drug concentrations in blood to optimize pharmacotherapy [14]. Fiorentini et al. used UPLC-MS-MS to characterize the pharmacokinetic properties of givinostat in pediatric patients [15]. UPLC may also be a useful method for determining antituberculosis drugs, as demonstrated by measuring the concentration of rifampicin and its metabolic products in the plasma of infected patients [16]. The UPLC method also proved effective in separating acetylcarnitine, which is important in newborn screening for metabolic diseases. Plasma (approximately 10 µL) and dried blood drops were used as the material [17]. Among biological and forensic samples, blood (whole, plasma or serum) is probably one of the most popular samples for cannabinoid analysis [18]. Various procedures are used to properly prepare samples for UPLC analysis. Erceg et al. used a mixture of methanol and acetonitrile to precipitate protein from plasma prior to analysis. The samples were then frozen, the solvent evaporated, and the dry residue was dissolved in the mobile phase [19]. In the study by Cai et al., 5 mL of collected blood was used, centrifuged to remove plasma, and then acetonitrile was added to precipitate proteins. After centrifugation, the solution was evaporated to dryness and dissolved in a mixture of acetonitrile and water [20]. It is also possible to analyze smaller sample volumes like 100 µL of a rat plasma [21]. An undeniable advantage of UPLC is its ability to analyze samples of just a few microliters in volume, which makes it possible to analyze dried blood spots consisting of just a few drops of blood, as well as samples from newborns [22]. The storage time of collected biological material can affect the results and varies depending on the type of study. Dried blood spots are stored at 4 °C, while plasma is stored at −20 °C [17], or even −70 °C [23] until analysis. [24]. However, despite its many benefits, miniaturization presents analytical challenges due to the limited volume available for repeat measurements and the difficulty in separating interfering compounds at low volumes [25]. It is also worth mentioning that the interfering compounds present in blood may disrupt the analysis process. The main problem is the presence of proteins and phospholipids, which have a significant effect on the chromatographic system and the MS detector. One of the most substantial effects is the attenuation or amplification of the signal through the disruption of the ionization process by phospholipids [26]. Effective reduction in the matrix effect requires a combination of appropriate sample preparation—such as protein precipitation or SPE—and optimization of chromatographic conditions, including adjustments to the gradient, in order to separate the eluting analyte from the main phospholipid peak [27]. Detailed parameters of the methods for determining drugs in blood samples are presented in Table 1.

Table 1. UPLC technique in the analysis of various substances in blood.

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
human plasma	midazolam (MDZ) morphine (MOR) 1-hydroxymidazolam (OHM) hydroxymidazolam glucuronide (HMG) morphine-3-glucuronide (M3G) morphine-6-glucuronide (M6G)	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid in water B—formic acid in methanol	3	0.4 mL/min	MS-MS	LLOQ [ng/mL]: MDZ 5.1 OHM 3.1 HMG 7.2 MOR 2.4 M3G 1.2 M6G 2.5	[6]
human plasma	doxazosine	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—pentadecafluorooctanoic acid in ACN B—pentadecafluorooctanoic acid in water	2	0–1.45 mL/min	MS-MS	LOD [ng/mL]: 0.02	[7]
whole blood	amphetamine, methamphetamine, ephedrine, pseudoephedrine, phentermine, MDMA, MDA, MDEA, ketamine	BEH C18 (50 × 2.1 mm, 1.7 µm)	glacial acetic acid, pyrrolidine in water, methanol (50:50, *v*/*v*)	<3	0.4 mL/min	MS	N/A	[8]
human blood plasma	amoxicillin, ampicillin, cefuroxime, cefazolin, ceftazidime, meropenem, piperacillin, clavulanic acid, tazobactam	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid in water B—formic acid in ACN	5.5	0.4 mL/min.	MS-MS	LLOQ [mg/L]: 0.44–1.59	[9]
human plasma	linezolid (L) heme (H)	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—0.1% formic acid water B—ACN	3.0	0.3 mL/min	MS-MS	LOD [ng/mL]: L 0.5 H 1.3	[10]
human blood plasma	lidocaine (LI) monoethyl-glycinexylidide (MG)	RP-select B C18 (250 × 4 mm, 5 µm)	phosphate buffer solution with trimethylamine, ACN (60:40, *v*/*v*)	35	1.0 mL/min.	UV	LOD [ng/mL]: LI 20 MG15 LOQ [ng/mL]: LI, MG 50	[12]
rat plasma and lipid microsphere	diclofenac sodium	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ACN B—aqueous ammonium hydroxide	2	0.2 mL/min	MS-MS	LLOQ [µg/mL]: 0.1	[13]
human plasma	22 psychotropic drugs	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ammonium acetate, formic acid B—methanol	10	0.4 mL/min	MS-MS	LOQ [µg/mL]: 0.01–260	[14]
human plasma	rifampicin (RIF) rifampicin quinone (RIF-Q) 3-formylrifampicin (3-F-RIF) 25-desacetylrifampicin (25-D-RIF), isoniazid (INH) pyrazinamide (PZA)	C18 (150 × 3 mm, 2.6 µm)	gradient: A—water, ammonium formate, formic acid B—ACN, formic acid	12	0.35 mL/min	MS-MS	LLOQ [µg/mL]: RIF 0.1 RIF-Q 0.1 3-F-RIF 0.1 25-D-RIF 0.1 INH 0.05 PZA 0.2	[16]
human dried blood spots and plasma	acylcarnitine profiling: (free carnitine and 43 derivatives)	C18 (15 cm × 2.1 mm, 1.7 µm)	gradient: A—trifluoroacetic acid in water B—trifluoroacetic acid in ACN	15	400 µL/min	MS-MS	LOD [µM]: 0.002–0.063 LOQ [µM]: 0.004–0.357	[17]

Table 1. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
canine plasma	doxazosin	XTerra MS C18 (150 × 2.1 mm, 3.5 µm) Xterra MS C18 (20 × 2.1 mm, 3.5 µm)	gradient: A—ACN, ammonium acetate (10:90, *v*/*v*) B—ACN, ammonium acetate (90:10, *v*/*v*)	15	400 µL/min	MS-MS	LOD [ng/mL]: 1.2	[19]
human blood plasma	cytosine, theophylline, caffeine, nalidixic acid, amitriptyline, 1-aminopyrene, 3-aminofluoranthene, leucine, norleucine, phenylalanine, tryptophan, hippuric acid	C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—water, formic acid B—ACN, formic acid	35	500 µL/min	QTOF-MS	N/A	[24]
human dried blood spots	succinylacetone	BEH C18 (50 × 2.1 mm, 1.7 µm)	ACN, aqueous ammonium acetate (80:20, *v*/*v*)	1	0.4 mL/min	MS-MS	LOD [µmol/L]: 0.2	[28]
human serum	aleuria aurantia lectin phytohemagglutinin-L4 concanavalin A *Datura stramonium* agglutinin	C18 (300 × 5 mm, 5 µm) Michrom C18 (100 × 75 mm, 5 µm)	gradient: A—ACN, acetic acid B—ACN, formic acid	74	20 µL/min	MS-MS	LOQ [fmol]: 1–30	[29]
human serum	iohexol	HLB (20 × 2.1 mm, 5 µm)	A—ACN B—formic acid	7.5	0.4 mL/min	MS-MS	LOD [mg/L]: 2.5 LOQ [mg/L]: 1500	[30]
human blood plasma and seminal	efavirenz fluorinated analog of efavirenz	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid in water B—formic acid in methanol	8	0.5 mL/min	MS-MS	LLOQ [ng/mL]: 0.5	[31]
mouse and human plasma	primaquine enantiomers	Chiralcel OD (250 × 4.6 mm, 10 µm)	gradient: A—aqueous ammonium formate, 0.1% formic acid B—CAN, 0.1% formic acid	50	0.7 mL/min	MSD-TOF	LOD [ng/mL]: 3 LOQ [ng/mL]: 10	[32]
human plasma	amitriptyline (AM) nortriptyline (NO)	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ACN B—ammonium acetate	1.2	0.3 mL/min	MS-MS	LOQ [ng/mL]: AM 0.406 NO 0.401	[33]
human plasma	paroxetine	Hypersil Gold C18 (100 × 2.1 mm, 1.9 µm)	ACN, glacial acetic acid (50:50, *v*/*v*)	1.9	0.35 mL/min	MS-MS	LOQ [ng/mL]: 0.05	[34]
rabbit plasma	E- and Z-guggulsterone isomers	Symmetry-Shield C18 (150 × 4.6 mm, 5 µm)	gradient: A—methanol B—formic acid C—ACN	20	1 mL/min	MS-MS	LLOQ [ng/mL]: 1.56	[35]
human plasma	oxcarbazepine (OXC) 10,11-dihydro-10-hydroxycarbamazepine (MHD)	BEH C18 (50 × 2.1 mm, 1.7 µm)	ACN, aqueous ammonium acetate (85:15, *v*/*v*)	1.5	0.25 mL/min	MS-MS	LLOQ [ng/mL]: OXC 9.580 MHD 19.444	[36]
human plasma	fenofibric acid	BEH C18 (50 × 2.1 mm, 1.7 µm)	ACN, water, formic acid (70:30:0.2, *v*/*v*/*v*)	1.8	0.2 mL/min	MS-MS	LLOQ [g/mL]: 0.05	[37]
human whole blood	45 of psychotropic drugs	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid B—ACN	13.5	0.6 mL/min	TOF-MS	LOQ [ng/g]: 0.06–27	[38]

Table 1. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
human whole blood and lymphocytes	cyclosporine	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ammonium acetate, formic acid, ACN B—ammonium acetate, formic acid, ACN	5	400 µL/min	MS-MS	LOQ in blood [µg/mL]: 5 LOQ in lymphocytes [µg/L]: 2	[39]
human plasma	chlorpromazine	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—water B—formic acid C—ACN	2	0.5 mL/min	MS-MS	LLOQ [ng/mL]: 0.5	[40]
human plasma	metformin	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid in water B—formic acid in ACN	40	0.25 mL/min	MS-MS	N/A	[41]
rat plasma	phenytoin, imipramine, cyclobenzaprine, lidocaine, haloperidol, trifluoperazine, risperidone, thioradazine, caffeine, diazepam, cegalopram, gabapentine, paroxetine, morphine, chloropromazine, fluoxetine, prophenazine, rofecoxib, carbamazepine, diclofenac	BEH C18 (30 × 2.1 mm, 1.7 µm)	gradient: A—methanol, water (10:90, *v*/*v*) in ammonium acetate and isopropanol B—methanol, water (99:1, *v*/*v*) in ammonium acetate and isopropanol A—ACN, water (2:98, *v*/*v*) in acetic acid B—ACN, water (95:5, *v*/*v*) in acetic acid	1.1	0.6 mL/min	MS-MS	LOQ discrete [nM]: 5–32 LOQ cassette [nM]: 5–110	[42]
human plasma	highly polar metabolites	BEH HILIC (100 × 2.1 mm, 1.7 µm)	gradient: A—water B—ACN, ammonium acetate	15	0.3 mL/min	MS	N/A	[43]
		BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid B—ACN		0.4 mL/min			
rat plasma	norisoboldine (NIB) norisoboldine-9-*O*-aglucuronide (NIB-Glu)	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ACN B—water C—formic acid	6	0.5 mL/min	MS	LOQ [mg/mL]: NIB: 0.01 NIB-Glu: 0.025	[44]
rat plasma	mosapride	Hypurity C18 (25 × 4.6 mm, 5 µm)	gradient: A—ACN B—potassium dihydrogen phosphate aqueous solution	20	1 mL/min	UV	LOQ: 0.015 µg/mL	[45]
rat plasma	taurine, creatinine p-cresol sulfate palmitoylcarnitine	C8 (100 × 2.1 mm, 1.7 µm)	gradient: A—ammonium formate, formic acid B—ACN	30	0.35 mL min	QTOF-MS	N/A	[46]
rat plasma	oleic amide, stearic amide, eicosanoic amide, indoxyl sulfate, p-cresol sulfate, oleic acid, linoleic acid, palmitoylcarnitine		gradient: A—water, formic acid B—ACN		0.35 mL min	MS	N/A	
rat plasma	mangiferin	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ACN B—water, formic acid	3	0.20 mL/min	MS-MS	LLOQ [µg/mL]: 0.4	[47]
rat plasma	20(*S*)-protopanaxadiol	BEH C18 (50 × 2.1 mm, 1.7 µm)	formic acid, ACN (10:90, *v*/*v*)	4	0.2 mL/min	MS-MS	LOD [ng/mL]: 0.5 LLOQ [ng/mL]: 2	[48]
human plasma	10 tryptic peptides	BEH C18 (150 × 1.0 mm, 1.7 µm)	gradient: A—formic acid in water B—formic acid in ACN	40	30 µL/min	MS-MS	N/A	[49]

Table 1. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
human plasma	untargeted plasma metabolite profiling	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid in water B—formic acid in ACN	12	0.5 mL/min	MS	N/A	[50]
mouse plasma and brain	irinotecan 7-ethyl-10-hydroxycamptothecin	BEH C18 (50 × 2.1 mm, 1.7 µm) HSS T3 (50 × 2.1 mm, 1.8 µm) BEH C18 (100 × 2.1 mm, 1.7 µm) Pinnacle DB C18, (50 × 2.1 mm, 1.9 µm) Hypersil Gold (50 × 2.1 mm, 1.9 µm)	gradient: A—ammonium acetate/formic acid B—ACN	4.1	0.4 mL/min 0.2 mL/min 0.15 mL/min 0.2 mL/min 0.2 mL/min	MS-MS	LOQ: plasma [ng/mL]: 5 brain [ng/g]: 1.25	[51]
turkey blood plasma	albendazole albendazole sulfoxide albendazole sulfone	Vision HT C18-P (50 × 2.0 mm, 1.5 µm) Synergi Fusion-RP 80a (150 × 4.6 mm, 4 µm) LiChrosorb RP8 (250 × 4 mm, 10 µm) Allure Basix (100 × 4.6 mm, 3 µm) Hypersil Gold (100 × 3 mm, 3 µm) XBridge Phenyl (150 × 3 mm, 3.5 µm)	gradient: A—ACN, ammonium acetate buffer (10:90, *v*/*v*) B—ACN, ammonium acetate buffer (60:40, *v*/*v*)	23	0.2 mL/min 1.0 mL/min 1.5 mL/min 1.0 mL/min 1.0 mL/min 0.5 mL/min	fluorescence	LLOQ [%] ≤ 15 LOQ [%] ≤ 20	[52]
porcine plasma	morphine morphine-3b-glucuronide morphine-6b-glucuronide 6-acetylmorphine morphine N-oxide 10-hydroxymorphine	HSS T3 (100 × 2.16 mm, 1.8 µm)	gradient: A—formic acid in water B—methanol	8.5	0.5 mL/min	MS-MS	LLOQ [ng/mL]: 0.1–0.25	[53]
human plasma	quetiapine N-desalkylquetiapine O-desalkylquetiapine 7-hydroxyquetiapine quetiapine sulfoxide	Spherisorb S5SCX (100 × 2.1 mm)	gradient: A—formic acid in water B—methanol	12	0.5 1mL/min	MS-MS	LOQ [µg/L]: 2–20	[54]
human dried blood spots	ramoplanin	BEH Phenyl (100 × 2.1 mm, 1.7 µm)	gradient: A—ammonium formate, formic acid B—ACN, formic acid	4	0.5 mL/min	MS-MS	LLOQ [ng/mL]: 7.59–12.0	[55]
human plasma	nicotine cotinine trans-3′-hydroxycotinine varenicline	HILIC BEH (100 × 2.1 mm, 1.7 µm)	gradient: A—ammonium formate buffer B—ACN, formic acid	8	0.4 mL/min	MS-MS	LLOQ [ng/mL]: 1–1000	[56]

