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Ultra-high performance liquid chromatography-MS/MS (UHPLC-MS/MS) in practice: analysis of drugs and pharmaceutical formulations

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Abstract

Background: UHPLC-MS/MS is connected in various research facilities for the qualitative and quantitative investigation of a pharmaceutical substance, pharmaceutical items, and biological specimen.

Main body: The commence review article is an endeavor to offer pervasive awareness around assorted aspects and details about the UHPLC-MS/MS and related techniques with the aim on practice to an estimation of medicinal active agents in the last 10 years. The article also focused on isolation, separation, and characterization of present impurity in drug and biological samples.

Conclusion: Review article compiles a general overview of medicinally important drugs and their analysis with UHPLC-MS/MS. It gives fundamental thought regarding applications of UHPLC-MS/MS for the study on safety limit. The summary of developed UHPLC-MS/MS methods gives a contribution to the future trend and limitations in this area of research.

Key words: UHPLC-MS/MS, UHPLC, Pharmaceutical analysis, Impurity, Bio-analytical

Background

Ultra-high performance liquid-chromatography (UHPLC) covers liquid chromatography separations implementing columns enclose particles smaller than the 2.5–5 μm sizes typically used in high-performance liquid chromatography (HPLC) [1]. UHPLC work on the same assumption as that of HPLC [2] and of which governing principle is that, as column packing particle size decrease, efficiency and thus resolution accretion [3]. Separations using column contain smaller particles display enhance efficiency per unit time [1, 2], but the efficiency cannot minimize at superior mobile phase flow rates or linear velocities [4]. After attribute, slighter particles, rapidity, and peak resolution can be absolute to new limits [5].

Since it is extremely well recognized from Van Deemter equations, the efficiency of the chromatographic process is proportional to particle size decrease [6]. Pursuant to his model characterized band broadening, it clarifies by the connection between height equivalent of a theoretical plate (HETP) and linear velocity, is reliant on a diameter of particle packed into the analytical column [4, 6]. These accomplishments show the very considerable increase in resolution, sensitivity, and efficiency with the quicker outcome and a smaller amount expenditure of solvents which lowers the cost and make the technology environment friendly [7].

The hyphenated technique has turned out a precious method for the assessment of pharmaceuticals in various biological samples. The hyphenated technique is an attachment of the chromatographic system linked with the spectroscopic system with the right interface, such as LC-MS/MS [8]. It is well known that the detection profit appreciably from the performance characteristics of the UHPLC technology. As there is reduced in chromatography dispersion with an increased concentration of analyte will encourage improved source ionization efficiency [5].

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Table 1 Acceptance criteria for UPLC-MS/MS

Characteristics	UHPLC
Particle size	< 2 μm
Maximum back pressure	1000 bars
Analytical column	UHPLC BEH C_{18}
Column dimensions	50 × 2.1 mm
Injection volume	2 μL
Column temperature	65 °C
Total run time	1.5 min
USP resolution	3.4
Plate count	7500
Flow rate	0.6 mL/min

The hyphenated techniques usually applied for identification as well as quantification of the analyte when it is compared with other analytical methods [8]. At present era, employing of UHPLC gives the full benefits of chromatography applications for the separations using shorter columns, and superior flow rates for augmented rapidity, with greater resolution and sensitivity. The recognition criterion of UHPLC-MS/MS is shown in Table 1 [7]. The current review recapitulates the applications of UHPLC-MS/MS method for assessing drug in pharmaceutical as well as the biological matrix. In literature, there are several methods reported for analysis of drugs using UHPLC-MS/MS, the major categorized such as antidiabetic, anticancer, antibiotics, cardiovascular, antiviral, nonsteroidal anti-inflammatory drug (NSAID), and others.

Main text

UHPLC columns

The Acquity UHPLC column involved in the front line of liquid chromatography (LC) column development by giving higher quality chromatographic data's in less time. For use in applying up to 15000 psi (1000 bar), UHPLC columns are designed, certified, and tested [9]. However, different technologies produced distinct nature of columns actuality used in UHPLC is depicted in Fig. 1.

Charged surface hybrid

Third-generation particle technology was developed by waters, designed to recover sample loadability and peak tailing in uncertain ionic strength mobile phase composition. The charged surface hybrid retains the low level surface charge with 1.7 μm particle size [9]. The basic charged surface hybrid (CSH) C_{18} column characteristics such as peak shape and increased loading capacity, mainly for basic compounds under low-pH, weak-ionic-strength mobile-phase [10]. The polyaromatic compound selective straight-chain-alkyl is especially used in Acquity UHPLC CSH Phenyl-Hexyl column and also it