Table 1. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
human plasma	nevirapine, indinavir, saquinavir, nelfinavir, amprenavir, atazanavir, ritonavir, efavirenz, lopinavir, tipranavir	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—ammonium, formic acid B—ACN	15	0.450 mL/min	DAD	LLOQ [mg/L]: 0.025–0.250 LOD [mg/L]: 0.003–0.235	[57]
human dried blood spots	ceruloplasmin	BEH C18 (50 × 2.1 mm, 1.7 µm)	linear gradient: ACN, formic acid	7.5	0.1 mL/min	MS-MS	N/A	[58]
human plasma	citrulline	HILIC (100 × 2.1 mm, 1.7 µm)	gradient: A—water with formic acid B—ACN with formic acid	5	0.45 mL/min	MS-MS	LOQ [µM/L]: 0.3—0.6	[59]
rabbit plasma	daptomycin	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—trifluoroacetic acid B—methanol	2.5	0.45 mL/min	UV	LOQ [µg/mL]: 0.45 LOD [µg/mL]: 0.15	[60]
rat plasma	saxagliptin	BEH C18 pre-column (5 × 2.1 mm, 1.7 µm) / C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—methanol B—formic acid	1.2	0.35 mL/min	MS-MS	LLOQ [ng/mL]: 0.5	[61]
human plasma	mycophenolate acid (MPA) MPA glucuronide acyl MPA glucuronide	BEH HSST3 (100 × 2.1 mm, 1.8 µm) BEH C18 (50 × 2.1 mm, 1.7 µm) BEH C8 (100 × 1 mm, 1.7 µm) MS C18 (20 × 4 mm, 3.5 µm)	gradient: A—water, methanol, formic acid, aqueous ammonium acetate B—methanol, formic acid, aqueous ammonium acetate	2	0.5 mL/min	MS-MS	LOQ [mg/L]: 0.1–1	[62]
human plasma	clopidogrel and its active metabolite	Luna C18 (20 × 4 mm, 3.5 µm) BEH C18 (50 × 2.1 mm, 1.7 µm) BEH C8 (100 × 1 mm, 1.7 µm)	gradient: A—distilled water, formic acid B—ACN, formic acid	1.5	0.2 mL/min	MS-MS	LOD [ng/mL]: 0.3 LLOQ [ng/mL]: 0.8	[63]
human plasma	dabigatran	BEH C8 (100 × 1 mm, 1.7 µm)	gradient: A—water with formic acid, B—methanol with formic acid	4.5	0.18 mL/min	MS-MS	LLOD and LLOQ [µg/L]: 2	[64]
human plasma	quinapril (QL) quinaprilat (QT)	BEH C18 (100 × 2.1 mm, 1.7 µm)	ACN, water, formic acid (70:30:0.1, *v*/*v*/*v*)	3	0.2 mL/min	MS-MS	LOQ [ng/mL]: QL 0.010 QT 10.012	[65]
human and murine plasma	sphingosine 1-phosphate	BEH Hilic (150 × 2.1 mm, 1.7 µm)	A—ammonium acetate with formic acid B—ACN, methanol, ammonium acetate (85:10:15, *v*/*v*/*v*)	20	0.55 mL/min	MS-MS	LOD [pg/mL]: < 5 LOQ [ng/mL]: 5.0	[66]
human plasma	toluene diisocyanate albumin coniugates (TDI—albumin)	BEH130 C18 (100 µm × 100 mm, 1.7 µm)	gradient: A—0.1% formic acid B—0.1% formic acid in ACN	60	15 µL/min	MS-MS	N/A	[67]
human plasma	mangiferin	C18 (250 × 4.6 mm, 5.0 µm)	methanol, aqueous formic acid (30:70, *v*/*v*)	10	1.0 mL/min	MS	LOD [ng/mL]: 2 LOQ [ng/mL]: 5	[68]

Table 1. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
human serum	toluene diisocyanate albumin binding sites (TDI—albumin)	BEH130 C18 (100 µm × 100 mm, 1.7 µm)	gradient: A—0.1% formic acid B—0.1% formic acid in ACN	60	15 µL/min	MS-MS	N/A	[69]
rat plasma	costunolide dehydrocostuslactone	BEH RP18 (100 × 2.1 mm, 1.7 µm)	methanol, formic acid in water (70:30, *v*/*v*)	3	0.2 mL/min	MS-MS	LOQ [ng/mL]: 0.19 and 0.23	[70]
rat serum	melamine cyanuric acid	BEH Amide (100 × 2.1 mm, 1.7 µm)	gradient: A—ACN B—ammonium acetate	5	600 µL/min	MS-MS	LOQ [ppb]: 5 and 10	[71]
mouse serum and tissues (liver, kidney, lung, and spleen)	ritonavir (RTV) indinavir (IDV) atazanavir (ATV) efavirenz (EFV)	BEH Shield RP 18 (100 × 2.1 mm, 1.7 µm)	gradient: A—ACN, methanol B—ammonium acetate	7	0.3 mL/min	MS-MS	ULOQ [ng/mL]: RTV 927.8 IDV 936.9 ATV 931.8 EFV 975.2	[72]
rat plasma	ginsenoside profiling	T3 (100 × 2.1 mm, 1.8 µm)	gradient: A—water B—ACN	23	0.50 mL/min	MS	N/A	[73]
spontaneously hypertensive rat plasma	LysoPC(22:6), LysoPC(20:4), LysoPC(18:1), cholylglycine, PE(P-16:0e/0:0), sphingosine-1-phosphate, 2-oxo-4-methylthio butanoic acid	ZORBAX SB-C18 (150 × 2.1 mm, 3.5 µm)	gradient: A—formic acid in water B—formic acid in ACN	20	0.20 mL/min	QTOF-MS	N/A	[74]
human dried blood spots	17a-hydroxyprogesterone 21-deoxycortisol 11-deoxycortisol 11- deoxycorticosterone cortisol	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—water, formic acid B—ACN/formic acid	1.25	0.6 mL/min	MS-MS	LOD [nnmol/mL]: 0.9–1.3 LOQ [nnmol/mL]: 2.8–4.3	[75]
human plasma	epinephrine (E) norepinephrine (NE)	BEH (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, ammonium acetate in water B—methanol	3.5	0.35 mL/min	MS-MS	LOD [ng/mL]: E 0.40 NE 2.00	[76]
rat plasma	components from Shexiang Baoxin pill: gamabufotalin, 17-hydroxyprogesterone, 11-hydroxyprogesterone, 1βhydroxylbufalin, resibufaginol, bufalin, 3-epi-bufalin, cinobufagin	C18 (250 × 4.6 mm, 5 µm)	gradient: A—formic acid with water B—ACN with water	90	0.8 mL/min	MS-MS	LOQ [ng/mL]: from 3 to 4	[77]
human serum	endogenous metabolites (metabolomic profiling; potential biomarkers of neural tube defects)	BEH C 18 (100 × 2.1 mm, 1.7 µm)	gradient: A—water with formic acid B—ACN	17	0.4 mL/min	TOF-MS	N/A	[78]
human plasma	diphenidol	BEH C18 column (50 × 2.1 mm, 1.7 µm)	formic acid, ACN (70:30, *v*/*v*)	2	0.4 mL/min	MS	N/A	[79]
human plasma	oseltamivir phosphate (OP) oseltamivir carboxylate (OC)	Chromatopack C18 (50 × 3.0 mm, 3.0 µm)	formic acid in ACN, ammonium acetate (80:20, *v*/*v*)	1	0.60 mL/min	MS-MS	LOQ [ng/mL]: OP 0.92 OC 5.22	[80]

Table 1. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
human plasma	S-adenosyl methionine (SAM) S-adenosyl homocysteine (SAH)	SymmetryShield RP18 (100 × 2.1 mm, 3.5 µm) BEH C18 (50 × 2.1 mm, 1.7 µm) BEH C18 VanGuard pre-column (5 × 2.1 mm, 1.7 µm)	glacial acetic acid	3	0.35 mL/min	MS-MS	LOQ [nmol/L]: SAM 0.5 SAH 0.7	[81]
human plasma	5-methyltetrahydrofolate 5-formyltetrahydrofolate 5,10-methenyltetrahydrofolate folic acid	HSS T3 (50 × 2.1 mm, 1.8 µm) BEH C18 VanGuard precolumn (5 × 2.1 mm, 1.7 µm)	gradient: A—glacial acetic acid B—methanol		0.5 mL/min	MS-MS	LOQ [nmol/L]: 0.17–1.79	
human whole blood	(6S)-5-CH3-H4folate (6S)-5-HCOH4folate (6R)-5,10-CH+-H4folate (6S)-H4folate folic acid non-CH3-H4folate	HSS T3 (50 × 2.1 mm, 1.8 µm) BEH C18 VanGuard precolumn (5 × 2.1 mm, 1.7 µm)	gradient: A—glacial acetic acid B—methanol	2.5	0.5 mL/min	MS-MS	LOD [nmol/L]: 0.12–0.40 LOQ [nmol/L]: 0.36–1.19	[82]
human, rat and rabbit plasma	methadone (MET) flunitrazepam (FNZ) 2-ethilidene-1,5-dimethyl-3,3-diphenylpyrrolidone (EDDP) 7-aminoflunitrazepam (7-AFNZ)	HSS T3 (50 × 2.1 mm, 1.8 µm)	gradient: A—ACN, formic acid B—ammonium acetate	3	3 mL/min	MS-MS	LOQ [ng/mL]: MET 0.509 FNZ 0.524 EDDP 0.520, 7-AFNZ 0.528	[83]
human plasma	N-glycome profiling	BEH Glycan (50 × 2.1 mm, 1.7 µm) TSKgel Amide 80 (150 × 4.6 mm, 3.0 µm)	gradient: A—ammonium formate buffer (aqueous) B—ACN	7.8 48	0.56 mL/min 0.48 mL/min	fluorescence	N/A	[84]
human plasma	metformin (M) glipizide (G)	Kromasil Phenyl (150 × 4.6 mm, 5 µm)	methanol/ammonium acetate (75:25, *v*/*v*)	4.8	0.35 mL/min	MS-MS	LLOQ [ng/mL]: M 4.10 G 2.55	[85]
human whole blood	galactose—metabolizing enzymes: GALK, GALE, GALT	(HSS)-T3 (100 × 2.1 mm, 1.8 µm)	gradient: A—triethylamine buffer B—distilled water	10	250 µL/min	MS-MS	N/A	[86]
human plasma and serum	mycophenolic acid (MPA) mycophenolic acid glucuronide (MPAG)	BEH C8 (50 × 2.1 mm, 1.7 µm)	gradient: A—water/methanol (95:5, *v*/*v*) with formic acid and ammonium acetate B—water/methanol (5:95, *v*/*v*) with formic acid and ammonium acetate	2	0.35 mL/min	MS-MS	LOQ [mg/L]: MPA 0.05 MPAG 2.30	[87]
human whole blood	isotope-labeled uridine diphosphate galactose ([$^{13}C_6$]-UDPGal)	Atlantis T3 (100 × 2.1 mm, 3 µm)	gradient: A—double-distilled water, tributylamine, acetic acid B—methanol	20	0.2 mL/min	MS-MS	N/A	[88]
rat plasma	neoeriocitrin (NE) naringin (NA)	BEH C18 (50 × 2.1 mm, 1.7 µm)	ACN, water (20:80, *v*/*v*)	2	0.20 mL/min	MS-MS	LLOQ [ng/mL]: NE 15 NA 12	[89]

Table 1. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
rat plasma	isorhamnetin (I) kaempferol (K) quercetin (Q)	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—methanol B—formic acid	7.5	0.4 mL/min	MS	LLOD [ng/mL]: I 3.48 K 0.78 Q 1.29 LLOQ [ng/mL]: I 5.88 K 3.63 Q 4.56	[90]
human plasma	epirubicin	BEH C18 (50 × 1.0 mm, 1.7 µm)	gradient: A—formic acid, water B—ACN	4	0.20 mL/min	MS-MS	LOD [ng/mL]: 0.10 LOQ [ng/mL]: 0.50	[91]
human plasma	sufentanil	BEH C18 (50 × 2.1 mm, 1.7 µm)	ACN, water (45:55, *v*/*v*)	3	0.2 mL/min	MS-MS	N/A	[92]
human serum	testosterone (Te) 5-dihydrotestosterone (DHT)	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—water B—ammonium acetate in ACN/water (98:2, *v*/*v*)	5	0.5 mL/min	MS-MS	N/A	[93]
rat plasma and brain	aripiprazole	Eclipse Plus C18 (50 × 2.1 mm, 1.8 µm)	gradient: A—aqueous formic acid B—ACN	3	0.3 mL/min	MS-MS	LOQ plasma [ng/mL] 0.5 brain [ng/g] 1.5	[94]
mouse blood plasma and heart	carnitine γ-butyrobetaine mildronate	HILIC BEH (100 × 2.1 mm, 1.7 µm)	gradient: A—ammonium acetate B—ACN	-	0.15 mL/min	MS-MS	N/A	[95]
rat plasma	emodin (E) emodin glucuronide (EG)	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ammonium acetate aqueous buffer B—ACN	3.2	0.45 mL/min	MS-MS	LOQ [ng/mL]: E 39 EG 78	[96]
rat plasma	vincristine (VI) verapamil (VE)	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ammonium acetate, acetic acid B—methanol	2	0.2 mL/min	MS-MS	LLOQ [ng/mL]: VI 0.5 VE 0.1	[97]
rat plasma	pimpinellin (P) isopimpinellin (IP) phellopterin (PH)	BEH C18 (50 × 2.1 mm, 1.7 µm)	methanol, ammonium acetate (65:35, *v*/*v*)	4.5	0.20 mL/min	MS-MS	LLOQ [ng/mL]: P 25.0 IP 10.0 PH 5.00	[98]
rat plasma	eleutheroside B and its metabolite	HSS T3 (100 × 2.1 mm, 1.8 µm)	gradient: A—ACN, formic acid B—water, formic acid	24	0.3 mL/min	QTOF-MS	N/A	[99]
human dried blood spots	ertapenem	Zorbax Eclipse Plus C18 Rapid Resolution (50 × 2.1 mm, 1.8 µm)	gradient: A—water, formic acid B—ACN, formic acid	2.2	0.4 mL/min	MS-MS	LLOD [mg/L]: 0.2 LLOQ [mg/L]: 0.5	[100]
rat plasma	flavonoids and related constituents	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, water B—ACN	21	0.4 mL/min	PDA-QTOF-MS	N/A	[101]

Table 1. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
rat plasma	procyanidins anthocyanins	HSS T3 (100 × 2.1 mm, 1.8 µm)	gradient: A—acetic acid B—ACN	12.5	0.4 mL/min	MS-MS	LOD [µM]: 0.007–0.70 LOQ [µM]: 0.01–1.38	[102]
rat plasma	Rhizoma Paridis saponins	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, water B—ACN	21	0.4 mL/min	QTOF-MS	N/A	[103]
human serum (renal transplanted patients)	platin	HiTrap Desalting Sephadex G-25 (25 × 16 mm, 17–70 µm)	gradient: A—tris(hydroxymethyl) aminomethane HCl, sodium hydrogencarbonate B—tris(hydroxymethyl)- aminomethane HCl with sodium hydrogencarbonate, sodium chloride	10	1 mL/min	EI-MS	N/A	[104]
human serum and plasma	L-lysine	AccQTag Ultra (100 × 2.1 mm, 1.7 µm)	gradient: A—aqueous buffer (acidified water) B—organic solvent (ACN or methanol)	9.5	0.7 mL/min	fluorescence	N/A	[105]
mouse plasma, liver, and heart tissue	lipids	Halo HILIC (50 × 2.1 mm, 2.7 µm)	gradient: A—isooctane, tetrahydrofuran B—acetone, dichloromethane C—isopropanol, chloroform D—isopropanol, water	10.5	1.2 mL/min	evaporative light-scattering detectors	LOQ [mg/mL]: 0.10	[106]
rat plasma	[E]-2-{4-[(tetrahydropyrrole) methyl] benzylidene}-5, 6-dimethoxy- 2,3-dihydroinden-one	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ammonium formate B—formic acid, ACN	2.5	0.25 mL/min	MS–MS	LOD [ng/mL]: 0.2	[107]
rat plasma	(-)-epicatechin (-)-epicatechin-3-O-gallate (-)-epigallocatechin (-)-epigallocatechin-3-O-gallate	BEH C18 (50 × 2.1 mm, 1.7 µm) VanGurad™ BEH C18 (5 × 2.1 mm, 1.7 µm)	gradient: A—formic acid B—methanol	3.5	0.25 mL/min	MS	LOQ [ng/mL]: 10	[108]
ovine plasma	ketamine (K) medetomidine (M)	Pursuit XRs diphenyl (150 × 2 mm, 3 µm)	gradient: A—water, formic acid B—ACN, formic acid	30	0.2 mL/min.	MS-MS	LOD [ng/mL]: K 1 M 2	[109]
human plasma and mouse liver	glutathione glutathione disulfide ophthalmic acid	BEH C18 (100 × 2.1 mm, 1.7 µm) BEH HILIC (100 × 2.1 mm, 1.7 µm) HSS T3 (C18) (100 × 2.1 mm, 1.8 µm)	gradient: A—formic acid, water B—formic acid, ACN gradient: A—ACN B—ammonium formate, water gradient: A—formic acid, water B—formic acid, ACN	12	0.45 mL/min N/A 0.45 mL/min	MS-MS	N/A	[110]
human plasma	donepezil, galantamine, memantine, rivastigmine and its metabolite	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ammonium acetate B—ACN	4.5	0.4 mL/min	MS-MS	LOD [ng/mL]: 0.2–50	[111]