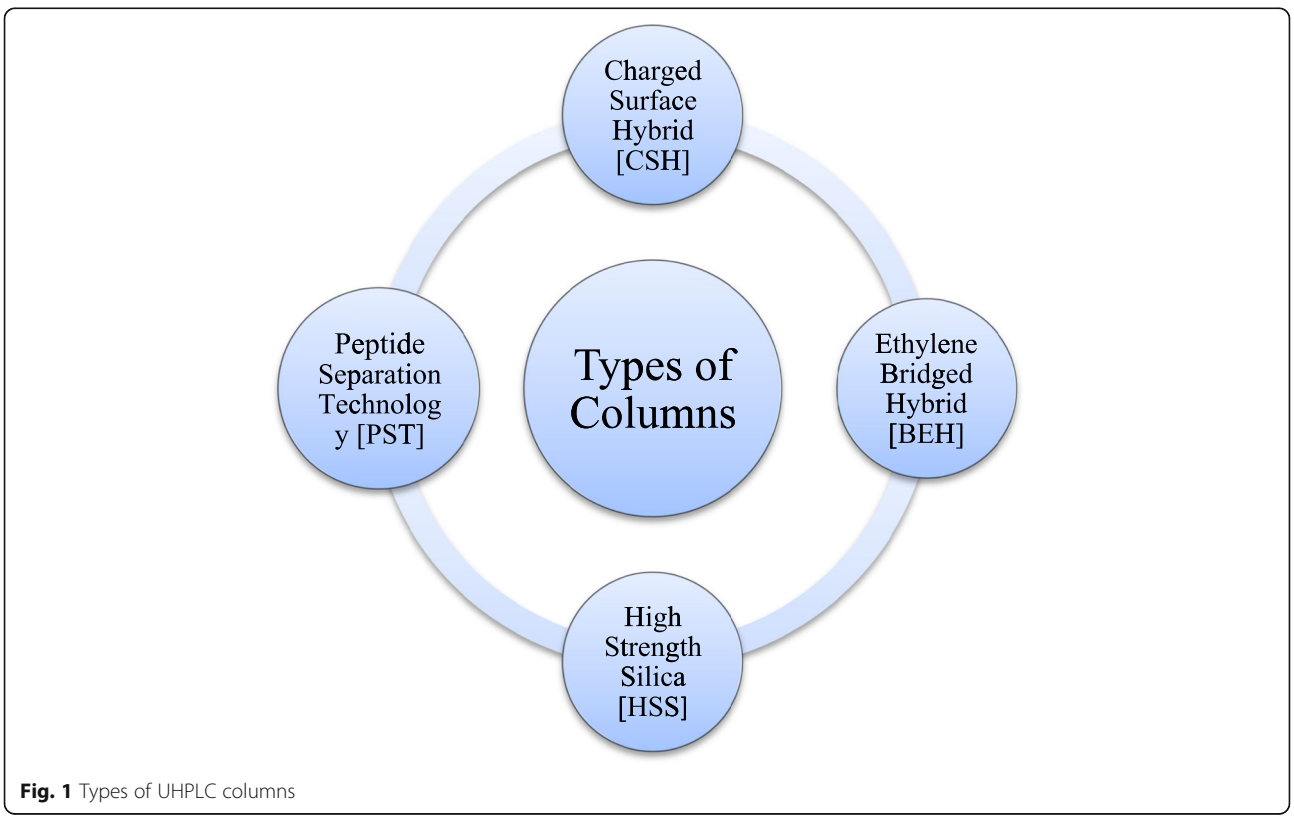

Fig. 1 Types of UHPLC columns

gives exceptional peak shape under different pH conditions [10]. The Acquity UHPLC CSH Fluoro-Phenyl columns show excellent selectivity for polar compounds, positional isomer, and halogenated compounds. This is due to a dipole-dipole, hydrogen-bonding, aromatic, and hydrophobic interaction [10].

Ethylene-bridged hybrid

The deficiency of mechanical strength or efficacy is essential to complete the potential speed, sensitivity, and resolution capabilities for primary generation methyl-hybrid particle of xTerra columns. Hence, there is need of a column with a new pressure-tolerant particle needed to create. An innovative, additional hybrid material columns were set that contains an ethylene-bridged hybrid material. It displayed enhanced efficiency, pH range, and strength as compared to first-generation columns [11]. The developed ethylene-bridged hybrid (BEH) columns fixed polar group attached to the silyl functionality with a C_6 alkyl and also for UHPLC BEH phenyl columns [7].

High strength silica

High strength silica (HSS) is another type of column used in UHPLC. In UHPLC, high pore volume UHPLC particles do not acquire the mechanical stability necessary to hold up the high pressure innate of UHPLC separations [9]. For that, there is established a novel silica particle and appropriate morphology required to give long and lifetime efficiency UHPLC column at high pressure likely 1000 bars. HSS particle technology is the modern automation; 1.8 μm UHPLC HSS particles are designed and exclusively for separations using UHPLC [12]. To overcome trouble during separation and retention of small water-soluble and polar organic molecules during reversed phase separation, Acquity UHPLC HSS T_3 columns were developed. The Acquity UHPLC HSS C_{18} selectivity for bases (SB) columns is a non-endcapped, low-coverage silica-based C_{18} chemistry that alternate selectivity for water-soluble compounds influenced by silanophilic interactions. The enhanced silanol activity of the HSS C_{18} SB column result in greater retention of basic compounds; due to secondary interactions with residual silanols while simultaneously

Table 2 Present perspective on UHPLC-MS/MS methods

Author(s)	Title	Year	Ref
Tatsuya Higashi, Kazutake Shimada, Toshimasa Toyo'oka	Advances in determination of vitamin D related compounds in biological samples using liquid chromatography–mass spectrometry: a review	2009	[20]
Aurelie Roux, Dominique Lison, Christophe Junot, Jean-François Heilier	Applications of liquid chromatography coupled to mass spectrometry-based metabolomics in clinical chemistry and toxicology: a review	2010	[21]
Alexander A. Zoerner, Frank-Mathias Gutzki, Sandor Batkai, Marcus May, Christin Rakers, Stefan Engeli, Jens Jordan, Dimitrios Tsikas	Quantification of endocannabinoids in biological systems by chromatography and mass spectrometry: a comprehensive review from an analytical and biological perspective	2011	[22]
Fabio Gosetti, Eleonora Mazzucco, Maria Carla Gennaro, Emilio Marengo	Ultra high performance liquid chromatography tandem mass spectrometry determination and profiling of prohibited steroids in human biological matrices. a review	2012	[23]
Marcus Bantscheff & Simone Lemeer & Mikhail M. Savitski & Bernhard Kuster	Quantitative mass spectrometry in proteomics: critical review update from 2007 to the present	2012	[24]
Mark R. Viant, Ulf Sommer	Mass spectrometry based environmental metabolomics: a primer and review	2012	[25]
Maria-Jose Motilva, Aida Serra, Alba Macia	Analysis of food polyphenols by ultra high-performance liquid chromatography coupled to mass spectrometry: an overview	2013	[26]
Nikalje Anna Pratima, Baheti Shraddha, Sayyad Zibran	Review of ultra performance liquid chromatography and its applications	2013	[27]
Maria Joao Gouveia, Paul J. Brindley, Lucio Lara Santos, Jose Manuel Correia da Costa, Paula Gomes, Nuno Vale	Mass spectrometry techniques in the survey of steroid metabolites as potential disease biomarkers: a review	2013	[28]
Muchena J. Kailemia, L. Renee Ruhaak, Carlito B. Lebrilla, and I. Jonathan Amster	Oligosaccharide analysis by mass spectrometry: a review of recent developments	2013	[29]
Linda Kortz, Juliane Dorow, Uta Ceglarek	Liquid chromatography–tandem mass spectrometry for the analysis of eicosanoids and related lipids in human biological matrices: a review	2014	[30]

Table 3 Bioanalytical/metabolite studies

UPLC (drug)	Column	Mobile phase system	Detector	Extraction method	Biological or/metabolite studies or pharmaceutical	Mode of analysis	Ref
Antibiotics agents							
Amoxicillin, Ampicillin, cefuroxime, cefazolin, ceftazidime, meropenem, piperacillin, clavulanic acid, and tazobactam	BEH C_{18}	Water (A) Acetonitrile (B) both containing 0.1% formic acid 5% solution (B) at 0.5 min to 55% at 4.0 min and column was rinsed with 95% solution (B) for 0.5 min and re-equilibrated to starting conditions for 1 min	Triple-quadrupole	PP	Biological	Gradient	[33]
Cefuroxime lysine	BEH C_{18}	Acetonitrile: 0.1% formic acid in 10 mM Ammonium Acetate (40:60, *v/v*).	Quadrupole	LLE	Biological	Isocratic	[34]
Clarithromycin	BEH C_{18}	(A) 50 mM ammonium Acetate solution and (B) Acetonitrile. 0.0 min 50 (A):50(B), 1.5 min 10(A): 90(B), 1.7 min 10(A): 90(B), 1.8 min 50(A):50(B), 2.0 min 50(A):50(B)	Triple-quadrupole mass spectrometer	LLE	Biological	Gradient	[35]
Indolinone derivative	HSS T_3 column	Water (A) and (B) acetonitrile, both containing 0.1% formic acid 0–0.5 min, (B) 2%;0.5–2 min, (B) 2–100%; 2–2.5 min, (B) 100%; 2.5–2.6 min, (B) 100–2%; 2.6–4 min, (B) 2%	Mass detector	PP	Biological	Gradient	[36]
Ertapenem	Agilent Zorbax Eclipse Plus C_{18}	Water : Acetonitrile (95:5% *v/v*) both containing 0.1 % formic Acid	Triple-quadrupole	LLE	Biological	Gradient	[37]
Amikacin, flucloxacillin, meropenem, penicillin G and vancomycin	RP_{18} column	Water (A) and methanol (B), both containing 4% of formic acid 0–0.3 min, 20% (B); 0.3–1.0 min, 50% (B); 1.0–2.0 min 50% (B); 2.0–2.7 min, 75% (B), 2.7–5.3 min, 75% (B) 5.3–5.5 min, 20% (B)	Triple-quadrupole mass spectrometer	PP	Biological	Gradient	[38]
Cephalomannine	BEH C_{18}	0.1% formic acid in water (A) and acetonitrile (B) 0–0.6 min, 20–85% (B); 0.6–1.8 min, 85% (B); 1.8–2.0 min, 80–30% (B)	Triple-quadrupole mass spectrometer	PP	Biological	Gradient	[39]
Tedizolid and linezolid	BEH C_{18}	(A) 0.1% formic acid in water and (B) Acetonitrile 0–0.3 min, 20–95% (B); 0.3–1.5 min, 95–95% (B); 1.5–1.6 min, 95–20% (B); 1.6–3.0 min, 20–20% (B)	Mass spectrometer	PP	Biological	Gradient	[40]
Anticancer agents							
Amrubicin	BEH C_{18}	(A) Acetonitrile: water, (1:99% *v/v*), 5 mM formic acid and (B) acetonitrile: water, (99:1% *v/v*), also containing 5 mM formic acid 0.00 min, 100(A) :0(B); 0.30 min, 0(A):100 (B); 0.70 min, 0(A):100 (B); 1.50 min, 100(A): 0(B)	Triple-quadrupole	SPE	Metabolite	Gradient	[41]