Table 1. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
human plasma	blonanserin	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—aqueous ammonium acetate B—formic acid, ACN	6	0.5 mL/min	MS-MS	LOD [ng/mL]: 0.25	[112]
rat plasma	indolinone	HSS T3 (100 × 2.1 mm, 1.8 µm)	gradient: A—formic acid, water B—formic acid, ACN	4	0.5 mL/min	MS-MS	LLOQ [ng/mL]: 30.0 ULOQ [ng/mL]: 3000	[113]
human blood	valproic acid	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ACN B—ammonium acetate buffer	7	0.5 mL/min	MS-MS	LOQ [mg/mL]: 0.5	[114]
human plasma	ramipril (RA) ramiprilat (RAM)	BEH C18 (100 × 2.1 mm, 1.7 µm)	ammonium formate buffer, ACN (40:60, *v*/*v*)	3.5	0.3 mL/min	MS-MS	LLOQ [ng/mL]: RA 0.35 RAM 1.0	[115]
human plasma	lisinopril	ODS-3 (50 × 2.1 mm, 3 µm)	methanol–water, formic acid (55:45, *v*/*v*)	2.5	0.20 mL/min	MS-MS	LOQ [ng/mL]: 1.03	[116]
rat plasma	ketorolac	BEH C8 (50 × 2.1 mm, 1.7 µm)	gradient: A—ammonium formate, ACN B—formic acid, ACN	4	0.4 mL/min	MS-MS	LOQ: 5 ng/ml	[117]
human plasma	anthraquinones	BEH C18 (100 × 2.1 mm, 1.7 µm)	methanol, aqueous acetic acid (12:82, *v*/*v*)	?	0.5 mL/min	DAD	N/A	[118]
human plasma	warfarin	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, ACN, water B—formic acid, ACN	4	0.3 mL/min	MS-MS	LOD: 0.25 ng/mL	[119]
human plasma and post-dialysis buffer	sunitinib (S) N-desethyl sunitinib (NS)	RP18 (20 × 2.1 mm, 3.5 µm)	ACN/water (60:40, *v*/*v*) with 0.1% formic acid	5	0.2 mL/min	LC-MS-MS	LLOQ [ng/mL]: S 0.1 NS 0.2	[120]
human plasma	hydroxytyrosol acetate sulphate	Inertsil ODS-3 (150 × 4.6mm, 5 µm)	gradient: A—water, acetic acid B—ACN	27	1.5 mL/min	MS-MS	N/A	[121]
mice plasma	etoposide (E) piperine analogue (PA-1)	BEH C18 (50 × 2.1 mm, 1.7 µm)	methanol, water (72:28, *v*/*v*)	6	250 µL/min	QTOF-MS-MS	LOQ [ng/mL]: E 2.0 PA-1 1.0	[122]
human plasma	eicosapentaenoic acid docosahexaenoic acid arachidonic acid	Pursuit™ C18 (50 × 2.0 mm, 3 µm)	ammonium acetate in formic acid, methanol (15:85, *v*/*v*)	3.5	0.4 mL/min	MS-MS	N/A	[123]
human whole blood	alprazolam, bromazepam, clonazepam, diazepam, flunitrazepam, lorazepam, midazolam, nitrazepam, nordiazepam, oxazepam, phenazepam	BEH C18 (100 × 2.1 mm, 1.7 µm) BEH C18 VanGuard pre-column (5 × 2.1 mm, 1.7 µm)	gradient: A—ACN B—ammo nium acetate	8	0.6 mL/min	MS-MS	LOD [ng/mL]: 0.002–1.0 LLOQ [ng/mL]: 0.2–21.5	[124]
human serum	peptides s	C18 (180 µm × 50 mm, 5 µm) C18 nanocolumn (75 µm × 200 mm, 1.7 µm)	gradient: A—water, 0.1% formic acid B—ACN, 0.1% formic acid	120	300 nL/min	MS-MS	N/A	[125]

Table 1. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
human plasma and urine	cytochrome P450 (CYP) probe drugs (caffeine, paraxanthine, dapsone, flurbiprofen, mephenytoin, debrisoquine, chlorzoxazone) and their relevant metabolites	Gold C18 (50 × 2.1 mm, 1.9 µm)	gradient: A—water B—methanol	8	1 mL/min	MS-MS	LLOQ [ng/mL]: 0.1–20	[126]
rat plasma	isofraxidin and its metabolites	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic B—ACN, formic acid	10	0.4 mL/min	MS	LOD [ng/mL]: 0.25	[127]
rat plasma	bioactive components and their metabolites	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, water B—ACN	20	0.4 mL/min	MS-MS	N/A	[128]
human plasma	profiling of oxylipins	Ascentis Express C18 (50 × 2.1 mm, 2.7 µm)	gradient: A—acetic acid B—ACN, isopropanol	26	0.35 mL/min	MS-MS	LOD [nM]: 0.1–11.4 LOQ [nM]: 0.3–38.2	[129]
human serum	total thyroxine (TT4), total triiodothyronine (TT3)	N/A	N/A	-	N/A	ID-LC-MS	N/A	[130]
rat plasma	active components in herbal medicines	Capcell Pak C18 (100 × 3 mm, 3 µm) Shiseido Capcell Pak C18 guard column (100 × 3 mm, 3 µm)	gradient: A—formic acid B—ACN	108	0.6 mL/min	DAD-TOF-MS	N/A	[131]
rat serum	biomarkers of myocardial infarction	BEH C18 (100 × 2.1 mm, 1.7 µm) BEH HILIC C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid B—ACN, formic acid gradient: A—ammonium formate, formic acid B—ACN, formic acid	35	350 µL/min	MS-MS	N/A	[132]
dog plasma	oxymatrine and matrine	C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—acetic acid, water B—methanol	4.7	0.3 mL/min	MS-MS	LOQ [ng/mL]: 15	[133]
human plasma	lovastatin	BEH C18 (50 × 2.1 mm, 1.7 µm)	ACN, water with ammonium acetate (85:15, *v*/*v*)	1.7	0.35 mL/min	MS-MS	LOQ [ng/mL]: 0.025	[134]
rat plasma	teniposide	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ACN B—water with 0.1% formic acid	3	0.20 mL/min	MS-MS	LOQ [ng/mL]: 10	[135]
murine plasma, liver, kidney	metabolite profiling	HSS T3-C18 (150 × 2.1 mm, 1.8 µm)	gradient: A—formic acid, water B—formic acid, ACN	40	0.4 mL/min	TOF-MS	N/A	[136]
rat plasma	toosendanin	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ACN B—water	8	0.3 mL/min	MS	LLOQ [ng/mL]: 20	[137]
rat plasma	Yin-Chen-Hao-Tang multicomponents	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, water B—formic acid, ACN	20.5	0.4 mL/min	MS	N/A	[138]
rat plasma	clarithromycin	BEH C18 (50 × 2.1 mm, 1.7 µm)	A—ammonium acetate B—ACN	2	0.3 mL/min	MS-MS	LLOQ [ng/mL]: 3	[139]
rat plasma	taxifolin	Sunfire™ (50 × 2.1 mm, 3.5 µm)	gradient: A—ACN, B—water with acetic acid	6.5	0.2 mL/min	MS	LOQ [ng/mL]: 6	[140]

Table 1. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
sea lamprey plasma	5-hydroxytryptamine 5-hydroxyindole-3-acetic acid tryptamine, melatonin	Discovery HS F5 (150 × 4.6 mm, 5 µm)	gradient: A—ammonium acetate, acetic acid B—ACN	12	1.5 mL/min	FLD	LOD [ng/mL]: 0.04–0.13	[141]
		Kinetex PFP 100A (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, water B—ACN, formic acid	9	150 µL/min	MS-MS	LOD [ng/mL]: 0.003–0.02	
human dried blood spots	sitamaquine terfenadine prazosin	HSS-T3 (50 × 2.1 mm, 1.7 µm)	gradient: A—ammonium acetate, acetic acid B—ACN	1.25	1.0 mL/min	MS-MS	N/A	[142]
rat plasma	paeoniflori (P) naringin (N) naringenin (NG) glycyrrhetinic acid (GA)	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—methanol B—water, ammonium acetate	4.5	0.25 mL/min	MS-MS	LOD [ng/mL]: P 9.8 N 5.1 NG 5.2 GA 10.6	[143]
rat plasma	metabolic profiling of obesity-associated metabolic alterations	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, water B—formic acid, ACN	10	0.6 mL/min	MS	N/A	[144]
human plasma	antigenic diphenylmethane diisocyanate-albumin reaction products	Vydac C-18 RP (250 × 1,0 mm, 5 µm)	gradient: A—trifluoroacetic acid B—trifluoroacetic acid, ACN	105	N/A	MS-MS	N/A	[145]
human plasma	neuropeptide Y (NPY), peptide YY (PYY), pancreatic polypeptide (PP)	Gracesmart RP C18 (150 × 2.1 mm, 5 µm)	gradient: A—formic acid B—ACN, formic acid	15	250 µL/min	MS	LOQ [µM]: NPY 0.25 PYY 0.1 PP 0.1	[146]
rat plasma	gestodene (G) ethinyl estradiol (ES)	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—water with formic acid B—ACN with formic acid	4	0.35 mL/min	MS-MS	LOQ [ng/mL]: G 1.59 ES 0.196	[147]
rat serum	1-^{13}C-L-methionine	TSK-GEL AMIDE-80 (50 × 2.0 mm, 3 µm)	gradient: A—ACN B—ammonium acetate, formic acid	4	0.2 mL/min	MS-MS	LOD [ng/mL]: 4 LLOQ [ng/mL]: 10	[148]
rat serum	senecionine adonifoline and their metabolites	BEH C18 50 mm × 2.1 mm, 1.7 µm	gradient: A—ACN B—formic acid	5.5	0.3 mL/min	ESI-MS	LLOQ [µg/mL]: 0.006–0.012	[149]
rat blood and kidney tissue	flavonoids	HSS T3 (100 × 2.1 mm, 1.8 µm)	gradient: A—ACN B—water, formic acid	15	0.4 mL/min	QTOF-MS	N/A	[150]
human plasma	lopinavir (LPV) ritonavir (RTV)	BEH C18 (50 × 2.1 mm, 1.7 µm)	ammonium formate, methanol (10:90, *v*/*v*).	1.2	0.3 mL/min	MS-MS	LOQ [ng/mL]: LPV 30.4 RTV 3.1	[151]
human plasma	methoxsalen	BEH C18 (50 × 2.1 mm, 1.7 µm)	ammonium formate, ACN (60:40, *v*/*v*)	1.5	0.5 mL/min	MS-MS	LLOQ [ng/mL]: 1.1	[152]
human plasma	pramipexole	BEH C18 (100 × 2.1 mm, 1.7 µm)	ammonium formate, ACN (15:85, *v*/*v*)	1.5	0.5 mL/min	MS-MS	LLOQ [ng/mL]: 20.5	[153]

Table 1. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
rat plasma, urine, bladder, submaxillary gland, heart and cerebral cortex tissue	nicotine, cotinine	N/A	A—ammonium acetate B—acetonitrile	-	0.25 mL/min	MS	N/A	[154]
rat plasma	chiisanogenin	BEH C18 (50 × 2.1 mm, 1.7 µm)	ACN, ammonium acetate (90:10, *v*/*v*)	1.1	0.2 mL/min	MS-MS	LLOQ: 5 ng/mL	[155]
rat plasma, intestinal perfusate, bile, microsomes, cell incubation media	matrine	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid B—ACN	3.4	0.45 mL/min	MS-MS	LLOQ: 0.305 ng/mL	[156]
murine blood	genistein (G) genistein-7-O-glucuronide (G-7-G) genistein-4-O-glucuronide (G-4-G) genistein-4-O-sulfate (G-4-S) genistein-7-O-sulfate (G-7-S)	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ammonium acetate B—ACN	4.5	0.45 mL/min	MS-MS	LLOQ [nM]: G 4.88 G-7-G 6.25 G-4-G 5 G-4-S 0.98 G-7-S 0.78	[157]
dog plasma	(Z)-5-(4-methoxybenzylidene) thiazolidine-2,4-dione	BEH C18 (50 × 2.1 mm, 1.7 µm)	methanol, water (80/20, *v*/*v*)	2	0.2 mL/min	MS-MS	LLOQ [ng/mL]: 5	[158]
human plasma	anastrozole	BEH C18 (50 × 2.1 mm, 1.7 µm)	methanol, ammonium acetate (75:25, *v*/*v*)	1.5	0.30 mL/min	MS-MS	LOQ [ng/mL]: 0.055	[159]
rat plasma	(E)-2-{2-[2-(2-[18F] luoroethoxy) ethoxy] ethoxy}-5-(4-methylaminostyryl) pyridine	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ammonium acetate, water B—ACN	2.5	0.4 mL/min	MS-MS	µLLOQ [ng/mL]: 2	[160]
human plasma	paclitaxel	BEH C18 (50 × 2.1 mm, 1.7 µm)	methanol, aqueous formic acid (75:25, *v*/*v*)	2	0.4 mL/min	MS-MS	LOD [ng/mL]: 2 LLOQ [ng/mL]: 5	[161]
rat plasma	bufalin cinobufagin resibufogenin	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ACN B—water with 0.1% formic acid	3	0.20 mL/min	MS-MS	LLOQ [ng/mL]:1	[162]
dog plasma	febuxostat	BEH C18 (50 × 2.1 mm, 1.7 µm)	ACN/water with formic acid (60:40, *v*/*v*)	2	0.2 mL/min	MS-MS	LOQ [ng/mL]: 5	[163]
human plasma	paclitaxel derivative	BEH C18 (50 × 2.1 mm, 1.7 µm)	methanol/formic acid (75:25, *v*/*v*)	3	0.4 mL/min	MS-MS	LOD [ng/mL]: 2	[164]
human plasma	D-[$^{13}C_6$]glucose	LC-18 (33 × 4.6 mm, 3 µm) BEH C18 (50 × 2.1 mm, 1.7 µm)	ammonium acetate in methanol/water (80:20, *v*/*v*)	4	N/A	MS	N/A	[165]
human plasma	epothilone D analog: AV-EPO-106	BEH C18 (50 × 2.1 mm, 1.7 µm)	water/methanol (10:90, *v*/*v*)	5	0.8 mL/min	MS-MS	LLOQ [ng/mL]: 100	[166]

Table 1. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
human serum	metabolic profiling of diabetic biomarkers	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, B—ACN, formic acid	15	0.4 mL/min	oa (acceleration time-of-flight) TOF-MS	N/A	[167]
rat plasma, tissues, bile	ergosta-4,6,8(14),22-tetraen-3-one (ergone)	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, water B—methanol	1.5	0.5 mL/min	ESCi-QTOF-MS	LLOQ: 5 ng/mL	[168]
rat plasma	3′-hydroxypuerarin (H) 6′′-O-xylosylpuerarin (X) mirificin (M) puerarin (P) 3′-methoxypuerarin (ME) daidzin (D)	Syncronis C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—acetic acid, water B—ACN	8	0.25 mL/min	MS-MS	LOQ [µg/mL]: H 0.0200 X 0.0101 M 0.0100 P 0.0100 ME 0.0098 D 0.0090	[169]
dog plasma	cefuroxime lysine	BEH C18 (50 × 2.1 mm, 1.7 µm)	ACN, formic acid in ammonium acetate (40:60, *v*/*v*)	1.5	0.2 mL/min	MS-MS	LLOQ [µg/mL]: 0.01	[170]
rat serum	ergosta-4,6,8(14),22-tetraen-3-one	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—water, formic acid B—ACN, formic acid	10	0.45 mL/min	QTOF-MS	N/A	[171]
rat plasma	ginsenosides	Hypersil Gold C18 (100 × 2.1 mm, 5 µm)	gradient: A—water, formic acid B—ACN	20	0.25 mL/min	MS	LLOQ [ng/mL]: 2.70–5.36	[172]
rat plasma	buspirone 1-(2-pyrimidinyl) piperazine 6′-hydroxybuspirone	HSS T3 (100 × 2.1 mm, 1.8 µm)	gradient: A—ACN, water, formic acid B—water, ACN, formic acid	6.5	0.2 mL/min	MS-MS	N/A	[173]
rat plasma	leonurine	Zorbax SB-C18 (150 × 2.1 mm, 5 µm)	ACN, ammonium acetate buffer (25:75, *v*/*v*)	55	0.2 mL/min	MS-MS	LLOQ [ng/mL]: 4	[174]
human plasma	2-arachidonoyl glycerol 1-arachidonoyl glycerol anandamide	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—water, ammonium acetate B—methanol, ammonium acetate	6.5	0.5 mL/min	MS-MS	LOQ [nM]: 0.5	[175]
human plasma	bupropion (BUP), hydroxybupropion (HBUP)	Zorbax Eclipse XDB C18 (150 × 4.6 mm, 5 µm)	ammonium acetate/ methanol (10:90, *v*/*v*)	2.8	1.0 mL/min	MS-MS	LLOQ [ng/mL]: BUP 0.10 HBUP 010	[176]
human plasma	nifedipine	BEH C18 (50 × 2.1 mm, 1.7 µm)	ammonium acetate/ACN (15:85, *v*/*v*)	1.2	0.25 mL/min	MS-MS	LLOQ [ng/mL]: 0.05	[177]
human plasma	anandamide (AEA) oleoylethanolamide (OEA) palmitoylethanolamide (PEA)	BEH (50 × 2.1 mm, 1.7 µm)	gradient: A—ammonium formate, water B—ACN	4	700 µL/min	MS	LOQ [pg/mL]: AEA 50 OEA, PEA 100	[178]
rat plasma	thymoquinone	HSS-T3 C18 (100 × 2.1 mm, 1.8 µm)	gradient: A—water B—ACN	6	0.5 mL/min	PDA	LOD [µg/mL]: 0.001 LOQ [µg/mL]: 0.0033	[179]
rat serum	7-hydroxy- artemisinin carbamate	BEH (50 × 2.1 mm, 1.7 µm)	ACN/formic acid (60:40, *v*/*v*)	3	0.3 mL/min	MS-MS	LLOQ [ng/mL]: 1 LOD [ng/mL]: 0.2	[180]
human serum	methylmalonic acid	BEH C18 (50 × 1.0 mm, 1.7 µm)	methanol/ammonium formate (53:47, *v*/*v*)	4	N/A	MS-MS	N/A	[181]