Table 3 Bioanalytical/metabolite studies *(Continued)*

UPLC (drug)	Column	Mobile phase system	Detector	Extraction method	Biological or/metabolite studies or pharmaceutical	Mode of analysis	Ref
Solasonine	HSS T_3 column	(A) 0.1% formic acid and (B) acetonitrile. 0–0.5 min, 15% (B); 0.5–3.5 min, 15–75% (B); 3.5–4.0 min, 75–85% (B); 4.0–5.0 min, 85% (B)	Triple-quadrupole mass spectrometer	PP	Biological	Gradient	[42]
Berberrubine	BEH C_{18}	(A) 0.1% formic acid and (B) acetonitrile. 1.5 min, 30–60% (B); within 0.5 min, 95% (B); then decreased to 30% (B) within in 0.1 min, then maintained 30% for 0.4 min	Triple-quadrupole mass spectrometer	LLE	Biological	Gradient	[43]
Pomalidomide	BEH C_{18}	Acetonitrile: 10 mM Ammonium Acetate (80:20% *v/v*)	Triple-quadrupole mass spectrometer	LLE	Biological	Isocratic	[44]
Docetaxel	BEH C_{18}	(A) Water containing 0.5% formic acid (pH 2.23) and (B) 0.5% formic acid in acetonitrile (pH 2.24). 0–0.9 min, 90% (A); 0.9–1.6 min, 100% (B); 1.6–1.7 min, 90% (A), 1.7–2.5 min, 90% (A)	Quadrupole	LLE	Biological	Gradient	[45]
Indolinone derivative	HSS T_3 column	Water (A) and (B) acetonitrile, both containing 0.1% formic acid. 0–0.5 min, 2% (B); 0.5–2 min, 2–100% (B); 2–2.5 min, 100% (B); 2.5–2.6 min, 100–2% (B); 2.6–4 min, 2% (B)	Mass detector	PP	Biological	Gradient	[36]
Lenalidomide	BEH C_{18}	Acetonitrile: water: formic acid (65:35: 0.1% *v/v/v*)	Triple-quadrupole mass spectrometer	PP	Biological	Isocratic	[46]
Paclitaxel	BEH C_{18}	Methanol–0.1% aqueous formic acid (75: 25% *v/v*)	Triple-quadrupole mass spectrometer	LLE	Biological	Isocratic	[47]
Irinotecan and 7-ethyl-10 hydroxy camptothecin (SN-38)	BEH C_{18}	(A) Ammonium acetate Buffer (10 mM; pH 3.5) with 0.1% formic acid and (B) acetonitrile. 0 min, 20% (B); 3 min, 20–70% (B), 0.2 min, 70–98% (B), 0.7 min 98% (B); 0.2 min, 98–20% (B)	Quadrupole	SPE	Biological	Gradient	[48]
Anticancer c-Met inhibitor LS-177	C_{18} column	(A) Acetonitrile and (B) 0.1% formic acid in water. 0 min, 20% (A); 1 min, 80% (A); 2 min, 80% (A); 2.5 min, 20% (A); 3 min, 20% (A)	Triple-quadrupole mass spectrometer	LLE	Biological	Gradient	[49]
TM-2	C_{18} column	(A) Acetonitrile and (B) 2 mmol/L ammonium acetate in water. 1.5 min, 60–90% (A); 2.8 min, 90% (A); 3.5 min, 90–60% (A)	Triple-quadrupole mass spectrometer	LLE	Biological	Gradient	[50]
Methotrexate polyglutamates	BEH C_{18}	(A) 10 mM Ammonium bicarbonate buffer With 5 mM of the desired ion-pair adjusted to pH 7.5 with formic acid and (B) acetonitrile. 1 min, 90% (A); 9 min, 70% (A): 30% (B)	Triple-quadrupole mass spectrometer	PP	Biological	Gradient	[51]

Table 3 Bioanalytical/metabolite studies *(Continued)*

UPLC (drug)	Column	Mobile phase system	Detector	Extraction method	Biological or/metabolite studies or pharmaceutical	Mode of analysis	Ref
Ciprofloxacin, cyclophosphamid, tamoxifen, and azathioprine	HSS T_3	(A) 0.1 % formic acid (A) and (B) acetonitrile. 0 min, 90% (A) and 5% (B); 10 min, 0% (A) and 100 % (B)	Triple-quadrupole mass spectrometer	SPE	Pharmaceutical	Gradient	[52]
Temozolomide	BEH C_{18}	(A) Water (containing 0.1% formic acid and 10 mM ammonium acetate) and (B) acetonitrile. 0 min, 20% (B); 2 min, 20–50% (B); 1 min, 50% (B); 1 min, 50–20% (B)	Quadrupole mass spectrometer	PP	Biological	Gradient	[53]
Dendrobine	BEH C_{18}	(A) 0.1% formic acid and (B) acetonitrile. 0–1.0 min, 20–40 (B); 2 min, 40–95% (B), 0.5 min, 95% (B); then decreased to 20% (B) within 0.1 min, maintained at 20% (B) for 0.4 min	Triple-quadrupole mass spectrometer	PP	Biological	Gradient	[54]
Simotinib	Zorbax SB-C_8 column	0.1 % formic Acid with 10 mM ammonium formate: methanol (20: 80% *v/v*)	Mass detector	LLE	Biological	Isocratic	[55]
Nintedanib	BEH C_{18}	(A) acetonitrile and (B) 0.1% formic acid in water 0–0.3 min, 20–95% (A); 0.3–2.0 min, 95–95% (A); 2.0–2.1 min, 95–20% (A); 2.1–3.0 min, 20–20% (A)	Triple-quadrupole mass spectrometer	PP	Metabolite	Gradient	[56]
Letrozole	C_{18} column	(A) Acetonitrile and 0.1% formic acid in water (B). 0 min, 20% (A): 80% (B); 0.3 min, 20% (A): 80% (B); 2 min, 95% (A): 5% (B); 2.5 min, 95% (A): 5% (B); 2.6 min, 20 % (A): 80% (B)	Triple-quadrupole mass spectrometer	PP	Biological	Gradient	[57]
Parthenolide	BEH C_{18}	(A) Acetonitrile and 0.1% formic acid in water (B). 0–0.3 min, 20–95% (B); 0.3–1.5 min, 95–95% (B), 1.5–1.6 min, 95–20% (B)	Triple-quadrupole mass spectrometer	SPE	Biological	Gradient	[58]
Tamoxifen	BEH C_{18}	(A) 10 mM Ammonium formate in water and acetonitrile (B) both are containing 0.1%formic acid 0.0 min, 70%(A): 30%(B); 9.0 min, 48% (A): 52%(B); 9.01 min, 48% (A): 52%(B); 9.50 min, 70% (A): 30%(B); 13 min 70% (A): 30%(B)	Triple-quadrupole mass spectrometer	PP	Metabolite	Gradient	[59]
Vincristine	HSS T_3 column	(A) Methanol and (B) water containing 0.2% formic acid. 3 min, 30–95% (A); and returned to initial condition within 1 min	Triple-quadrupole mass spectrometer	LLE	Biological	Gradient	[60]
Palonosetron	HSS T_3 column	Methanol : water containing 0.1% formic acid 80: 20% *v/v*	Triple-quadrupole	LLE	Biological	Isocratic	[61]

Table 3 Bioanalytical/metabolite studies *(Continued)*

UPLC (drug)	Column	Mobile phase system	Detector	Extraction method	Biological or/metabolite studies or pharmaceutical	Mode of analysis	Ref
Kurarinone	BEH C_{18}	(A) Acetonitrile and 0.1% formic acid in water (B) 0–0.3 min, 30–30% (A); 0.3–1.0 min, 30–90% (A); 1.0–2.0 min, 90–90% (A); 2.0–2.1 min, 90–30% (A); 2.1–3.0 min, 30–30% (A)	Triple-quadrupole	LLE	Biological	Gradient	[62]
Antiviral agents							
Elbasvir	BEH C_{18}	(A) Acetonitrile and water (containing 5.0 mM ammonium acetate with 0.01% acetic acid, pH 4.5) (B) 0.0–0.5 min, 90–90% (A) 0.5–1.2 min, 90–5% (A); 1.2–2.0 min, 5–5% (A); 2.0–2.2 min, 5–90% (A); 2.2–3.0 min, 90–90% (A)	Triple-quadrupole	PP	Biological	Gradient	[63]
Daclatasvir	HSS C_{18}	10 mM Ammonium formate, pH 3.5 and acetonitrile (50:50% *v/v*)	Quadrupole	LLE	Biological	Isocratic	[64]
Ribavirin, sofosbuvir	BEH C_{18}	(A) Acetonitrile and 0.1% formic acid in water (B) 0–0.5 min, 10–10% (A); 0.5–1.0 min, 10–95% (A); 1.0–2.0 min, 95–95% (A); 2.0–2.1 min, 95–10% (A); 2.1–3.0 min, 10–10% (A)	Triple-quadrupole mass spectrometer	PP	Metabolite	Gradient	[65]
Atazanavir, Darunavir and Ritonavir	C_{18} column	(A) 10 mM Ammonium Formate, pH 4.0, adjusted with formic acid in water, and acetonitrile (B). 0.0–0.8 min, 50%(A) and 50%(B); 0.8–1.2 min, 30%(A) and 70%(B)	Mass detector	PP	Biological	Gradient	[66]
Oleanolic acid	C_{18} column	10 mM Ammonium Acetate with 0.1% formic acid in water: acetonitrile (10: 90% *v/v*)	Triple-quadrupole mass spectrometer	SPE	Biological	Isocratic	[67]
Antifungal agent							
Tizoxanide	BEH C_{18}	Aq. ammonium formate buffer 10 mM, adjusted to pH 3.0 with formic acid, and acetonitrile (40: 60% *v/v*)	Mass detector	LLE	Biological	Isocratic	[68]
Voriconazole	BEH C_{18}	Acetonitrile and water containing 1% formic acid (45: 55% *v/v*)	Triple-quadrupole mass spectrometer	LLE	Biological	Isocratic	[69]
Amphotericin B	BEH Shield RP_{18} column	(A) Methanol: acetonitrile (50 : 50% *v/v*) containing 0.1% formic acid; and (B) 10 mM ammonium formate (pH 3 ± 0.2), containing 0.2% formic acid and 1% acetonitrile 0.0–2.0 min, 35–90% (A); 2.0–2.7 min, 90–35% (A)	Triple-quadrupole mass spectrometer	SPE	Biological	Gradient	[70]

Table 3 Bioanalytical/metabolite studies *(Continued)*

UPLC (drug)	Column	Mobile phase system	Detector	Extraction method	Biological or/metabolite studies or pharmaceutical	Mode of analysis	Ref
Fluconazole, Itraconazole, Hydroxyitraconazole, Posaconazole, Voriconazole	C_{18} column	(A) 10 mM Ammonium formate in ultrapure water with 0.1% formic acid and acetonitrile with 0.1% formic acid (B)	Triple-quadrupole mass spectrometer	PP	Biological	Isocratic	[71]
Posaconazole	BEH C_{18}	(A) 10 mM Ammonium formate in water containing 0.1% formic acid, (B) 1% acetic acid in methanol, and (C) 1% acetic Acid in acetonitrile. 0–0.9 min, 90% (A) and 10% (B); 0.9–1.9 min, 5% (A) and 95% (B); 1.9–2 min, 100% (B); 2–3.6 min. 100% (C); 3.6–3.7 min, 90% (A) and 10% (B); 3.7–5.0 min, 90% (A) and 10% (B)	Triple-quadrupole mass spectrometer	PP	Biological	Gradient	[72]
Cardiovascular agents							
Atorvastatin, Ezetimibe	BEH C_{18}	(A) 0.1% Formic acid in water : (B) acetonitrile (95: 5% *v/v*) 0.0–0.4 min, 95% (A) and 5%(B); 0.4–1.1 min 10 %(A) and 90% (B); 1.1 min, 95% (A) and 5% (B)	Triple-quadrupole	LLE	Biological	Gradient	[73]
4-hydroxyphenyl carvedilol	BEH C_{18}	Acetonitrile- 4.0 mM ammonium formate, pH 3.0 adjusted with 0.1% formic acid (78: 22% *v/v*)	Triple-quadrupole mass spectrometer	SPE	Metabolite	Isocratic	[74]
Ivabradine, Reboxetine, Metoprolol	BEH C_{18}	(A) Water and (B) methanol, both containing 2 mM ammonium acetate.0.0–0.5 min, 20% (B); 0.5–3.0 min, 20–90% (B); 3.0–3.5 min, 90% (B) 3.5–4.5 min, 20% (B)	Quadrupole mass spectrometer	LLE	Biological	Gradient	[75]
Meldonium	BEH HILIC column	Water: acetonitrile: formic acid (adjusted to pH 3.0 with 12.5% ammonia hydroxide) (25: 70: 5% *v/v/v*)	Triple-quadrupole mass spectrometer	PP	Biological	Isocratic	[76]
Candesartan, Hydrochlorthiazide	C_{18} Phenomenex	Methanol : Acetonitrile 1 (15: 85% *v/v*)	Triple-quadrupole mass spectrometer	LLE	Biological	Isocratic	[77]
Doxazosine	BEH C_{18}	(A) and (B) consisted of 0.05 (*w/v*) pentadecafluorooctanoic acid in acetonitrile and 0.05 (*w/v*) pentadecafluorooctanoic acid in water. 1.0–1.45 min, 10–99% (A); 1.45–1.55 min, 99–10% (A); 1.55–2.0 min, 10% (A)	Triple-quadrupole mass spectrometer	LLE	Biological	Gradient	[78]
Lercanidipine	BEH C_{18}	70% Acetonitrile in water containing 0.2% *v/v* formic acid	Triple-quadrupole mass spectrometer	LLE	Biological	Isocratic	[79]
Aliskiren Hemifumarate, Amlodipine Besylate and Hydrochlorothiazide	BEH C_{18}	0.1% Formic acid in ammonium acetate buffer (0.02 M, pH 3.5) and Methanol (25: 75% *v/v*)	Triple-quadrupole mass spectrometer	LLE	Biological	Isocratic	[80]