Table 1. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
murine plasma	NiK-12192 (anticancer agent)	BEH C18 (50 × 2.1 mm, 1.7 µm) Luna C18 (50 × 2.1 mm, 5 µm) XBridge C18 (50 × 2.1 mm, 3.5 µm)	gradient: A—water, ACN, formic acid B—water, ACN, formic acid	1.5 (BEH)3.5 (Luna/XBridge)	0.5 mL/min	MS-MS	LOQ [ng/mL]: 0.1–1	[182]
human plasma	finasteride	BEH C18 (50 × 2.1 mm, 1.7 µm)	ammonium formate buffer with formic acid. acetonitrile (58:42, *v*/*v*)	3.5	0.2 mL/min	MS-MS	LOQ [ng/mL]: 0.1	[183]
human plasma	meldonium	BEH HILIC (50 × 2.1 mm, 1.7 µm)	water, ACN, formic acid (25:70:5, *v*/*v*/*v*)	1.4	0.3 mL/min	MS-MS	LLOQ [ng/mL]: 10	[184]
rat plasma	givinostat	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid and water B—ACN	3	0.3 mL/min	MS-MS	LLOQ [ng/mL]: 2 LOQ [ng/mL]: 5	[185]
human whole blood	colchicine	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—water with 0.01% formic acid B—ACN with 0.01% formic acid	3	0.4 mL/min	MS-MS	LLOQ [ng/mL]: 0.5	[186]
human plasma	paraquat (P) diquat (D)	CORTECS HILIC (100 × 2.1 mm, 1.6 µm)	gradient: A—ammonium acetate, formic acid B—ACN	3.5	0.45 mL/min	MS-MS	LOD [ng/mL]: P 0.5 D 0.5 LLOQ [ng/mL]: P 1.00 D 1.00	[187]
rat plasma	trans-ferulic acid-4-β-glucoside	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid in water B—methanol	3	0.5 mL/min	MS-MS	LLOQ [µg/g]: 0.1	[188]
mouse plasma	3-(2-(azepan-1-yl)ethyl)-6-benzylbenzo[d]thiazol-2-(3H)-one hydrochloride	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid in water B—ACN	3.2	0.3 mL/min	MS-MS	LLOQ [ng/mL]: 2	[189]

2.2. Urine

UPLC analysis of biological samples, such as urine, is widely used to analyze a wide range of compounds, including drug metabolites, hormones, toxic substances, and disease biomarkers [190]. Alwis et al. used the UPLC method to quantify 28 metabolites of volatile organic compounds [191]. Determination of exogenously administered steroids that also occur naturally in animals, such as testosterone, is particularly challenging. The UPLC technique combined with mass spectrometry has found application in profiling phase II metabolites. These compounds, thanks to their low volatility and high polarity, can be determined by this method in urine samples [192]. For advanced analysis of biological samples, such as urine, UPLC coupled with MS offers the highest sensitivity and specificity, as well as extensive identification capabilities. It is suitable for metabolic profiling, determination of low drug concentrations, toxicology and identification of unknown substances. However, the cost of the equipment and software required for this technique is very high [1]. A cheaper alternative is UPLC coupled with UV detection. This method enables the determination of known, pre-defined substances (e.g., the measurement of creatinine levels, specific amino acids or metabolites) that are capable of absorbing UV radiation. However, when it comes to determining the concentration of compounds that do not absorb UV light, this method is inadequate. Even in the case of a heavily contaminated sample, the method may produce overestimated results and make interpretation difficult [4]. Urine has one of the most complex matrices among biological materials. It contains sodium, potassium, calcium and ammonium ions, as well as chlorides, organic molecules, mineral salts and proteins, including albumin. These compounds can interfere with the detection of the target analyte by MS, mainly through ion suppression. This can cause distorted results, reduced method sensitivity and an increase in the LOQ value [193]. The presence of early-eluting urine components (e.g., high levels of salt) may distort the chromatograms, causing peaks to overlap. Moreover, high concentrations of salts and insoluble components in urine can lead to rapid fouling of the MS capillaries and then contribute to the degradation of the chromatographic column [194]. In order to minimize the impact of urine constituents on the analysis, it is essential to prepare the sample properly. The sample preparation process involves diluting the urine with water or a buffer in the appropriate proportion, which reduces the concentration of interfering salts [195]. SPE ensures a high degree of sample purification, allowing polar components of the urine to be removed and only the target analytes to be retained on the sorbent bed [196]. Moreover, the use of stable isotope-labeled internal standards of the analyzed compound is one of the most effective methods of matrix effect compensation. The standard behaves the same way as the analyte and exhibits the same suppression [197]. The advantages of the UPLC method were utilized for the simultaneous determination of bisphenol A and its metabolites in urine samples. These substances are classified as endocrine disrupting compounds, and the use of bisphenol A in plastics production raises concerns about its migration into food [198]. A small amount of horse urine was used to analyze samples for the presence of quaternary ammonium compounds, which may be abused prior to equestrian competition [199]. Zhao et al. used UPLC to analyze nucleosides and other cis-diol metabolites, which are potential cancer biomarkers. The goal of the study was to distinguish cancer patients from healthy individuals and compare the results with those obtained by HPLC. The UPLC method proved to be approximately three times faster and more efficient, with improved resolution and sensitivity (HPLC detected 79 files, compared to UPLC 94) [200]. UPLC analysis of urine samples identified as many as 355 acetylcarnitines, a significant achievement compared to the previously reported 43 acetylcarnitines, which may be important biomarkers of various diseases. Urine samples were prepared by SPE, then sequentially decanted and purified by solid-phase extraction. Gradient elution was used with two mobile phases: eluent A: 0.1% formic acid in water, 4%

ACN in water, and eluent B: 0.1% formic acid in ACN [201]. Johnson and Plumb compared the performance of two LC-MS methods: monolithic columns and UPLC columns with sub-2 µm particles for the identification and detection of acetaminophen metabolites in urine. The results showed that the UPLC system had three times higher sensitivity and detected a greater number of metabolites [202]. UPLC-Q-TOF-MS has been used to profile endogenous metabolites in urine to elucidate metabolic differences between normal-weight and obese individuals with hyperlipidemia. Urine samples were centrifuged at 14,000 rpm for 10 min. In total, 2 µL of the supernatant was used for analysis. Analytes were eluted from the column with a gradient where A was water and B was ACN, with the initial composition of B being 2% and increasing to 20% after 5 min, 35% after 2 min, 70% after 2 min, and 100% after another 1.5 min, and then re-equilibrated to the initial conditions after 10 min. Each cycle lasted 20.5 min, and the flow rate was 300 µL/min [202]. The UPLC-ESI-MS method was also used to evaluate the effect of repeated nicotine treatment on nicotinic and muscarinic receptors located in the urinary bladder by determining the nicotine concentration in the urine of rats [203]. Sugar is a significant energy component of the diet, but when consumed in excess, it can lead to metabolic disorders and obesity. Currently, the food industry is striving to reduce sugar content in products or replace it with so-called sweeteners, but an effective method for measuring exposure to these substances is needed. Therefore, Diepeveen-de Bruin et al. validated and applied a UPLC-MS-MS method to quantify sugars and other sweeteners in human urine [204]. The study of plant substances in urine using UPLC has a wide range of applications, including the evaluation of the effects of dietary supplements, herbs, or herbal medicines on the body. In addition, it can be used to assess the bioavailability and metabolism of substances of plant origin, and to study interactions between various plant components and other substances in the body. The research team of Wang et al. using UPLC quantified 17 ginseng-derived glycoside saponins, ginsenosides, in rat urine. Collected samples were centrifuged for 10 min at 3500 rpm, and sequentially stored at −20 °C until analysis [205]. The use of UPLC-MS-MS has also proven to be a sensitive, accurate and precise method for the quantification of hesperitin and its enantiomers in urine samples [206]. UPLC was also used for metabolic profiling of urine samples to detect potential biomarkers of chronic renal failure. Urine samples from rats were stored at −80 °C and then thawed, centrifuged, the supernatant diluted with distilled water, and then filtered through a 0.22 µm membrane filter. Radiant elution was performed using a mobile phase composed of: A was 0.1% formic acid, and B was ACN with 0.1% formic acid and 10 mmol/L ammonium acetate) [207]. Alwis et al. performed the analysis of human urine by ESI-MS-MS technique of a mixture of acrolein, acrylamide, acrylonitrile, benzene, 1-bromopropane, 1,3-butadiene, carbondisulfide, crotonaldehyde, cyanide, N,N-dimethylformamide, ethylbenzene, ethylene oxide, propylene oxide, styrene, tetrachloroethylene, toluene, trichloroethylene, vinyl chloride, xylene using the HSST3 column (150 × 2.1 mm, 1.8 µm) and a gradient mobile phase: A—ammonium acetate, B—ACN), obtaining LOD values in the range of 0.5–20 ng/mL [191]. Data on the analysis of urine samples are summarized in Table 2.

UPLC also allows for the determination of substances in both plasma and urine. This is particularly helpful in identifying patterns in the metabolic pathways of various compounds. Colchicine, an alkaloid extracted from the seeds and bulbs of the colchicum plant, has potent anti-inflammatory properties, but its dosing regimen is unclear, as there are no clear boundaries between therapeutic, toxic, and lethal doses. UPLC-MS-MS has proven to be a suitable, rapid, and economical method for the determination of colchicine in human urine and whole blood [186]. Mao et al. used UPLC-MS-MS to determine paraquat and diquat (quaternary ammonium herbicides with high toxicity) in urine and plasma of patients hospitalized for poisoning, obtaining rapid and reliable results [187].

UPLC-MS-MS analysis of morphine-3-O-sulfate (M3S) and morphine-6-O-sulfate (M6S) in human blood and urine was performed using HSS T3 (100 × 2.1 mm, 1.8 µm) and HSS T3 (5 × 2.1 mm, 1.8 µm) columns with M-d3 Morphine-d3 as the Internal Standard. The mobile phase was a mixture of: A—formic acid, B—methanol (gradient). The obtained LOD values [ng/mL] were: in urine M3S 6, M6S 4, and in blood M3S 0.6 and M6S 0.3, respectively [208]. Udenafil and its active metabolite DA-8164 were determined in human urine and blood by UPLC-MS-MS on a BEH C18 column (50 × 2.1 mm, 1.7 µm) using an isocratic elution mixture (ACN/formic acid (75:25, *v*/*v*) with a detection limit of 1 ng/mL [207]. Taspoglutide was determined by UPLC-MS-MS in human urine and plasma using BEH C18 (50 × 2.1 mm, 1.7 µm) and HILIC Si (50 × 2.1 mm, 3 µm) columns, in a gradient mobile phase: A1: water–methanol–aqueous ammonium formate–formic acid (50:50:12.5:5, *v*/*v*/*v*/*v*); B1: water–acetonitrile–methanol–ammonium formate–formic acid (50:700:250:12.5:5, *v*/*v*/*v*/*v*/*v*); A2: water–ammonium bicarbonate with ammonium hydroxide (985:15, *v*/*v*); A3: water–acetonitrile–ammonium bicarbonate (735:250:15, *v*/*v*/*v*); B3: water–acetonitrile–methanol (10:45:45, *v*/*v*/*v*) obtaining a limit of quantification of 4 pg/mL for plasma and 10 pg/mL for urine [209,210]. N^G,N^G-dimethyl-l-arginine (ADMA), symmetric dimethylarginine (SDMA), N^G-monomethyl-l-arginine (NMMA), L-homo-arginine (H-Arg), citrulline (Cit) and citrulline butyl esters were analyzed by UPLC-MS-MS in human plasma, serum or urine. A BEH C18 column (50 × 2.1 mm, 1.7 µm) and a mobile phase composed of: A—water with 0,1% formic acid, B—methanol with 0,1% formic acid (gradient) were used, obtaining LOD values of 0.01 µM and LOQ: 0.05—0.5 µM [211]. Human whole blood and urine samples were analyzed for gamma-hydroxybutyrate, beta-hydroxybutyrate, pregabalin, 1,4-butanediol, and gamma-butyrolactone using UPLC-MS-MS. The mobile phase was an HSS T3 column (100 × 2.1 mm, 1.7 µm), and the mobile phase was a mixture of A—0,2% formic acid and B—methanol (gradient elution). LOD values were set at 0.65, 0.004, 0.23, and 1.1 µg/mL, while LOQ values were set at 1.3, 0.008, 0.37, and 2.15 µg/mL [212]. Chemical profile of *Epimedium brevicornum* Maxim. (epimedoside A, epimedin A, eEpimedin B, epimedin C, icariin, 2′′-O-rhamnosoyl icaride, icariside II, icaritin, icaritin-3-O-α-L-rhamnopyranosyl-7-O-β-D-glucopyranuronoside) analyzed by UPLC-MS system in rat urine and blood samples. A BEH C18 column (50 × 2.1 mm, 1.7 µm) and an eluent of the following composition were used: A: 0.1% formic acid in water and B: 0.1% formic acid in acetonitrile with a flow rate of 0.25 mL/min [213]. Lévèques et al. determined hesperetin and its enantiomers in human plasma and urine samples using a UPLC-MS-MS system. The mobile phase used was a mixture of: A—water with 0.1% formic acid, B—ACN with formic acid (gradient elution) and columns: UPLC HSS T3 (100 × 2.1 mm, 1.8 µm) and Chiralpak IA-3 (150 × 2 mm, 3 µm) [206]. *Glechoma longituba* metabolites were analyzed in rat plasma and urine by UPLC-QTOF-MS system with BEH C18 (100 × 2.1 mm, 1.7 µm) column and gradient elution (A—water, formic acid, B—ACN) [214]. Onoue et al. analyzed quantity of nicotine, cotinine and antipyrine in human plasma, urine and tissues (bladder, salivary gland, heart and cortex) by UPLC-ESI-MS system with BEH C 18 (50 × 2.1 mm, 1.7 µm) and A—ACN, B—ammonium acetate (gradient elution), obtaining LOD and LOQ values of 5 and 2.5 ng/mL [203]. Rat urine, bile, feces, and plasma were analyzed for the content of mosapride, mosapride N-oxide, and morpholine ring-opened mosapride using an BEH C18 column (100 × 2.1 mm, 1.7 µm), gradient elution (A–formic acid, B—ACN), and MS-MS detection. The obtained LOD values were in the range of 10—25 ng/mL [45]. Phosphorus and sulfur metabolites were analyzed by UPLC-MS system in rat liver, plasma, urine, bile. BEH C18 (100 × 2.1 mm, 1.7 µm) stationary phase, and eluent containing: A—water with formic acid, B—methanol with formic acid (for the organic/aqueous tissue extracts and plasma extracts), A1—ammonium acetate with formic acid, B1—methanol with formic acid (for bile and urine) (gradient) were used. The determined LOQ values

were within the range 0.15–0.25 ng [215]. Human urine and whole blood are the materials in which the content of narcotic analgesics (buprenorphine, O-desmethyltramadol, fentanyl, norbuprenorphine, norfentanyl, pethidine, piritramide, tilidine, tramadol) was determined. An C18 column (50 × 2.1 mm, 1.7 µm) and an eluent gradient with the following composition: A: water with ammonium bicarbonate and ammonium hydroxide B: methanol and an MS-MS detector were used. The LOQ values for the determined compounds were in the range 0.025—1.25 ng/mL [216]. Waterval et al. determined underivatized amino acids in human plasma and urine by UPLC-MS-MS system. An BEH C18 column (100 × 2.1 mm, 1.7 µm) and a mobile phase gradient, A—tridecafluoroheptanoic acid, B—trifluoroacetic acid/ACN, with a flow rate of 650 µL/min were used, obtaining LOQ values in the range 40–287 µmol/L [217].

Table 2. UPLC technique in the analysis of various substances in urine.

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
human urine	Se-methylseleno-N-acetylgalactosamine, Semethylseleno-N-acetylglucosamine, Se-methylselenogalactosamine, trimethylselenonium iodide trimethylselenonium ion	BEH C18 (50 × 1.0 mm, 1.7 µm) or (100 × 1.0 mm)	gradient: A—ammonium acetate B—methanol	2.5	50–200 mL/min	ICP-MS	LOD [µg Se/L]: 0.4	[218]
human urine	theophylline, hippuric acid, caffeine, nortriptyline, citrate, succinate	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—water with formic acid B—ACN/water (80:20, *v*/*v*) with formic acid	40	400 µL/min	TOF-MS	N/A	[43]
human urine	16-hydroxy-stanozolol 3-hydroxy-stanozolol 4-hydroxy-stanozolol tetrahydrogestrinone methandienone epimethandienone 6-hydroxy-methandienone 2-hydroxymethyl-17-methyl-androsta-1,4-diene-11,17-diol-3-one 5-androst-1-ene-17-ol-3-one boldenone 17-methyltestosterone	RX-C8 (150 × 2.1 mm, 5 µm)	gradient: A—ammonium acetate, acetic acid B—methanolic ammonium acetate, acetic acid	19	300 µL/min	QTOF-MS	N/A	[219]
human urine	28 urinary volatile organic compounds metabolites	AHSS T3 (150 × 2.1 mm, 1.8 µm)	gradient: A—ammonium acetate B—ACN	9	250–300 µL/min	MS-MS	LOD [ng/mL]: 0.5–20	[191]
human urine	colchicine	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—water with 0.01% formic acid B—ACN with 0.01% formic acid	3	0.4 mL/min	MS-MS	LLOQ [ng/mL]: 2	[186]
human urine	paraquat (P) diquat (D)	CORTECS HILIC (100 × 2.1 mm, 1.6 µm)	gradient: A—ammonium acetate, formic acid B—ACN	3.5	0.45 mL/min	MS-MS	LOD [ng/mL]: P 0.5 D 0.5 LLOQ [ng/mL]: P 1.00 D 1.00	[187]

Table 2. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
human urine and faecal	porphyrins: uroporphyrin uroporphyrin heptacarboxylic acid porphyrin heptacarboxylic acid porphyrin hexacarboxylic acid porphyrin pentacarboxylic acid porphyrin coproporphyrin coproporphyrin mesoporphyrin	C18 (50 × 4.6 mm, 2.7 µm) Gold C18 (50 × 2.1 mm, 1.9 µm) BDS C18 (100 × 2.1 mm, 2.4 µm)	gradient: A—ACN, ammonium acetate, acetic acid buffer B—ACN/methanol	14	1.8 mL/min	fluorescence	N/A	[190]
bovine urine	28 compounds: androsteron, androstane, testosterone, DHEA, glucuronide, estradiol, and its derivatives	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid in water B—formic acid in ACN	16.5	600 µL/min	MS-MS	N/A	[192]
human urine	bisphenol A (BPA) nonylphenol (NP) octylphenol (OP)	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—methanol B—water	9	0.3 mL/min	MS	LOD [ng/mL]: BPA 0.10 NP 0.10 OP 0.15	[198]
equine urine	38 quaternary ammonium drugs	4u Fusion-RP 80 Å (15 cm × 2.0 mm, 4 µm)	gradient: A—ammonium formate, deionized water B—ACN	16	200 µL/min	MS-MS	LOD [ng/mL]: 0.05–1	[199]
human urine	nucleosides and other metabolites with cis-diol structure	BEH C18 (100 × 2.1 mm, 1.7 µm) Symmetry C18 (150 × 2.1 mm, 3.5 µm)	gradient: A—water, formic acid B—ACN	13	0.25 mL/min	MS	N/A	[200]
human urine	metabolic profiling of acylcarnitines	BEH C18 (150 × 1.0 mm, 1.7 µm)	gradient: A—ACN, water, formic acid B—ACN, formic acid	146	50 µL/min	MS-MS	N/A	[201]
human urine	metabolites of acetaminophen	ChromSpeed (50 × 4.6 mm) BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid B—ACN, formic acid	10	500 µL/min	MS	N/A	[202]
human urine	acesulfame, cyclamate, glucose, fructose, sucrose, sucralose, saccharine, steviol acyl glucuronide	Shodex Asahipak NH2P-40 2D (150 × 2.0 mm, 4 µm)	gradient: A—ammonium acetate, 0.1% ammonia B—ACN	20	0.25 mL/min	MS-MS	LOD [ng/mL]: 0.07–23 LLOQ [ng/mL]: 0.2–76	[204]
rat urine	ginsenosides	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—water B—ACN	14	0.35 mL/min	MS	LOD [ng/mL]: 2–18 LOQ [ng/mL]: 8–55	[205]

Table 2. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
human urine	3-hydroxybenzo[a]pyrene 1-hydroxypyrene	LC-18 (50 × 4 mm, 5 µm) PAH-C18 (250 × 3 mm, 5 µm)	gradient: A—water B—methanol	45	0.8 mL/min	MS-MS	LOQ [pmol/L]: 0.20 LOD [pmol/L]: 0.07	[209]
rat urine	indomethacin	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, water B—formic acid, ACN	10	0.5 mL/min	MS	N/A	[219]
human urine	metabolomic analysis	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, water B—ACN, formic acid	-	N/A	MS	N/A	[220]
human urine	hyperlipemia metabolic profiling	HSS-T3C18 (50 × 4.6 mm, 1.8 µm)	gradient: A—water B—ACN	20.5	300 µL/min	QTOF-MS	N/A	[221]
rat urine	[14C]-propranolol	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid in water B—formic acid in ACN	60	600 µL/min	TOF-MS	N/A	[222]
human urine	amphetamine 13C6-ampetamine 2H3-amphetamine 2H11-amphetamine methamphetamine 13C6-methamphetamine 2H5-methamphetamine 2H11-methamphetamine	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ammonium formate buffer B—methanol	13.4	0.4 mL/min	MS-MS	LOD and LOQ [µM]: 0.10	[223]
human urine	morphine, codeine 6-monoacetylmorphine (6-MAM), pholcodine oxycodone, ethylmorphine cocaine, benzoylecgonine	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ammonium bicarbonate buffer B—methanol	5.7	0.4 mL/min	MS-MS	LOD [µg/mL]: 0.001–0.02 LOQ [µg/mL]: 0.003–0.06	[224]
human urine	β-blockers isoflavones flavonoids	Hypersil GOLD (50 × 2.1 mm, 1.9 µm)	gradient: A—0.05% trifluoroacetic acid in water B—ACN	4.5	0.3–0.8 mL/min	UV	LOD [ng/mL] 10.3–66.2 LOQ [ng/mL] 26.7–198.5	[225]
human urine	quinine (3S)-3-hydroxyquinine	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ammonium bicarbonate, ammonium hydroxide B—methanol	2.5	0.6 mL/min	MS-MS	LLOQ [ng/mL]: 1	[226]

Table 2. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
human urine and amniotic fluid	leucine, isoleucine, carnitine, glutamine, estriol-3-glucuronide/estriol-16-glucuronide estriol-3-sulfate-16glucuronide, valine, lysine, hexose, glutamate, methionine, phenylalanine, hippurate	BEH HSS (100 × 2.1 mm, 1.8 µm)	gradient: A—water, formic acid B—ACN, formic acid	12	0.5 mL/min	TOF-MS	N/A	[227]
		BEH HILIC (100 × 2.1 mm, 1.7 µm)	gradient: A—ammonium acetate, ACN with formic acid (95:5, *v*/*v*) B—ammonium acetate, ACN with formic acid (50:50, *v*/*v*)	15	0.4 mL/min			
rat urine	polar and non-polar urinary metabolites	BEH C18 (150 × 2.1 mm, 1.7 µm) BEH HILIC (150 × 2.1 mm, 1.7 µm)	gradient: A—formic acid in water B—formic acid in ACN gradient: A—ACN, ammonium acetate B—ACN, ammonium acetate	15 16.4	0.3 mL/min 0.4 mL/min	MS	N/A	[228]
human urine	111 psychotropic drugs	SB-C8, (50 × 2.1 mm, 1.8 µm)	gradient: A—ammonium acetate, acetic acid, water B—ammonium acetate, acetic acid, methanol	10	300 µL/min	HRMS	LOD [ng/mL]: 5–500	[229]
murine urine	trimethylamine-n-oxide creatine, carnitine phenylalanine	C18 (100 × 2.1 mm, 1.7 µm)	N/A	39	N/A	MS	N/A	[230]
rat urine and feces	acarviostatin II03 acarviostatin III03	BEH C18 (50 × 2.1 mm, 1.7 µm)	ACN, aqueous ammonia (3:97, *v*/*v*)	20	0.2 mL/min	MS-MS	N/A	[231]
postmenopausal female urine	endogenous estrogens and their metabolites	Extend-C18 RP (100 × 2.1 mm, 1.8 µm)	gradient: A—formic acid in water B—ACN	16	300 µL/min	MS-MS	LOQ [pg/mL]: 2	[232]
nonsmokers human urine	D/L-phenylmercapturic acid D/L-benzylmercapturic acid	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—acetic acid in water B—methanol	7	0.30 mL/min	QTOF-MS	N/A	[233]
human urine	oxytetracycline tetracycline chlortetracycline	BEH C18 (5 × 2.1 mm, 1.7 µm) BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid in water B—formic acid in ACN	6.5	0.4 mL/min	QTOF	LOD [ng/mL]: 0.089–0.138 LOQ [ng/mL]: 0.294–0.455	[234]

Table 2. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
human urine	testosterone glucuronide (TG) epitestosterone glucuronide (ETG)	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—ammonium acetate, water, formic acid B—ammonium acetate, methanol, formic acid	5	0.125 mL/min	MS-MS	LOD [ng/mL]: TG 9.9 ETG 98	[235]
human urine	potential urinary biomarkers	BEH RP18 (150 × 2.1 mm, 1.7 µm) Luna NH_2 (150 × 3 mm, 3 µm)	gradient: A—ACN B—ammonium acetate, acetic acid	8 30	0.5 mL/min	MS	N/A	[236]
rat urine	urinary metabolits of pravastatin	BEH C18 (50 × 2.1 or 1 mm, 1.7 µm)	gradient: A—water, formic acid B—ACN, formic acid	30/32	136 µL/min/500 µL/min	oa-TOF-MS ^{1}H NMR	N/A	[237]
human urine	cotinine (C) nicotine (N)	BEH Phenyl (50 × 2.1 mm, 1.7 µm) BEH Phenyl pre-column (5 × 2.1 mm, 1.7 µm)	gradient: A—water with formic acid and ammonium acetate B—methanol with formic acid and ammonium acetate	1.5	0.5 mL/min	MS-MS	LOD [g/L]: C 0.4 N 0.7 LOQ [g/L]: C 1.1 N 1.7	[238]
human urine	S-phenylmercapturic acid	C18 (50 × 2.1 mm, 1.7 and 2.6 µm)	gradient: A—methanol B—acetic acid	31	0.2 mL/min	PDA	LOD [µg/L]: 1 LOQ]: 2 µg/L	[239]
rat urine	estrone 2-methoxy-estradiol5 androstanedione cortisone	Cadenza HS-C18 2.0 mm × 100 mm × 3.0 mm	gradient: A—formic acid, ACN (95:5, *v*/*v*) B—formic acid, ACN (5:95, *v*/*v*)	14	0.4 mL/min	TOF-MS	LOD [µmol/L]: 80–100 LOD [nmol/L]: 0.2–50	[240]
human urine	psychotropic drugs (28) profiling	HSS T3 (100 × 2.1 mm, 1.8 µm)	gradient: A—formic acid B—methanol	17	0.3 mL/min	TOF	N/A	[241]
mouse urine	S-carboxymethylcysteine thiodiglycolic acid	BEH C18	gradient: A—water, formic acid B—ACN, formic acid	10	0.5 mL/min	QTOF-MS	N/A	[242]
mouse urine	ifosfamide cyclophosphamide and their metabolites	BEH C18	gradient: A—formic acid B—ACN, formic acid	10	0.5 mL/min	QTOF-MS	N/A	[243]
human urine and shrimp and squid water extracts	taurine	AccQTag Ultra (100 × 2.1 mm, 1.7 µm)	gradient: A—AccQTag Ultra eluent concentrate 10%/water 90% B—AccQTag Ultra eluent	9.5	0.7 mL/min	fluorescence	N/A	[244]

Table 2. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
human urine	metabolomics urine profiling	HSS T3 (100 × 2.1 mm, 1.8 µm)	gradient: A—water, formic acid B—methanol, formic acid	11.5	0.4 mL/min	TOF	N/A	[245]
human urine	13 benzodiazepines	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—water with formic acid, B—methanol with formic acid	4	0.4 mL/min	MS-MS	LOD [ng/mL]: 0.5–2 LOQ [ng/mL]: 20	[246]
human urine	Di-(2-ethylhexyl)phthalate mono-(2-ethylhexyl)phthalate mono-(2-ethyl-5-hydroxyhexyl)phthalate mono-(2-ethyl-5-oxohexyl)phthalate mono-(2-ethyl-5-carboxypentyl)phthalate mono-(2-carboxymethylhexyl)phthalate	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid B—ACN, formic acid	10	0.6 mL/min	MS-MS	LOQ [ng/mL]: 1.2–2.6	[247]
human urine	21 diuretics 19 beta-blockers 8 stimulants 2 steroidal drugs	BEH Shield RP18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, water B—methanol	6	0.5 mL/min	MS-MS	LOD [ng/mL]: 6–158 LOD [ng/mL]: 3–200	[248]
		Atlantis T3TM (100 × 2.1 mm, 3 µm)	gradient: A—ammonium formate B—ACN	12.5	0.30 mL/min			
human urine	urinary endogenous metabolites	Acclaim 120 C18 (10 × 2 mm, 5 µm) Acclaim RSLC 120, C18, (100 × 2.1 mm, 2.2 µm)	gradient: A—water, formic acid B—methanol, formic acid	12.5	400 mL/min	MS	N/A	[249]
rat and mice urine	metabonomics	C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid B—CAN, formic acid	1	1 mL/min	MS	N/A	[250]
human urine	endogenous human urinary metabolites	C18 BEH (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, water B—formic acid, ACN	7	0.2 mL/min	MS	N/A	[251]
human urine	desmosine isodesmosine	AccQ-Tag™ Ultra (100 × 2.1 mm, 1.7 µm) Van Guard Precolumn (5 × 2.1 mm, 1.7 µm)	gradient: A—heptafluorobutyric acid, water B—ACN	15	0.6 mL/min	MS-MS	LLOQ [pmol/mL]: 1	[252]
human urine	18 acylglycines	Kinetex C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ACN, formic acid, water B—water, formic acid, ACN	45	0.25 µL/min	MS	LLOQ [nM]: 1–5 LOD [nM]: 1–2	[253]

Table 2. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
rat urine	acetaminophen metabolites	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, water B—formic acid, ACN	12.1	0.15 mL/min	MS	N/A	[254]
human urine	IGF-1, IGF-2, Des1-3-IGF-1	BEH130 C18, (150 × 75 mm, 1.7 µm) Symmetry C18, (180 × 20 mm, 5 µm)	A—formic acid, water B—acetonitrile	35	750 nL/min	MS-MS	LOD [pg/mL]: 20 for all analytes	[255]
human urine	allantoin	BEH HILIC (100 × 2.1 mm, 1.7 µm)	formic acid in ACN, deionized water (95:5, *v*/*v*)	4	200 µL/min	TQD-MS	LOQ [µmol/L]: 1	[256]
human urine	corticosteroids	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, water B—formic acid, ACN	7.5	0.35 mL/min	TOF-MS	LOD [µg/L]: 0.1–2.8 LOQ [µg/L]: 0.4–4.4	[257]
dog urine	trantinterol	Ultimate™ C8 (50 × 4.6 mm, 5 µm)	formic acid in water methanol (70:30, *v*/*v*)	20	0.1 mL/min	MS	N/A	[258]
rat urine	endogenous urinary metabolites in rat disease models	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, deionized water B—formic acid, ACN	23.5	500 µL/min	HDMS	N/A	[259]
human urine	endogenous urinary metabolites in healthy subjects (day/night metabolomic variation)	C18 2.16 × 100 mm	gradient: A—formic acid, water B—formic acid, ACN	14	0.4 mL/min	QTOF-MS	N/A	[260]
human urine	colorectal carcinoma metabolomic profiling	BEH C18, (100 × 2.1 mm, 1.7 µm)	gradient: A—water, formic acid B—ACN	18	0.35 mL/min	MS	N/A	[261]
human urine	phenylacetylglutamine (PH) 4-cresyl sulphate (CS) hippurate (H)	BEH C18, (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid B—ACN, formic acid	2	0.6 mL/min	MS-MS	LLOQ [ng/mL]: PH 1 CS 1000 H 3	[262]
human urine	untargeted urinary metabolite profiling	HSS T3 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid, water B—ACN, formic acid	10	600 µL/min	MS	N/A	[263]
equine urine	anti-diabetics, anti-ulcers, cyclooxygenase-2 inhibitors, sedatives, corticosteroids, anabolic steroids, sulfur diuretics, xanthines (140 drugs)	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—acetic acid, deionised water B—methanol	13	200 µL/min	MS-MS	LOD [ng/mL]: 0.0075–30	[264]

Table 2. *Cont.*

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
camel urine and intestinal tissue	disaccharides prepared from heparin and heparan sulfate	BEH C18 (150 × 2.1 mm, 1.7 µm)	gradient: A—water, ACN B—water, acetonitrile	40	100 µL/min	MS	N/A	[265]
human urine	2,3-dinor-8-isoprostaglandin-$F_{2\alpha}$	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ammonium hydroxide, water B—ammonium hydroxide, methanol, ACN	6	400 µL/min	MS-MS	LOQ [µg/L]: 0.5	[266]
human urine	metabolic profiling of liver-stagnation and spleen-deficiency syndrome	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—water, formic acid B—ACN, formic acid	13	0.5 mL/min	QTOF-HDMS	N/A	[267]
rat urine	metabolic profiling of chronic renal failure	HSS T3 (100 × 2.1 mm, 1.8 µm)	gradient: A—formic acid B—ACN, formic acid, ammonium acetate	15	0.4 mL/min	QTOF-MS	N/A	[268]
murine urine	schistosomiasis metabolomic profiling	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—water, formic acid, ACN	10	0.5 mL/min	MS	N/A	[269]