Table 3 Bioanalytical/metabolite studies *(Continued)*

UPLC (drug)	Column	Mobile phase system	Detector	Extraction method	Biological or/metabolite studies or pharmaceutical	Mode of analysis	Ref
Irbesartan	BEH C_{18}	Acetonitrile: Methanol: 10 mM Ammonium acetate (70:15: 15% *v/v/v*)	Triple-quadrupole	SPE	Biological	Isocratic	[81]
Amlodipine, benazeprile and benazeprilat	BEH C_{18}	(A) 0.1% Formic acid and Acetonitrile (B) 0–0.2 min, 95% (A) and 5% (B); 0.2–0.3 min, 0%(A) and 100%(B); 0.3–2.0 min, 0%(A) and 100%(B); 2.0–2.5 min, 95% (A) and 5% (B), 2.5 min, 95% (A) and 5% (B)	Triple-quadrupole mass spectrometer	LLE	Biological	Gradient	[82]
Candesartan	Betasil C_8 column	Methanol : ammonium tri-floro acet ate buffer with formic acid (60: 40% *v/v*)	Mass detector	PP	Biological	Isocratic	[83]
N-butylscopolamine	C_{18} column	Acetonitrile: 5 mM ammonium acetate: 0.1% formic acid (90: 10% *v/v*)	Triple-quadrupole mass spectrometer	SPE	Biological	Isocratic	[84]
Udenafil	BEH C_{18}	Acetonitrile: 0.1% formic acid (75: 25% *v/v*)	Quadrupole mass spectrometer	LLE	Metabolite	Isocratic	[85]
Alprostadil	BEH C_{18}	(A) Acetonitrile and water (B), containing 0.1% formic acid 0.0–0.6 min, 30% (A); 0.6–0.8 min, 60% (A); 1.4 min, 30% (A)	Quadrupole mass Spectrometer	LLE	Biological	Gradient	[86]
Analgesic agents							
Sumatriptan	Hypersil gold C_{18}	Methanol:water (90:10% *v/v*)	Mass detector	PP	Biological	Isocratic	[87]
Sufentanil	BEH C_{18}	Acetonitrile : water (4:55% *v/v*)	Triple-quadrupole mass spectrometer	SPE	Biological	Isocratic	[88]
Mitragynine	BEH HILIC column	10 mM Ammonium formate buffer containing 0.1% formic acid: acetonitrile (15:85% *v/v*)	Quadrupole	LLE	Biological	Isocratic	[89]
Tapentadol and tapentadol-O-glucuronide	BEH C_{18}	0.01 M Ammonium formate (adjusted to pH 4 using formic acid) (A) and methanol (B). For Tapentadol-0.00 min, 80% (A):20%(B); 0.85 min, 65%(A):35%(B); 0.90 min, 2%(A):98% (B); 1.25 min, 2%(A):98% (B); 1.30 min, 80% (A): 20%(B); 1.60 min, 80% (A): 20%(B) Tapentadol-O-glucuronide-0.0 min, 80% (A): 20%(B); 0.50 min, 70% (A): 30%(B); 0.55 min, 2% (A): 98%(B); 1.05 min, 2% (A): 98%(B); 1.10 min, 80% (A): 20%(B); 1.50 min, 80% (A): 20%(B)	Triple-quadrupole mass spectrometer	SPE	Biological	Gradient	[90]
Dexmedetomidine	BEH C_{18}	0.1% Formic acid in water (A) and 0.1% formic acid in acetonitrile (B). 0 min, 25%(B); 3.0 min, 25%(B); 3.1 min, 95%(B); 5.0 min, 95%(B); 8.0 min, 2%(B)	Triple-quadrupole mass spectrometer	SPE	Biological	Gradient	[91]

Table 3 Bioanalytical/metabolite studies *(Continued)*

UPLC (drug)	Column	Mobile phase system	Detector	Extraction method	Biological or/metabolite studies or pharmaceutical	Mode of analysis	Ref
Nalbuphine	BEH HILIC column	Acetonitrile : water (83:17% *v/v*) that contained 0.2% formic acid and 4 mM ammonium formate	Triple quadrupole mass spectrometer	LLE	Biological	Isocratic	[92]
Buprenorphine and norbuprenorphine	BEH C_{18}	Ammonium formate buffer 20 mM adjusted to pH 3.05 with formic acid (A) and acetonitrile (B) (90:10% *v/v*) 0.0 min, 10 % (B); 2.5 min, 25% (B); 3.2 min, 25% (B); 5.0 min. 30% (B)	Quadrupole mass spectrometer	PP	Biological	Gradient	[93]
Anti-steroid							
Testosterone and 5-dihydrotestosterone	BEH C_{18}	(A) Water, (B) consisted of 2 mM ammonium acetate (native pH) in acetonitrile: water (98:2% *v/v*) 0.1 min, 0% (B); 1.0 min, 30% (B); 2.0 min, 32% (B); 3.4 min, 32% (B)	Triple-quadrupole	LLE	Biological	Gradient	[94]
Triamcinolone acetonide palmitate and triamcinolone acetonide	Phenomenex Luna C_{18} column	(A) Acetonitrile and (B) 0.1% ammonia solution. 0–1.3 min, 34% (A); 1.3–1.5 min, 34–95%(A); 1.5–5.0 min, 95% (A); 5.0–5.2 min, 95–34% (A); 5.2–5.5 min, 34% (A)	Triple-quadrupole mass spectrometer	LLE	Biological	Gradient	[95]
Anti-inflammatory (NSAID)							
Hesperetin	Chiralpak IA-3	(A) Water with 0.1% CHOOH and (B) acetonitrile with 0.1% CHOOH. 0 min, 33% (B); 0.5 min 33% (B); 5 min 40% (B); 5.1 min, 100% (B); 6 min, 100% (B); 6.1 min 33% (B); 8 min 33% (B)	Triple-quadrupole	SPE	Biological	Gradient	[96]
Epiafzelechin a flavan-3-ol with osteoprotective	BEH C_{18}	Water (A) and acetonitrile (B) both containing (0.1% Formic Acid *v/v*) 1–11 min, 0–70% (B); 0–1 min, 100 % (A); 11–16 min, 100% (A)	Triple-quadrupole mass spectrometer	LLE	Biological	Gradient	[97]
E6005, Phosphodiesterase 4 inhibitor	BEH C_{18}	(A) Water: acetonitrile: 1 mol/L ammonium formate (950:50: 5% *v/v/v*) and (B) water: acetonitrile: 1 mol/L ammonium formate (100:900: 5% *v/v/v*). Gradient-2.0 min, 5–95% (B); Isocratic- 2.0 min, 95% (B); 1.5 min, 5% (B)	Triple-quadrupole mass spectrometer	SPE	Metabolite	Gradient/ Isocratic	[98]
Naringin	BEH C_{18}	Acetonitrile-0.4% acetic acid (80: 20% *v/v*)	Triple-quadrupole mass spectrometer	LLE	Biological	Isocratic	[99]
Ibuprofen	BEH C_{18}	Water: methanol (35:65% *v/v*) both containing 10 mM ammonium acetate and 0.1% formic acid. 0–12 min, 35% (A) and 65% (B); 12.01–14 min 100% (B); 15.1 min, 35% (A) and 65% (B)	Triple-quadrupole mass spectrometer	LLE	Biological	Gradient	[100]

Table 3 Bioanalytical/metabolite studies *(Continued)*

UPLC (drug)	Column	Mobile phase system	Detector	Extraction method	Biological or/metabolite studies or pharmaceutical	Mode of analysis	Ref
Avicularin	BEH C_{18}	0.1% Formic acid in water (A) and (B) acetonitrile. 0–0.50 min, 30–80% (B); 0.50–1.40 min, 80 % (B); 1.40–1.60 min, 80–30% (B)	Triple-quadrupole mass spectrometer	PP	Biological	Gradient	[101]
Hupehenine	BEH C_{18}	0.1% Formic acid (A) and Acetonitrile (B) 0.0–2.0 min, 40–90 % (B); maintained for 0.5 min, 90%(B); 90–40% (B) within 0.1 min and then maintained 0.4 min, for 40% (B)	Triple-quadrupole mass spectrometer	LLE	Biological	Gradient	[102]
Picfeltarraenins IA and IB	C_{18} column	Methanol:water (70 : 30% *v/v*)	Mass detector	PP	Biological	Isocratic	[103]
Diclofenac sodium	BEH C_{18}	Acetonitrile–0.1% ammonium hydroxide aqueous solution (20:80% *v/v*). 0.0 min, 20% (A); 0.6–1.5 min, 50% (A); 1.6–2.0 min, 20% (A)	Triple-quadrupole mass spectrometer	LLE	Biological	Gradient	[104]
21-hydroxy deflazacort	BEH C_{18}	Acetonitrile and 4.0 mM ammonium formate, pH 3.5 (90:10% *v/v*)	Triple-quadrupole mass spectrometer	SPE	Biological	Isocratic	[105]
Acetaminophen and dihydrocodeine	BEH C_{18}	(A) 0.1% formic acid in water and (B) Acetonitrile 0–0.3 min, 50–95% (B); 0.3–0.9 min, 95–95% (B); 0.9–1.0 min, 95–50% (B)	Triple-quadrupole mass spectrometer	PP	Biological	Gradient	[106]
Anti-diabetes							
Glipizide	BEH C_{18}	(A) Acetonitrile and water containing 1% formic acid (B). 0.0 min, 30 % (A): 70%(B); 0.3 min, 75% (A)25% (B); 0.7 min, 75% (A) 25% (B); 1.0 min, 30% (A): 70% (B)	Triple-quadrupole mass spectrometer	SPE	Biological	Gradient	[107]
Lysophosphatidylcholine	BEH C_{18}	(A) 0.1% Formic acid in water, (B) 0.1% formic acid in acetonitrile. 0 min, 100% (A); 37 min, 100% (B)	Mass detector	PP	Metabolite	Gradient	[108]
Miglitol	C_{18} inertsil column	Acetonitrile and 2 mM Ammonium Acetate (pH 3.5, 80: 20% *v/v*)	Triple-quadrupole mass spectrometer	LLE	Biological	Isocratic	[109]
Exenatide	C_{18} column	0.2% Formic acid (A) and methanol (B) 1.5 min, 10% (B); 1.0 min, 10–90% (B); 0.5 min, 90% (B) a linear decrease from 90–10% (B) in 0.1 min	Mass detector	SPE	Biological	Gradient	[110]
Anti-depressant							
Vortioxetine	BEH C_{18}	0.1% Formic acid in water (A) and acetonitrile (B). 0–0.5 min, 20–95% (A); 0.5–1.9 min, 95–95% (A); 1.9–2.0 min, 95–20% (A); 2.0–3.0 min, 20–	Triple-quadrupole mass spectrometer	PP	Biological	Gradient	[111]

Table 3 Bioanalytical/metabolite studies *(Continued)*

UPLC (drug)	Column	Mobile phase system	Detector	Extraction method	Biological or/metabolite studies or pharmaceutical	Mode of analysis	Ref
		20% (A)					
Bupropion	BEH Phenyl column	(A) Ammonium formate buffer (2 mM, pH 4.0) and (B) acetonitrile. 3.5 min, 95% (A); 4.2 min, 70% (A); 4.7 min, 68.5% (A); 4.8 min, 5% (A) 5.7 min, 95% (A)	Triple-quadrupole mass spectrometer	SPE	Metabolite	Gradient	[112]
Venlafaxine and O-desmethylvenlafaxine	BEH C_{18}	10 mmol/L Ammonium acetate and methanol (85: 15% *v/v*)	Triple-quadrupole	SPE	Biological	Isocratic	[113]
Paroxetine	Hypersil Gold C_{18} column	Acetonitrile and 0.1% Glacial acetic acid (50: 50% *v/v*)	Triple-quadrupole mass spectrometer	LLE	Biological	Isocratic	[114]
Antiepileptic agents							
Carbamazepine, carbamazepine-10, 11-epoxide, gabapentin, lamotrigine, levetiracetam	BEH Phenyl column	5 mM Ammonium bicarbonate buffer pH 7.9 (A) and methanol (B) 0.00 min, 97.5% (A): 2.5%(B); 1.00 min, 95.0% (A): 5.0% (B); 2.00 min, 0.0% (A): 30.0% (B); 3.60 min, 50.0% (A): 50.0% (B); 4.00 min, 50.0% (A): 50.0% (B); 4.30 min, 20.0% (A): 80.0% (B); 4.75 min, 20.0% (A) 80.0% (B); 4.85 min, 97.5% (A): 2.5% (B)	Triple-quadrupole mass spectrometer	PP	Biological	Gradient	[115]
Haloperidol, olanzapine, quetiapine, fluoxetine, paroxetine, bromazepam, lorazepam, risperidone and benzodiazepines	HSS T_3	Acetonitrile (A) and 0.1% formic acid in water (B) 0–1 min, 75% (B); 1–6 min, 75–40%(B); 6 min, 75% (B)	Triple-quadrupole mass spectrometer	SPE	Biological	Gradient	[116]
Oxcarbazepine	BEH C_{18}	Acetonitrile–10 mM ammonium acetate (85:15% *v/v*)	Triple-quadrupole mass spectrometer	SPE	Biological	Isocratic	[117]
Benzodiazepine 21	BEH C_{18}	0.1% Formic acid in water (A) and 0.1% formic acid in Methanol (B). 70% A–30% B, ramping to 65% B over 2.5 min, 70% B over 0.75 min, 77% B over 0.75 min, then to 95% B over 0.05 min and holding at 95% B for 1 min, returning to 30% B and re-equilibrating for 2 min	Mass detector	LLE	Biological	Gradient	[118]
Aripiprazole	Agilent Eclipse Plus C_{18}	(A) 0.1% Formic acid aqueous and (B) acetonitrile. 0–1.2 min, 10–40% (B); 1.2–1.6 min, 40–100% (B); 1.6–1.9 min, 100% (B); 1.91–2.0 min, 10% (B)	Mass detector	SPE	Biological	Gradient	[119]
CNS							
Levodopa, Carbidopa	BEH C_{18}	(A) 5 mM Ammonium formate/ formic acid at 1000/1 (*v/v*) and (B)	Triple-quadrupole and electro chemical	PP	Biological	Gradient	[120]