2.3. Tissues

UPLC tissue analysis can provide precise information about their chemical composition, which can be useful in scientific research, medical diagnostics, and the evaluation of treatment efficacy. UPLC enables accurate determination of drug and metabolite concentrations in various tissues, allowing for precise monitoring, testing, and optimization of drug therapies, as well as understanding the pharmacokinetic and pharmacodynamic processes occurring in the patient's body. This leads to increased treatment efficacy and minimized adverse effects. Biological tissues are among the most complex matrices in UPLC analysis. The presence of proteins, lipids and salts has a significant impact on the determination of compounds and, consequently, on the reliability of the results. Furthermore, the direct introduction of unfractionated tissue lysates leads to contamination of the chromatographic column and the ion source in MS detection. Sample preparation is the most important step in minimizing the matrix effect when analyzing compounds in tissue samples. This process involves SPE, which allows for the selective removal of proteins and lipids (including phospholipids) from tissue homogenates, leaving a pure extract. It is also possible to precipitate proteins; however, the extract obtained using this technique is less pure than that obtained by SPE [270,271]. Ackermans et al. developed a method for determining thyroid hormones and their metabolites in various tissue samples obtained from male Wistar rats, including liver, heart, and hypothalamus. Because the thyroid gland in rats is significantly small, human thyroid tissues obtained during surgery for a benign multinodular tumor were also used. Solid-phase liquid chromatography with tandem mass spectrometry (SPE LC-MS-MS) was used in this study. The mobile phase consisted of eluent: A—5% ACN in water containing 0.1% acetic acid, and B—95% ACN in water containing 0.1% acetic acid. The use of UPLC instead of HPLC lowered the detection limits, allowing for the use of smaller tissue sample volumes [272]. Drug abuse in animals has a number of serious consequences for humans, ranging from growing drug resistance to increasing environmental pollution, which is why it is extremely important to have appropriate methods for determining drugs in animal tissues. Chan et al. developed a screening method for the analysis of antiviral drugs (amantadine, zanamivir, oseltamivir, acyclovir) in poultry tissues. Collected tissues were extracted with a mixture of ACN, water, and acetic acid. After purification of the sample using a cation exchange column, the eluate was divided into two fractions, which were evaporated to dryness. The first fraction was dissolved in a mixture of methanol and water, and the second in a mixture of ACN, methanol, and water. These fractions were analyzed by UPLC-MS-MS [273]. A similar method was used to quantify 13 aminoglycoside antibiotics in pork, fish and veal livers and kidneys [274]. UPLC-MS-MS was applied for monitoring the use of growth promoters in animals. Thirteen synthetic growth promoters were identified, confirmed, and assayed, including dexamethasone, methylboldenone, and dienestrol. The analysis was conducted on 5 g of beef muscle, which, after appropriate preparation, was analyzed by UPLC-MS-MS using electrospray ionization (ESI), in both positive and negative polarities. The total analysis time was 14 min. The use of UPLC allowed for faster analysis, which is crucial for meat quality and safety control in the food market [275]. Examining brain tissue with UPLC can help diagnose and study neurological disorders such as Alzheimer's disease, Parkinson's disease and multiple sclerosis. It allows the identification of biomarkers and pathological changes in brain tissue. Using LC-MS-MS QTOF, 18 phospholipids were identified which can be used to identify brain areas enriched in neurons and glial [276]. Ma et al. used UPLC-MS to quantify the mass of radiotracers extracted from rat tissues. The results were very close to those obtained with the traditional method of measuring radiotracers, demonstrating the accuracy and utility of this technique. The use of UPLC in positron emission tomography (PET)) studies can significantly speed up the process of developing new probes for molecular imaging and makes it possible to

accurately quantify substances in tissues [277]. UPLC-MS-MS is also a useful method for quantitative determination of trans-ferulic acid-4-β-glucoside (FAG) in rat liver and plasma. FAG can increase thermogenesis in brown adipose tissue, which is a promising feature in treatment of cold injury [188]. Sigma-1 receptors are nonopioid receptor proteins involved in modulation of pain. 3-(2-(azepan-1-yl)ethyl)-6-benzylbenzo[d]thiazol-2-(3H)-one hydrochloride (MCI-77) is a selective sigma-1 receptor ligand, which may have potential in the treatment of neuropathic pain and nerve injury. Popa et al. used UPLC-MS-MS to quantify MCI-77 and determine its pharmacokinetic parameters in mouse plasma and brain homogenate and obtained satisfactory results [189]. Details of drug determination methods in tissue samples are summarized in Table 3.

Table 3. UPLC technique in the analysis of various substances in tissues.

Material	Substance	COLUMN TYPE	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
mouse brain homogenate	3-(2-(azepan-1-yl)ethyl)-6-benzylbenzo[d]thiazol-2-(3H)-one hydrochloride	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid in water B—ACN	3.2	0.3 mL/min	MS-MS	LLOQ [ng/mL]: 2	[189]
rat liver	trans-ferulic acid-4-β-glucoside	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid in water B—methanol	3	0.5 mL/min	MS-MS	LLOQ [µg/g]: 0.0626	[188]
rat liver, heart and hypothalamus tissues; human thyroid tissue	3,5-diiodo-L-thyronine 3,3′,5-triiodo-L-thyronine 3,3′,5′-triiodo-L-thyronine 3,3′,5,5′-tetraiodo-thyronine 3,3′-diiodo-L-thryonine	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—5% ACN in water containing 0.1% of acetic acid B—95% ACN in water containing 0.1% of acetic acid	12	0.2 mL/min	MS-MS	LOD [pg on column]: 0.16–0.59 LOQ [pg on column]: 0.98–1.73	[272]
poultry tissue	acyclovir, amantadine, ganciclovir, imiquimod oseltamivir, rimantadine, oseltamivir carboxylate zanamivir	HILIC (150 × 2.1 mm, 5 µm)	gradient: A—ammonium acetate, ACN B—ammonium acetate, ACN	15	0.3 mL/min	MS-MS	NA	[273]
pork muscle, fish, veal livers, kidneys	spectinomycin, streptomycin, dihydrostreptomycin, amikacin, kanamycin, paromomycin, apramycin, tobramycin, sisomycin, neomycin B, gentamycin	C-18 (150 × 2.1 mm, 2.6 µm)	gradient: A—ACN, heptafluorobutyric acid, water B—water, heptafluorobutyric acid	9	0.3 mL/min	MS-MS	LOQ [µg/kg]: liver 1–30 kidney 1–60 muscle 1–30 fish 2–25	[274]
bovine muscle	α-trenbolone, β-trenbolone, 16β-OH-stanozolol, fluoxymesterone, methylboldenone, medroxyprogesterone acetate, megestrol acetate, melengestrol acetate, hexestrol, methyltestosterone, dienestrol, dexamethasone, flumethasone	C18 (50 × 2.1 mm)	gradient: A—ammonium acetate, methanol (70:30, *v*/*v*) B—ammonium acetate, methanol (5:95, *v*/*v*)	14	0.5 mL/min	MS-MS	N/A	[275]
mouse brain	lipid molecules	HILIC (1.7 mm)	gradient: A—water, ammonium acetate 5 mM B—ACN, ammonium acetate 5 mM	45	40 µL/min	QTOF-MS-MS-	N/A	[276]

Table 3. *Cont.*

Material	Substance	COLUMN TYPE	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
rat brain tissue (hippocampus, cortex, cerebellum, caudate, brain stem, thalamus, plasma)	biodistribution of PET 5-HT1A ligand FPWAY	BEH Shield RP18 (150 × 2.1 mm, 1.7 µm)	gradient: A—ammonium acetate 25 mM in ACN B—ACN	12	NA	QTOF- MS	N/A	[277]
thyroid tissue	2-thiouracil 6-methyl-2-thiouracil 6-propyl-2-thiouracil 6-phenyl-2-thiouracil 1-methyl-2-mercaptoimidazole 2-mercaptobenzimidazole	BEH (100 × 2.1 mm, 1.7 µm)	gradient: A—0.1% formic acid B—ACN with 0.1% of formic acid	12.1	0.3 mL/min	MS-MS	NA	[278]
rat tissue	5-aminolevulinic acid	BEH C18 (2.1 × 50 mm, 1.7 µm)	ACN/0.1% formic acid	2.5	0.5 mL/min	MS-MS	LOQ [ng/mL]: 5.0	[279]
hepatic microsomes	acetaminophen 4′-hydroxy-mephenytoin 4-hydroxy-tolbutamide dextrorphan 6-hydroxy-chlorzoxazone 1-hydroxy-midazolam	BEH C18 (50 x 2.1 mm, 1.7 µm)	gradient: A—water with 0.1% formic acid B—ACN with 0.1% formic acid	5.25	400 µL/min	MS-MS	LOQ [ng/mL]: 1.5	[280]
secretomes of human pancreatic cancer cells	soluble and exosomal forms of epidermal growth factor receptor	BEH 130 C18 (100 µm × 100 mm, 1.7 µm)	gradient: A—98.9% water, 1% ACN, 0.1% formic acid B—99.9% ACN, 0.1% µL formic acid	60	400 nL/min	MS-MS	NA	[281]
fish tissues	cyadox (CYX) quinoxaline-2-carboxylic acid (QCA) 1-desoxycyadox (1-DCYX) 1,4-bisdesoxycyadox (BDCYX)	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—0.1% formic acid B—methanol/0.1% formic acid in water	5	0.3 mL/min	MS-MS	LOD [mg/kg]: CYA 0.52 QCA 1.07 1-DCYA 0.69 BDCYA 0.38 LOQ [mg/kg]: CYA 1.73 QCA 3.57 1-DCYA 2.30 BDCYA 1.27	[282]
swine tissues	ractopamine	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—0.1% formic acid in water B—0.1% formic acid in ACN	4	0.3 mL/min	MS-MS	LOD [µg/kg]: 0.2 LOQ [µg/kg]: 0.5	[283]

Table 3. *Cont.*

Material	Substance	COLUMN TYPE	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
chicken muscle	ampicillin, amprolium, chlortetracycline, ciprofloxacin, enrofloxacin, erythromycin, lincomycin, oxolinic acid, oxytetracycline, penicillin, spectinomycin, spiramycin, sulfadimethoxine, tetracycline, tylosin, tilmicosin, pirlimycin, dihydrostreptomycin, streptomycin, amoxicillin, sulfadiazine, sulfathiazole, danofloxacin, sulfamethazine	ZIC–HILIC (100 × 2.1 mm, 3.5 µm)	gradient: A—50mM ammonium formate in water B—ACN	15	0.2 mL/min	MS-MS	LOD [µg/kg]: 0.5–25.0 LOQ [µg/kg]: 0.3–60.0	[284]
human hepatic bile	endogenous metabolites including bile acids, amino acids and organic acids	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—water (0.1% formic acid) B—ACN (0.1% formic acid)	12	0.3 mL/min	MS	LOQ [µM]: 2,4,5-TBP 0.0625 4-OH 0.010 5′-OH 0.010 6′-OH 0.010	[285]
rat brain tissue	3-phenyl-4-aminobutyric acid	BEH Shield RP18 (100 × 2.1 mm, 1.7 µm)	ACN, formic acid (0.1% in water) (8:92, *v*/*v*)	5	0.2 mL/min	MS-MS	N/A	[286]
aqueous humour	levofloxacin	HSS T-3 C18 (100 × 2.1 mm, 1.8 µm)	gradient: A—0.1% aqueous trifluoroacetic acid B—ACN	5	0.45 mL/min	UV	LOQ [µg/mL]: 0.05 LOD [µg/mL]: 0.015	[287]
cultured fish	101 veterinary drugs	C-18 (150 × 2.1 mm, 2.6 µm)	gradient: A—ACN, formic acid (50:3, *v*/*v* with water up to 1 L) B—water, formic acid (50:3 *v*/*v* with ACN up to 1L)	10	0.4 mL/min	HR MS	N/A	[288]
human hepatocytes, brain capillary endothelial cells, humanized mouse liver	organic anion transporting polypeptides	HSS T3 (150 × 2.1 mm, 1.7 µm)	gradient: A—0.1% formic acid in water B—ACN	15.5	0.35 mL/min	MRM-MS	LOD [µg/mL]: 0.016–0.080	[289]
fish, pork kidney, pork liver, honey extracts	nitroimidazole	C18 (100 × 2.1 mm, 1.8 µm)	gradient: A—water, ACN, formic acid B—ACN, water, formic acid	15.6	0.4 mL/min	MS-MS	N/A	[290]

Table 3. *Cont.*

Material	Substance	COLUMN TYPE	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
rat brain	substrates and products which are the effects of prolyl oligopeptidase inhibition	C18 (2.1 × 15 cm)	gradient: A—20 mM TEA in water at pH 11.5 B—20 mM TEA in ACN	40	150 µL/min	MS-MS	N/A	[291]
swine liver	mequindox 1-desoxymequindox 1, 4-bisdesoxymequindox	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid in water B—methanol	8	0.3 mL/min	MS-MS	LOD [mg/kg]: 0.58–1.02 LOQ [mg/kg]: 1.93–3.40	[292]
mice liver and skeletal muscle	2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)	XTerra MS C8 (100 × 2.1 mm, 3.5 µm)	gradient: A—water, formic acid B—ACN, formic acid	30	0.2 mL/min	QTOF-MS	N/A	[293]
liver microsomes (human, rat, dog, mini pig)	paeonol	BEH C18 (50 × 2.1 mm, 1.7 µm)	water/ACN (70:30, *v*/*v*)	3	0.3 mL/min	MS	N/A	[294]
chicken muscle	fluoroquinolones	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—water, formic acid B—ACN	40	0.4 mL/min	TOF-MS	N/A	[295]
Bufo bufo gargarizans	hellebrigenin stereoisomer c-bufarenogin gamabufotalin bufarenogin arenobufagin stereoisomer arenobufagin	XTerra MS C18 (100 × 4.6 mm, 5 µm)	gradient: A—water with formic acid B1—ACN B2—ACN with formic acid	75	1.0 mL/min	UV HRMS ^{1}H NMR ^{13}C NMR 2D-NMR	N/A	[296]
		TSK-GEL ODS-100 V C18 (150 × 4.6 mm, 3 µm)		70	1.0 mL/min			
		TSK-GEL AMIDE-80 (150 × 4.6 mm, 3 µm)		40	1.0 mL/min			
		Click b-CD (150 × 4.6 mm, 5 µm)		40	1.0 mL/min			
		XTerra MS C18 (150 × 2.1 mm, 5 µm)		60	0.2 mL/min			
human liver microsome	propranolol, metoprolol, verapamil, lidocaine, S-methylthiopurine, 2-acetamidofluorene	T3 1.8 µm, 100 × 2.1 mm	gradient: A—formic acid, methanol B: methanol	29	300 mL/min	MS	N/A	[297]
fruit fly homogenates	paraquat	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—sodium 1-octanesulfonate monohydrate, formic acid in ACN, water B—ACN	3	200 mL/min	DAD	N/A	[298]

Table 3. *Cont.*

Material	Substance	COLUMN TYPE	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
human gall, bladder bile, liver graft	bile acid metabolic profiles	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—water, formic acid B—ACN and formic acid	12	0.5 mL/min	TOF-MS	N/A	[299]
human liver microsomes	cinitapride	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—ACN, ammonium formate B—ACN	20.6	0.35 mL/min	MS	LOD [µmol/L]: 0.03	[300]
human female reproductive tissues (fetal membranes and placenta)	anandamide	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—ammonium acetate, formic acid B—ACN, formic acid	2.30	N/A	MS-MS	LOD [fmol/g]: placenta 187.5 membranes 125.0 LOQ: [fmol/g]: placenta 312.5 membranes 187.5	[301]
dog liver protein microsomes	fatty acid amide hydrolase activity	ZIC-HILIC (100 × 2.1 mm, 3.5 µm)	gradient: A—ammonium formate in water, formic acid B—ACN	4	0.2 mL/min	MS-MS	N/A	[302]
pig liver, kidney and muscle	16 illegal residual β-agonists	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—methanol B—water, formic acid	16.5	0.3 mL/min	MS-MS	CCα [µg/kg]: 0.02–0.79 CCβ [µg/kg]: 0.04–1.62	[303]
fish tissue	chrysoidine	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid in water B—ACN	6	0.4 mL/min	MS-MS	LOQ [ng/g]: 0.25	[304]
mouse tissue (heart, kidney, brain, lung, pancreas)	lipoyllysine	ULTRON VXODS (150 × 4.6mm, 5 µm) GL CARTO Inertsil ODS-3 (5 × 4.6 mm, 5 µm)	gradient: A—water and ACN with H_3PO_4 B—water and ACN with H_3PO_4	25	1.0 mL/min	TOF-MS	N/A	[305]
rat tissue (heart, kidney, brain, lung, pancreas)		TSK-gel ODS-100Z (150 × 2.0 mm, 5 µm)	gradient: A—formic acid in water B—formic acid in ACN	20	0.2 mL/min			
human bone	collagen crosslinks hydroxyproline	HSS T3 (100 × 2.1 mm, 1.8 µm)	gradient: A—heptafluorobutyric acid in water B—heptafluorobutyric acid in water and ACN	15	0.67 mL/min	fluorescence	N/A	[306]

Table 3. *Cont.*

Material	Substance	COLUMN TYPE	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
zebrafish embryos, aqueous-exposure solution	triptolide	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—formic acid in water B—ACN	6	0.4 mL/min	MS-MS	LLOD [ng/mL]: 0.02 LLOQ [ng/mL]: 0.06	[307]
fish tissue	methyl-3-quinoxaline-2-carboxylic acid	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—methanol B—aqueous formic acid	5	0.3 mL/min	MS-MS	LOD [ng/g]: 0.1 LOQ [ng/g]: 0.25	[308]
fish tissues	pipemidic acid, enoxacin, norfloxacin, ciprofloxacin, lomefloxacin, enrofloxacin, gatifloxacin, difloxacin, oxolinic acid, nalidixic acid, flumequine	HT Eclipse XDB-C18 (20 × 3 mm, 1.8 µm) XBridge C18 (150 × 2.1 mm, 5 µm) Symmetry Shield RP18 (250 × 4.6 mm, 5 µm)	gradient: A—formic acid in water B—formic acid in ACN	13	0.5 mL/min	FLD	LOD [µg/L]: 1.5–50.1 LOQ [µg/L]: 5.3–142.9	[309]
				25	0.2 mL/min		LOD [µg/L]: 0.9–37.5 LOQ [µg/L]: 2.5–90.9	
				25	0.8 mL/min		LOD [µg/L]: 1.9–50.3 LOQ [µg/L]: 7.7–166.6	
		BEH C18 (100 × 2.1 mm, 1.7 µm)		7	0.45 mL/min		LOD [µg/L]: 1.2–49.6 LOQ [µg/L]: 3.0–140.1	
human colorectal cancer tumor tissue, adjacent normal tissue	global DNA methylation	BEH HILIC (100 × 2.1 mm, 1.7 µm)	gradient: A—ACN B—water with ammonium formate	8	0.2 mL/min	MS-MS	LOQ [pg]: 0.05 LOQ [pg]: 0.50	[310]
swine kidney	dimetridazole, metronidazole, ronidazole, ipronidazole and their major metabolites	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—water B—ACN	4	0.3 mL/min	MS-MS	LOD [µg/kg]: 0.05–0.5 LOQ [µg/kg]: 0.1–0.5	[311]
retinal swine tissue	ractopamine	HSS C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—formic acid in water B—formic acid in ACN	25	0.45 mL/min	MS-MS	N/A	[312]
mice lung tissue	glycerophosphocholines molecular structure (diacyl-, alkyl-acyl- and alk-1-enyl-acyl-GPC, related lyso-GPCs)	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—ammonium acetate in water B—ACN in methanol (65:35, *v*/*v*) with 1M ammonium acetate	6	0.7 mL/min	MS-MS	LOD [ng/µL]: 0.002–0.016	[313]

2.4. Hair

Various substances both external (e.g., drugs) and internal (e.g., biological amines) have the ability to accumulate in both the hair bulb and hair shaft [314]. An unquestionable advantage of hair analysis is the ability to assess long-term exposure, spanning several years. Analyses of other biological materials, e.g., urine or blood, do not offer such possibilities. Hair is a very good sample for forensic and clinical research due to its high durability, stability and often higher content of tested substances in comparison with blood or urine. Previous hair analysis techniques have been characterized by time-consuming compound separation processes using gas chromatography or HPLC. The ability to omit derivatization during analysis is undoubtedly a significant advantage [315]. Hair, due to its ease of collection, transportation and maintenance, is a convenient sample for analysis. Ease of downloading is a notable advantage for children and elderly. In drug abusers, substances such as cocaine, codeine, benzodiazepines, morphine and 6-monoacetylmorphine can be detected in hair samples [316]. Separation of ketamine and norketamine, the main metabolite of ketamine by a combination of micro-powder extraction and UPLC-MS is possible within 2 min [317]. Another study shows that UPLC-MS-MS can be a useful method for detecting ethyl glucuronide (EtG) in hair. EtG is a biomarker of long-term alcohol abuse and can be tested more reliably in hair than blood [318]. There is also a need to determine endogenous compounds that perform important functions in the organism. Blanco-Ces et al. used UPLC-MS-MS to separate and detect gamma-hydroxybutyrate (GHB) in hair samples with satisfactory results [319]. Hair consists mainly of proteins, primarily keratin, as well as lipids, melanin and minerals. During extraction, these natural components leach into the solution and may cause a matrix effect by ion suppression, which can reduce the sensitivity and accuracy of the method [320]. Proper preparation of the hair sample plays a key role in ensuring the analysis is carried out correctly. Preliminary decontamination is carried out, which involves thoroughly washing and degreasing the hair using alcohol or other organic solvents. SPE is then performed to remove interfering substances, primarily proteins [321]. Míguez-Framil et al. used human hair samples washed with a diluted soap solution, followed by cleaning with water and drying (40 °C, 30 min). They pulverized the hair to obtain an average particle size of about 50 µm [315]. Yao et al. used a different pretreatment method, washing the hair with dichloromethane, water, and methanol. After air-drying, the hair was cut into small pieces and further analysis was performed [321]. Human hair was used as a screening material for the analysis of alprazolam, amitriptyline, amphetamine, benzoylecgonine, bromazepam, buprenorphine, chlordiazepoxide, chlorprothixene, citalopram, clonazepam, aminoclonazepam, clozapine, cocaine, codeine, diazepam, flunitrazepam, aminoflunitrazepam, fluoxetine, ketamine, ketobemidone, lamotrigine, levomepromazine, lidocaine, lorazepam, 6-MAM, MDA, MDEA, MDMA, methamphetamine, methadone, metoclopramide, metoprolol, mianserin, mirtazapine, morphine, nitrazepam, aminonitrazepam, norfluoxetine, dibenzepine, nortriptyline, orphenadrine, oxazepam, oxycodone, paroxetine, promethazine, quetiapine, sertraline, tramadol, triazolam, venlafaxine, zaleplon, zolpidem and zopiclone by UPLC-TOF-MS on a C18 column (100 × 2.1 mm, 1.8 µm) and using the mobile phase: A—0.05% formic acid B—100% methanol, satisfactory results were obtained, with LOD values: 0.01–0.1 ng/mg and LOQ: 0.05–2.00 ng/mg [322]. Details of other hair analysis studies using UPLC are summarized in Table 4.

Table 4. UPLC technique in the analysis of various substances in hair.

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
mice hair	histamine and metabolites	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—20 mmol/L $HCOONH_4$ B—CH_3CN	25	0.4 mL/min	TOF-MS	N/A	[314]
rat hair	biomarkers	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—0.1% formic acid in water, B—0.1% formic acid in acetonitrile	8	400 uL/min	TOF-MS	N/A	[316]
rat hair	ketamine norketmine	BEH C18 (100 × 2.1 mm, 1.7 µm) BEH C18 precolumn (5 × 2.1 mm, 1.7 µm)	water, ACN (85:15→20:80, v/v) + 0.1% formic acid	3	0.6 mL/min	MS	N/A	[317]
human hair	ethyl glucuronide	BEH C18 (100 × 2.1 mm, 2.5 µm)	gradient: A—aqueous solution B—organic solvent; belonging to COMEDICAL M3® Line	8	0.4 mL/min	MS-MS	LOD [pg/mg]: 0.75 LOQ [pg/mg]: 2.5	[318]
human hair	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	XDB C18 (50 × 4.6 mm, 1.8 µm)	water/methanol (40/60, v/v)	5	0.3 mL/min	MS-MS	N/A	[321]
bovine hair	estradiol-3-benzoate testosterone salts boldenone salts nandrolone salts medroxyprogesterone acetate	BEH C18 (100 × 2.1 mm, 1.7 µm) BEH C18 precolumn (5 × 2.1 mm, 1.7 µm)	gradient: A—methanol/water (40:60. v/v) with 0.05% ammonia B—methanol with 0.05% ammonia	17	0.5 mL/min	MS-MS	N/A	[323]
human hair	GHB	CORTECS HILIC (100 × 2.1 mm, 1.6 µm)	gradient: A—10 mM aqueous ammonium acetate in water B—ACN	10	0.3 mL/min	MS-MS	LOD [ng/mg]: 0.1 LOQ [ng/mg]: 0.5	[319]

2.5. Nails

Nails can be used as a material for testing substances that accumulate in the nail plate. A nail is a highly keratinized tissue. Incomplete destruction of this structure can lead to low recovery of analytes. To remedy this situation, cryogenic grinding should be used instead of traditional cutting. Low-temperature grinding assisted by liquid nitrogen breaks down the keratin structure and significantly increases the extraction surface area [324]. Previous studies have primarily involved the analysis of drugs or doping agents. Nail sampling is non-invasive, easy, and safe, minimizing patient discomfort. Analysis can also be performed on nail samples collected postmortem due to the high stability of the compounds in this material [325]. Nails can also be used to diagnose chronic diseases. A method of determining compounds intermediate advanced glycation end products that are associated with the development of diabetic complications has been successfully carried out. For this purpose, UPLC with time-of-flight UPLC-ESI-TOF-MS was used [326]. The same method was applied to determine the concentration of ultraviolet (UV) filters in human nail samples. In order to determine the concentration of filters, nails were treated by ultrasonic cleaning, then washed with ultrapure distilled water, rinsed with acetone and methanol, freeze-dried and ground to small powder [327]. UV-filters are chemicals that play an important role in protecting the skin from the sun radiation, but they can also accumulate in the skin and cause skin irritation and photoallergic reactions. The compounds studied are present in the nail in small amounts, so the high sensitivity of UPLC was essential to detect the dicarbonyl intermediates of advanced glycation end products. The collected nail samples were rinsed with 0.1% sodium dodecyl sulfate solution and distilled water, dried under vacuum and ground into powder [325]. Lorazepam and 3-O-glucuronide were determined from human fingerprint deposits using UPLC-MS-MS. The analysis was performed on a Waters C18 column (150 × 2.1 mm, 1.7 µm) using a mobile phase gradient, A—ammonium formate/formic acid, B—ACN/formic acid, and a flow rate of 250 µL/min [328,329]. A summary of other UPLC studies using nails is presented in Table 5.

Table 5. UPLC technique in the analysis of various substances in nails.

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
human nail	benzophenone-1 benzophenone-2 benzophenone-3 benzophenone-6 benzophenone-8 4-hydroxybenzophenone 2,3,4-trihydroxybenzophenone avobenzone	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—water with formic acid B—methanol with formic acid	10	0.3 mL/min	TOF-MS-MS	LOQ [ng/g]: 1.0–5.0 LOD [ng/g]: 0.2–1.5	[325]
human nail	3-deoxyglucosone (3-DG) 1 methylglyoxal (MG) glyoxal (GO) and their advanced glycation end products	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—0.1% formic acid in water B—0.1% formic acid in ACN	7	0.6 mL/min	TOF-MS	LOD [fmol]: 3-DG 30 MG 10 GO 50	[327]
human nail	R(−)-4-(3-isothiocyanatopyrrolidin-1-yl)-7-(N,N-dimethylaminosulfonyl)-2,1,3-benzoxadiazole	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A1—0.1% formic acid in water A2—ammonium acetate B1—0.1% formic acid in ACN B2—ACN	35	0.4 mL/min	TOF-MS	LOD [fmol]: 1.00–300	[326]
human nail	R(-)-DBD-PyNCS labeled DL-amino acids	BEH C18 (100 × 2.1 mm, 1.7 µm)	gradient: A—0.1% formic acid in water B—0.1% formic acid in ACN A—ammonium acetate B—0.1% formic acid in ACN	35	0.4 mL/min	TOF-MS	LOD [fmol]: L-Ala 1.0 L-Glu 150 LOD [pmol]: D-Leu 0.3 D-Ser 1.0	[328]

2.6. Saliva, Tears and Gastric Fluid

Unlike blood samples, the oral fluid collection method is non-invasive and possible even by non-medical personnel. Saliva and gastric fluid are highly complex biological matrices. Their direct injection into an UPLC system, particularly when combined with MS, leads to significant analytical problems. Salts, mucins, bile acids and proteins present in body fluids interfere with the ion generation process in the MS source, most commonly leading to ion suppression [330]. Furthermore, the extremely low pH of gastric juice and the presence of digestive enzymes, like pepsin, can cause chemically unstable compounds to degrade before the separation [331]. To overcome the negative impact of the matrix and protect the UPLC column, it is essential to follow appropriate sample preparation procedures. The most effective methods include SPE and protein precipitation [332]. Oral fluid is a biological material that can be used for roadside testing, for example, because of its ability to detect recently consumed drugs. In testing for the presence of illegal substances, it is important to use a multicomponent method with a low detection limit due to the limited amount of oral fluid. Badawi et al. developed a UPLC-MS-MS method for detecting 29 illegal substances and drugs in oral fluid samples in one chromatographic run. The substances detected included benzodiazepines, opioids, amphetamine and cocaine. For the determination 200 mg of oral fluid was collected using a Saliva-Sampler, diluted with ammonium acetate/methanol buffer (90:10, v/v). The prepared samples were applied to columns and eluted with acetonitrile and aqueous ammonium hydroxide solution [333]. The UPLC method is also used for pharmacokinetic studies and assessing how drug actives are absorbed and metabolized in the body after their oral administration. This allows for a better understanding of drug absorption and distribution processes, which can help optimize the dosage and effectiveness of drug therapy. Onoue et al. used the UPLC method for pharmacokinetic profiling after oral administration of tranilast formulations. Based on the results of the UPLC analysis, it was possible to determine the absorption time, the maximum concentrations (C_{max}) and the time at which the maximum concentration (T_{max}) of the drug in the gastric fluid was reached [334]. The system parameters used for saliva and gastric fluid determinations are presented in Table 6.

Table 6. UPLC technique in the analysis of various substances in saliva, tears and gastric fluid.

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
oral fluid	29 psychotropic drugs	C18 (100 × 2.1 mm, 1.8 µm)	gradient: A—2 mM ammonium acetate B—methanol	20	0.4 mL/min	MS-MS	ULOQ [µg/kg] <100 LLOQ [µg/kg]: 0.5	[333]
saliva	lactic acid (LA) 3-hydroxybutyric acid and D-, L-, DLenantiomers	C18 (100 × 2.1 mm, 1.7 µm)	methanol, ACN, water mixture with 0.1% formic acid	7	0.35 mL/min	MS-MS	LOD [fg]: LA 5.38 S-PMP-HA 11.5 S-AI-HA 32.8	[334]
saliva	salivary propteomic profoles of denture wearers	C4 (20 × 5 mm, 1.7 µm) BEH (100 × 100 mm, 1.7 µm)	gradient: A—water, ACN, formic acid B—water, ACN, formic acid	65	0.2 mL/min	TOF-MS-MS	N/A	[335]
saliva	prolactininducible protein, serum amyloid A, proteinalpha-2-macroglobulin, carbonic anhydrase, uteroglobin, Protein Plunc, amylase 2B, serotransferrin, alpha-amylase 1, alpha-2-macroglobulin	BEH 130 C18 (250 × 75 mm, 1.7 µm)	gradient: A—water, formic acid B—ACN, formic acid	65	N/A	MS-MS	N/A	[336]
gastric fluid	tranilast	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—methanol B—ammonium acetate	4.5	0.25 mL/min	MS	N/A	[337]
tears	prolactin-inducible protein precursor, lipocalin-1, protein S100-A11, protein S100-A8, protein S100-A4, lysozyme C	C18 (180 × 20 mm, 5 µm) precolumn BEH C18 (250 × 75 mm, 1.7 µm)	gradient: A—water with formic acid B—formic acid in ACN	170	250 nL/min	TOF-MS	N/A	[338]

2.7. Cerebrospinal Fluid

UPLC is a powerful tool in cerebrospinal fluid testing that is used in diagnosis, research and monitoring treatment of neurological diseases. An UPLC-MS-MS technique with positive ESI was developed and validated for the determination of histamine and its major metabolite tele-methylhistamine in cerebrospinal fluid. The LOD obtained (12.5 pM) was about 200 lower than that obtained previously by LC-MS-MS method [339]. UPLC can be used to identify and measure various biomarkers associated with Alzheimer's disease, such as β-amyloid, tau-phosphorylated protein, and brain metabolites. Changes in the levels of these biomarkers in biological samples can be an indicator of the presence and severity of the disease. The goal of the study by Lame et al. was to develop a more efficient method for quantifying amyloid-β peptides. Current methods are mainly based on immunological techniques that require very specific antibodies and reagents. However, these tests are very time-consuming and expensive. A mixed-phase solids extraction and UPLC-MS-MS method for the simultaneous determination of amyloid beta peptides in human cerebrospinal fluid was described. The method used has similar sensitivity to enzymatic assays but provides higher throughput and is more cost-effective [340]. UPLC also enables monitoring drug concentrations in cerebrospinal fluid, which is important in the treatment of nervous system diseases. For example, the UPLC-MS-MS method was used to quantify vitamin B6 in human cerebrospinal fluid collected via lumbar puncture. Sample preparation involved precipitation of protein with trichloroacetic acid containing a stable isotope labeled vitamin B6 compounds. This method enables the detection of reduced concentrations of pyridoxal and pyridoxal-5-phosphate and therefore has potential for routine diagnostic use [341]. Information on the determination of cerebrospinal fluids is provided in Table 7.

Table 7. UPLC technique in the analysis of various substances in cerebrospinal fluid.

Material	Substance	Column Type	Mobile Phase	Total Run Time [min]	Flow Rate	Detection	LOD/LOQ	Ref.
cerebrospinal fluid	histamine, 1-methylhistamine	BEH C18 (50 × 2.1 mm, 1.7 µm)	gradient: A—0.1% formic acid, ACN, water B—0.1% formic acid, ACN	3.5	600 µL/min	MS-MS	LOD [pM]: 12.5 LOQ [pM]: 50	[339]
cerebrospinal fluid	synthetic peptides Aß1–38, Aß1–40, Aß1–42	BEH300 C18, (150 × 2.1 mm, 1.7 µm)	gradient: A—0.3% ammonia, water B—ACN	6.5	0.2 mL/min	MS-MS	N/A	[340]
cerebrospinal fluid	pyridoxal, pyridoxamine, pyridoxine, pyridoxic acid, pyridoxal 5-phosphate, pyridoxamine 5-phosphate, pyridoxine 5-phosphate	BEH C18, (100 × 2.1 mm, 1.7 µm) HSS-T3 (100 × 2.1 mm, 1.8 µm)	gradient: A—acetic acid, 0.01% heptafluorobutyric acid B—ACN	3.5	0.4 mL/min	MS-MS	LOD [nM]: 0.01–1.61	[341]
cerebrospinal fluid	isofraxidin	HSS (100 × 2.1 mm, 1.8 µm)	gradient: A—0.1% methanoic acid, ACN B—0.1% methanoic acid, water	5	0.3 mL/min	MS	N/A	[342]
cerebrospinal fluid	human CSF protein biomarkers	C18 (100 × 75 mm, 3 µm)	gradient: A—0.1% aqueous formic acid B—0.1% formic acid in ACN	90	250 nL/min	MS	N/A	[343]

2.8. Feces

Girlanda et al. used UPLC-QTOF-MS to monitor intestinal transplant rejection. The study used metabolomics, which involves analyzing the metabolic profile of intestinal transplant patients. For the analysis, they used ileostomy fluid or fecal samples from 11 cases of bowel rejection and 45 cases of non-rejection. Separation was performed using a reversed phase system consisting of: 2% ACN in water with 0.1% formic acid (A) and 2% water in ACN with 0.1% formic acid (B) as eluent and C18 column (50 × 2.1 mm, 1.7 µm) as stationary phase [344]. UPLC/Q-TOF was also used to study the fecal metabolome of healthy people and patients with cirrhosis and hepatocellular carcinoma. Collected fecal samples were stored at −80 °C. For analysis, the samples were thawed at room temperature and mixed with methanol. The supernatants were filtered and injected directly onto the BEH C18 (100 × 2.1 mm, 1.7 µm) column. The mobile phase consisted of water and acetonitrile, each containing 0.1% formic acid. The method proved effective and convenient for analyzing stool samples, and therefore may be useful in the early diagnosis of liver cirrhosis and hepatocellular carcinoma [345]. Ileostomy and colostomy secretions, aspirated colonoscopy fluid, and stool were used to determine biomarkers of intestinal transplant rejection. The analysis was performed using UPLC-TOF-MS using a C18 column (50 × 2.1 mm, 1.7 µm) and a mobile phase composed of: A—2% ACN in water containing 0.1% formic acid; B—2% water in ACN containing 0.1% formic acid (gradient elution) at a flow rate of 0.5 mL/min [344]. Cao et al. analyzed the fecal metabolome by UPLC-QTOF-MS using a BEH C18 column (100 × 2.1 mm, 1.7 µm) and a gradient mobile phase composed of water and ACN, each containing 0.1% formic acid (flow rate 0.4 mL/min) [345].