Table 3 Bioanalytical/metabolite studies *(Continued)*

UPLC (drug)	Column	Mobile phase system	Detector	Extraction method	Biological or/metabolite studies or pharmaceutical	Mode of analysis	Ref
		acetone. 0.2 min, 25% (B); 0.2–1.8 min, 25–50% (B); 90% (B) for 0.9 min					
Acetylcholine, histamine (HA)	BEH HILIC column	(A) 0.2% Formic acid and 20 mM ammonium formate in Water (B) acetonitrile. 0 min, 90% (B); 0–1.25 min, 10–70% (B)	Triple-quadrupole mass spectrometer	PP	Metabolite	Gradient	[121]
Proton pump inhibitor							
Esomeprazole, Rabeprazole and Levosulpiride	Hypersil gold C_{18}	(A) 2 mM Ammonium formate in water and (B) acetonitrile. 0.01 min, 10% (B); 0.20 min, 10% (B); 0.50 min, 90% (B); 0.70 min, 90% (B); 0.80 min, 10% (B); 1.00 min, 10% (B)	Triple-quadrupole mass spectrometer	LLE	Biological	Gradient	[122]
Anti-tubercular							
Ethambutol, isoniazid and rifampicin	HSS T_3	Water: methanol (50: 50% *v/v*)	Quadrupole	PP	Biological	Isocratic	[123]
Vitamin							
Thiamin, riboflavin, Flavin, adenine dinucleotide, nicotinamide, and pyridoxal	HSS T_3	10 mM Ammonium formate (A) and acetonitrile (B). 0 min, 95% (A); 1 min, 65% (A); 2 min, 45% (A); 2.1–3 min, 5% (A), 3.1–4 min, 95% (A)	Mass detector	LLE	Biological	Gradient	[124]
Uracil and dihydrouracil	HSS T_3 column	(A) 0.1% (*v/v*) Formic acid in UPLC-grade water and (B) 0.1% (*v/v*) formic acid in UPLC-grade acetonitrile. 0–.0 min, 0% (B); 3.0–3.2 min, 0–90% (B); 3.2–3.7 min, 90% (B); 3.7–5 min, 0% (B)	Triple-quadrupole mass spectrometer	LLE	Biological	Gradient	[125]
Immunosuppressant							
Tacrolimus	BEH C_{18}	10 mM Ammonium acetate, pH 6.00, adjusted with Formic acid and methanol (5:95% *v/v*)	Triple quadrupole mass spectrometer	SPE	Biological	Isocratic	[126]
Typhaneoside and Isorhamnetin-3-O-Neohesperidoside	BEH C_{18}	(A) Acetonitrile and water (containing 0.1% formic acid) (B) 0 min, 80% (A); 1.7 min, 68% (A); 3.2 min 30% (A); 4.0 min, 20% (A)	Mass detector	Pollen typhae extract	Biological	Gradient	[127]
Mycophenolic acid	BEH C_{18}	Acetonitrile and 10 mM Ammonium formate, pH 3.0 (75:25% *v/v*)	Mass detector	PP	Biological	Isocratic	[128]
Anticoagulant							
Warfarin	BEH C_{18}	(A) 0.2% Formic acid and 1% acetonitrile in water; and (B) 0.2% formic acid in acetonitrile. 80–70% (A) in 1.5 min and then changed linearly to 35% A for another 1.5 min, and remained	Mass detector	PP	Biological	Gradient	[129]

Table 3 Bioanalytical/metabolite studies *(Continued)*

UPLC (drug)	Column	Mobile phase system	Detector	Extraction method	Biological or/metabolite studies or pharmaceutical	Mode of analysis	Ref
		for a further 0.8 min before changing back to 80% (A)					
Clopidogrel	BEH C_{18}	Acetonitrile and water containing 0.15% formic acid (75: 25% *v/v*)	Triple-quadrupole mass spectrometer	LLE	Biological	Isocratic	[130]
Expectorant							
Hupehenine	BEH C_{18}	(A) 0.1% Formic acid and acetonitrile (B). 0–2.0 min, 40–90% (B); maintained for 90% (B) for 0.5 min, then decreased to 40% within 0.1 min, then maintained at 40% for 0.4 min	Triple-quadrupole mass spectrometer	LLE	Biological	Gradient	[102]
Multicomponent analysis of drug							
Gestodene, Ethinyl estradiol	BEH C_{18}	Water (A) and acetonitrile (B) (both containing 0.1% formic acid). 1.5 min, 70% (B); 70–98% (B) within 1.1 min and returned to 70% (B)	Quadrupole	LLE	Biological	Gradient	[131]
Liensinine, Isoliensinine, and Neferine	BEH C_{18}	(A) Water with 0.1 formic acid and acetonitrile (B). 0–1.0 min, 15–90% (B); 1.0–1.8 min, 90% (B); 1.8–2.0 min, 90–15% (B)	Triple-quadrupole mass spectrometer	PP	Biological	Gradient	[132]
Pinaverium Bromide	BEH C_{18}	Acetonitrile: 5 mM ammonium formate (80:20% *v/v*)	Triple-quadrupole mass spectrometer	PP	Biological	Isocratic	[133]
Pimpinellin, Isopimpinellin and Phellopterin	BEH C_{18}	Methanol: ammonium acetate (65:35% *v/v*)	Triple-quadrupole mass spectrometer	LLE	Biological	Isocratic	[134]
Endocannabinoids 2-arachidonoyl glycerol (2AG), 1-arachidonoyl glycerol (1AG), and anandamide	BEH C_{18}	(A) Water contained 2 mM ammonium acetate and (B) methanol and contained 2 mM ammonium acetate. 0.0–0.5 min, 75% (B); 0.5–5.0 min, 79% (B); 5.0–5.5 min, 90% (B); 5.5–6.5 min, 75% (B)	Tandem mass spectrometry	PP	Biological	Gradient	[135]
Paeoniflorin, albiflorin, ferulic acid, tetrahydropalmatine, protopine, typhaneoside, senkyunolide I	BEH C_{18}	(A) 0.1% Formic acid and (B) acetonitrile. 0–1 min, 5–10% (B); 1–6 min, 10–30% (B); 6–7 min, 30–40% (B); 7–8 min, 40–95% (B); 8–10 min, 95–5% (B)	Triple-quadrupole mass spectrometer	PP	Biological	Gradient	[136]
Caffeine, Tolbutamide, Metoprolol, Dapsone	BEH HILIC C_{18}	Acetonitrile: water containing 0.1% formic acid (15:85% *v/v*)	Triple-quadrupole mass spectrometer	LLE	Biological	Isocrati	[137]
Xylazine, Free Morphine, Codeine, 6 Acetylmorphine, Cocaine, Benzoylecgonine in Postmortem	HSS T_3	0.1% Formic acid in water (A) and acetonitrile (B). 0 min, 90% (A): 10% (B); 0.48 min, 90% (A): 10% (B); 0.50 min, 100% (A): 0% (B); 0.60 min, 85% (A): 15% (B); 2.0 min, 66% (A): 34% (B); 2.10 min, 5%	Triple-quadrupole mass spectrometer	SPE	Biological	Gradient	[138]