The main problem with the analysis is that feces are a heterogeneous material, which makes it difficult to obtain reproducible results between successive weightings of the same sample [346]. One solution may be homogenization through the precipitation of proteins and lipids, followed by extraction using pure solvents such as methanol or acetonitrile [347]. Freezing and centrifugation also allow for the removal of larger solid particles and precipitated lipids [348].

2.9. Seminal Plasma

UPLC can help identify potential abnormalities in the composition of seminal fluid, which can be crucial in diagnosing male infertility, which has become a global problem. This technique is also used in scientific research aimed at understanding the chemical composition of seminal fluid and its impact on male reproduction and health. Currently, HPLC is a widely used method, but limitations such as long analysis time, low sensitivity, and the need to analyze large amounts of genomic DNA make it unsuitable for large-scale clinical analysis. Wang et al. developed a UPLC-MS-MS method for detecting global DNA methylation in human sperm. As the mobile phase, they used: 5.0% methanol and 95% water (with 0.1% formic acid) at a flow rate of 0.3 mL/min. The presented method may find application in studying epigenetic mechanisms of male infertility [349]. The analysis of uridine content in seminal plasma was performed by UPLC-MS system using an HSS T3 column (100 × 2.1 mm, 1.7 µm) and a mobile phase composed of: A—water, 0.1% formic acid B—ACN, 0.1% formic acid (gradient elution) [350]. Wang et al. analyzed seminal plasma samples for DNA methylation using a UPLC-MS-MS system equipped with a Zorbax SB-C18 column (100 × 2.1 mm, 1.8 µm) and a mobile phase gradient: 5% methanol, 95% water (with 0.1% formic acid) at a flow rate of 0.3 mL/min [349].

3. Summary

UPLC appears to be highly efficient and reliable compared to other chromatographic techniques. Operating at higher pressures translates to faster flow rates, and the use of

shorter columns shortens retention times, which are significant advantages over HPLC. The technique can also be more environmentally friendly, using fewer solvents and generating less waste than HPLC. The aim of this article was to collect data from various publications to discuss the applications of UPLC in the study of different classes of chemical compounds (drugs, biomarkers, metabolites, hormones, nutrients and toxic substances) in biological samples, which are highly complex. They contain proteins, lipids, phospholipids and salts, which elute alongside the analyte. In techniques such as UPLC-MS-MS, these components can compete with the analyte for ionization, leading to ion suppression, ion enhancement and a reduction in the sensitivity and accuracy of quantitative measurements. To minimize these interferences, advanced sample preparation techniques such as SPE and protein precipitation are employed, and isotope-labelled internal standards are used. In UPLC, matrices cause signal attenuation or amplification, which adversely affects precision. In accordance with regulatory guidelines (e.g., ICH M10), the assessment of matrix effects is an integral and critical part of the validation of a bioanalytical method. Validation checks whether the use of a suitable internal standard (preferably isotopically labelled) effectively compensates for signal variability caused by the matrix. Robustness refers to the ability of an analytical method to remain unaffected by small, deliberate changes to the method's parameters [351]. Repeatability and precision are measures of the consistency of results between independent repetitions of an analysis of the same material. Validation ensures the reliability of the method in accordance with FDA guidelines, whilst high robustness and reproducibility ensure its stability during routine analysis of biological samples. In accordance with the current ICH M10 guidelines, which have also been adopted by the FDA and the EMA, the lower limit of quantification (LLOQ) should be the lowest point on the calibration curve for which acceptable accuracy (±20%) and precision (CV ≤ 20%) have been demonstrated. For the remaining levels of the calibration curve, the criteria required are ±15% for accuracy and ≤15% for precision, respectively. The limit of detection (LOD), on the other hand, is of secondary importance; it serves only to confirm the ability to detect the analyte and is not subject to the accuracy and precision requirements applicable to quantitative determinations. The guidelines require an assessment of selectivity, matrix effects, calibration curve linearity, recovery, stability, precision and accuracy, both within a single analytical run and between runs. In LC-MS-MS methods, the LLOQ should be confirmed experimentally in the biological matrix by demonstrating the required accuracy and precision, and not solely on the basis of detector sensitivity. The use of appropriately selected internal standards, including isotopically labelled ones in many cases, and the optimization of sample preparation (SPE or protein precipitation) and chromatographic conditions (RP or HILIC, depending on the polarity of the analyte) help to minimize matrix effects and improve the reproducibility of determinations. Consequently, a validated method should demonstrate resistance to matrix variability and meet the accuracy and precision requirements set out in the ICH M10 guidelines [352–354].

Sample preparation before analysis is a crucial step in the entire process. Among the most commonly analyzed biological materials, whole blood, tissues, and plasma are the most challenging. Whole blood is widely considered one of the most difficult matrices for chromatographic analysis due to the presence of red blood cells, its high protein content and high viscosity. The preparation typically involves cell lysis, protein precipitation or SPE. Tissue homogenates are even more challenging than whole blood because they require homogenization, standardization of tissue mass, extraction from a highly complex mixture of lipids, proteins, and cellular components, and often multi-step purification. Liver and brain tissue contain vast amounts of phospholipids, which can strongly suppress ionization in UPLC-MS-MS. Plasma is the most commonly used matrix in bioanalysis, but not because it is the easiest to process. The main problem is the high concentration of albumin, globulins

and phospholipids. For this reason, protein precipitation or SPE extraction is routinely used [355]. Pretreatment of hair and nails often involves appropriate rinsing, for example, in methanol, acetone, or dichloromethane, drying, and pulverization to obtain appropriately small particles. Preparation of urine samples is similar but usually simpler, as urine contains significantly less protein. For more complex analyses, additional extraction techniques, such as SPE or liquid–liquid extraction, can also be used. The required sample volume for chemical and bioanalytical analysis depends on the sensitivity of the method, the matrix type, and the analyte concentration. Chromatographic techniques such as HPLC typically require relatively larger sample volumes, which translates to lower detection sensitivity (e.g., with UV detectors). Furthermore, they require sufficient material for extraction and purification, meaning that hundreds of µl to several ml are often required for biological samples (e.g., plasma, serum, urine). This can be problematic when sample size is limited (e.g., pediatrics, neonatology). The introduction of UPLC, often coupled with high-sensitivity detectors such as MS, has significantly reduced the required sample volume due to several key features, including increased sensitivity and separation efficiency, which allows for handling smaller amounts of analyte without signal loss; shorter columns with finer grain sizes, which translates into higher signal concentration and better signal-to-noise ratio; shorter analysis times and smaller dilutions (less analyte loss); and improved compatibility with microextraction (e.g., small-scale SPE). Thanks to this, it has become possible to analyze samples of very small volume, e.g., neonatal blood (several to a dozen or so µL), dried blood drops (DBS), microsamples of biological fluids collected in a minimally invasive manner. Typical sample volume requirements for the classical HPLC-UV method are often 0.5–2 mL, while for LC-MS-MS/UPLC-MS-MS 10–100 µL of serum or several mm of blood from DBS. In summary, UPLC, especially when combined with MS, has enabled the transition from milliliter to microliter analyses, revolutionizing diagnostics in situations where the available quantity of biological material is critically limited. At the same time, the smaller the sample, the greater the impact of preparation errors, matrix heterogeneity, and analyte losses.

Despite many advantages, miniaturization has certain limitations, including: limited repeatability of very small samples (pipetting error, matrix heterogeneity); problems with sample representativeness (e.g., DBS may not reflect all blood uniformly); analyte adsorption on surfaces (losses at very low concentrations); instrumentation requirements (UPLC-MS-MS is expensive and requires stable operating conditions); complicated microvolume sample preparation (more difficult SPE, higher risk of percentage losses); detection limit dependent on the matrix, not only on the instrumentation.

There is no single "most suitable" biological matrix for UPLC, as this technique can be applied to a wide range of materials; however, in practice, plasma or blood serum are most commonly chosen and best-characterized biological matrix. This is not due to limitations of the UPLC technique itself, but rather to the fact that plasma most accurately reflects the body's exposure to a substance, is widely used in pharmacokinetic studies, and has the largest number of validated analytical procedures [356]. The lowest LODs/LOQs are typically achieved in matrices with the lowest protein and lipid content, as these limit the matrix effects responsible for suppressing ionization. For this reason, cerebrospinal fluid, urine, and often saliva allow for lower limits of detection than plasma or whole blood, provided the analyte is present in these matrices at a sufficient concentration. At the same time, in bioanalytical practice, plasma remains the most commonly analyzed matrix, even though it does not provide the lowest LODs. It is chosen primarily because it best reflects the body's exposure to the drug and its metabolites [355].

The choice of column for research was determined by the type of matrix and the properties of the analytes. In the literature reports reviewed, BEH C18 columns were most

commonly used for analyzing compounds of moderate and low polarity, due to their wide applicability in analyzing compounds of moderate and low polarity. HSS T3 columns were preferred for analyzing metabolites of higher polarity, particularly when better retention under reversed-phase conditions was required, whereas HILIC columns were used less frequently and were typically reserved for highly polar compounds, including amino acids, nucleosides, and small endogenous metabolites.

UPLC is often coupled with other detection techniques that enable not only the separation but also the identification and quantification of compounds. Most often, this is MS or MS-MS, which enable highly selective and sensitive detection of compounds even in trace amounts, which is difficult to detect in biological samples. Such systems significantly improve analytical capabilities and are used in numerous fields, such as pharmacokinetics, bioanalysis, toxicology, and the analysis of drugs and their metabolites. Most studies using MS detection have used ESI, operating primarily in positive ion mode, while triple quadrupole mass spectrometers have been used primarily for targeted quantitative analyses, while high-resolution (QTOF) instrumentation has been used in metabolomics and biomarker discovery.

In summary, the reviewed literature clearly indicates a preference for reversed-phase UPLC using BEH C18 columns coupled with ESI-MS detection. Sample preparation depends primarily on the complexity of the matrix rather than the analytical procedure. Protein precipitation is sufficient for most liquid biological samples, whereas SPE is reserved for applications requiring increased sensitivity. However, HILIC is typically preferred only for highly polar analytes that cannot be adequately analyzed under reversed-phase conditions. Matrix effects, insufficient retention of polar metabolites, and the lack of harmonized sample preparation protocols remain the main analytical limitations.

Despite its many advantages, UPLC poses significant analytical and technical challenges. Operating at elevated pressures requires expensive equipment, fine stationary phase particles are more susceptible to contamination, and in the mass spectrometer, plasma components can affect analyte ionization, making the use of internal standards essential. Though some difficulties, UPLC has a fairly wide range of applications in the analysis of compounds in a complex matrix, such as biological material.

To sum up, the information collected in the above manuscript regarding the conditions of drug analysis in biological material should be useful for a wide range of researchers dealing with this subject and working with UPLC equipment (especially with MS detection). We hope that our work will serve as a guide, allowing for quick identification of the conditions under which a specific drug can be determined in the tested material. With the information contained in our work at hand, researchers can quickly find basic information on how to prepare a sample, what column to use, and what solvents they will need. Details on, for example, specific volumes can be found in the indicated publication, without the need to search through large databases.

4. Practical Recommendations

Based on the reviewed studies, a practical decision framework for UPLC-based bioanalytical method development can be proposed. For compounds with low to moderate polarity (including most pharmaceutical substances, lipids, xenobiotics, and their metabolites), BEH C18 columns remain the preferred first-choice stationary phase because of their broad applicability and successful use across diverse biological matrices. For more polar analytes, HSS T3 columns may provide enhanced retention while maintaining the advantages of reversed-phase chromatography. When analytes are highly polar and insufficiently retained under RP conditions, HILIC columns offer a more suitable alternative, particularly for amino acids, nucleosides, sugars, and endogenous metabolites. The studies analyzed consistently

demonstrated that the HILIC technique provides superior retention and separation of these analytes in cases where RP systems failed to ensure an adequate degree of retention.

The choice of sample preparation should be guided by analytical objectives and matrix complexity, with protein precipitation being most suitable for rapid, high-throughput analyses, whereas SPE is preferable when higher sensitivity, improved selectivity, and reduced matrix effects are required, particularly for trace-level quantification and complex matrices. For tissues, homogenization followed by extraction and additional purification was usually necessary, whereas urine often required only dilution, filtration, or SPE because of its lower protein content.

Similarly, the selection of the detection technique should reflect the study purpose: MS/MS remains the method of choice for targeted quantitative analysis, high-resolution MS (QTOF/TOF-MS) is most advantageous for untargeted profiling and metabolomics applications, while UV, PDA, DAD, or fluorescence-based detectors offer lower costs and simpler instrumentation but and generally provide lower sensitivity and selectivity and are therefore more suitable for routine analysis of known analytes present at relatively high concentrations.

This framework, derived from the reviewed literature, may facilitate a more rational selection of chromatographic conditions for specific analytes, matrices, and analytical goals.

These practical possibilities can be used to develop and optimize methods for UPLC applications.

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Abbreviations

6-MAM	6-Monoacetylmorphine
ACN	Acetonitrile
AD	Alzheimer's disease
ADMA	Asymmetric dimethylarginine
AGEs	Advanced glycation end products
AM	Amitriptyline
BDS	Base deactivated silica
BEH	Bridged ethyl hybrid
BZE	Benzoylecgonine
CCα	Decision limit
CCβ	Capacity of decision
C18	Octadecylsilane (reversed-phase column)
C8	Octylsilane (reversed-phase column)
CEMA	N-acetyl-S-(2-cyanoethyl)cysteine
CHEMA	N-acetyl-S-(1-cyano-2-hydroxyethyl)cysteine
DAD	Diode array detector

DBD-PyNCS	Derivatization reagent (benzoxadiazole derivative)
DHEA	Dehydroepiandrosterone
DL	Racemic mixture
ESI	Electrospray ionization
EtG	Ethyl glucuronide
F-EFV	Fluorinated efavirenz
FA	Formic acid
GC	Gas chromatography
GHB	Gamma-hydroxybutyrate
GO	Glyoxal
HDAC	Histone deacetylase
HEMA	N-acetyl-S-(2-hydroxyethyl)cysteine
HILIC	Hydrophilic interaction liquid chromatography
HMG	Hydroxymidazolam glucuronide
HP	High pressure
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
HSS T3	High strength silica T3 column
ICP-MS	Inductively coupled plasma mass spectrometry
KE	Ketamine
LC	Liquid chromatography
LI	Lidocaine
LLOQ	Lower limit of quantification
LLOD	Lower limit of detection
LOD	Limit of detection
LOQ	Limit of quantification
M3G	Morphine-3-glucuronide
M3S	Morphine-3-O-sulfate
M6G	Morphine-6-glucuronide
M6S	Morphine-6-O-sulfate
MDA	3,4-Methylenedioxyamphetamine
MDEA	3,4-Methylenedioxyethylamphetamine
MDMA	3,4-Methylenedioxymethamphetamine
MRM-MS	Multiple reaction monitoring mass spectrometry
MG	Methylglyoxal
MHD	Monohydroxy metabolite
MOR	Morphine
MS	Mass spectrometry
MS-MS	Tandem mass spectrometry
NA	Naringin
NE	Norepinephrine
NIB	Norisoboldine
NMMA	N-monomethylarginine
NO	Nortriptyline
OHM	Hydroxymidazolam
OV	Open vessel
OXC	Oxcarbazepine
PAH	Polycyclic aromatic hydrocarbons
QTOF-MS	Quadrupole time-of-flight mass spectrometry
SDMA	Symmetric dimethylarginine
SDS	Sodium dodecyl sulfate
SPE	Solid-Phase-Extraction
T3	High-strength silica column type
TDI	Toluene diisocyanate
TFA	Trifluoroacetic acid

TOF-MS	Time-of-flight mass spectrometry
UHPLC	Ultra-high-performance liquid chromatography
ULOQ	Upper limit of quantification
UPLC	Ultra-performance liquid chromatography
UV	Ultraviolet detection

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