Table 3 Bioanalytical/metabolite studies *(Continued)*

UPLC (drug)	Column	Mobile phase system	Detector	Extraction method	Biological or/metabolite studies or pharmaceutical	Mode of analysis	Ref
		(A): 95% (B); 2.25 min, 90% (A): 10% (B); 2.50 min, 90% (A): 10%(B)					
Bupropion, metroprolol, midazolam, phenacetin, omeprazole and tolbutamide	BEH C_{18}	Acetonitrile (A) and water (B) (containing 0.1% formic acid) 0.3-1.8 min, 30-60% (A); increasing to 95% over 0.2-0.5 min, then decreased to 30% within 0.1 min, and maintained at 30% for 0.4 min.	Triple-quadrupole mass spectrometer	PP	Biological	Gradient	[139]
Ketoconazole and Voriconazole on the Pharmacokinetics of Oxcarbazepine	BEH C_{18}	Acetonitrile (A) and water (B) (containing 0.1% formic acid) 0–1 min, 20–80% (A); 1–1.5 min, 80–80% (A), 1.5–2 min 80–95% (A); 2–2.5 min, 95–95% (A); 2.5–2.6 min, 95–20% (A)	Triple-quadrupole mass Spectrometer	PP	Metabolite	Gradient	[140]
Neochlorogenic acid, chlorogenic acid, cryptochlorogenic acid, and geniposide	BEH C_{18}	0.2% Acetic acid and methanol. 0–4.50 min, 15–30% (B); 4.50–5.50 min, 30–65% (B); 5.50–6.00 min, 65–15% (B); 6.00–7.50 min, 15–15% (B)	Triple-quadrupole mass Spectrometer	PP	Biological	Gradient	[141]
Evodiamine and Rutaecarpine	BEH C_{18}	Acetonitrile (A) and water (B) both containing 0.2% Formic acid. 0 min, 40% (A): 60% (B); 0–0.6 min, 70% (A): 30% (B); 0.6–1.0 min, 70% (A): 30% (B); then returned to 40% (A):/60% (B)	Triple-quadrupole mass Spectrometer	LLE	Biological	Gradient	[142]
Bosentan and glimepiride	BEH C_{18}	(A) 0.1% Formic acid in water and (B) acetonitrile. 0–0.5 min, 35% (B); 0.5–1.0 min, 35–80% (B); 1.0–1.5 min, 80–35% (B)	Triple-quadrupole	PP	Biological	Gradient	[143]
Amoxicillin and prednisolone	BEH C_{18}	0.1% Formic acid in water (A) and 0.1% formic acid in acetonitrile (B). 0–1 min, 98% (A); 1–1.5 min, 98–15% (A); 1.5–2.5 min, 15% (A); 2.5–3.0 min, 15–2% (A); 3.0–3.5 min, 2–98% (A); 3.5–5.5 min, 98% (A)	Triple-quadrupole mass Spectrometer	SPE	Biological	Gradient	[144]
Fenofibric acid and berberine	Eclipse XDB C_{18} column	(A) Acetonitrile and (B) water (containing 0.1% formic acid). 0.0 min, 30 % (A): 70% (B); 0.3 min, 30% (A): 70% (B); 0.5 min, 50% (A): 50% (B); 1.0 min, 90% (A): 10% (B); 2.5 min, 90% (A): 10% (B); 2.6 min, 30% (A): 70% (B); 3.0 min, 30% (A): 70% (B)	Triple-quadrupole mass Spectrometer	LLE	Biological	Gradient	[145]

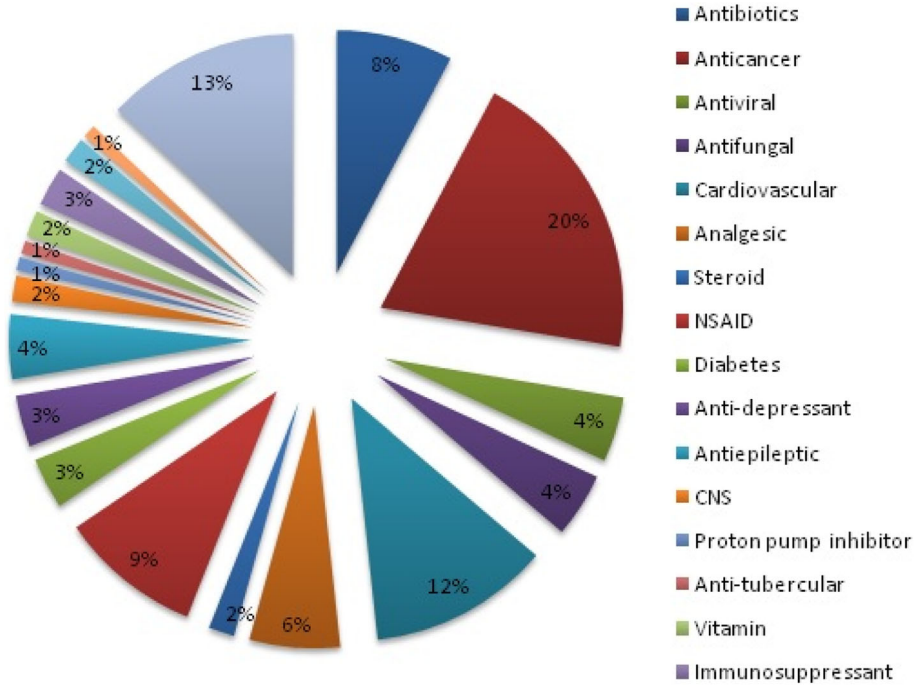

Fig. 2 Analysis of different classes of drugs using UHPLC-MS/MS in between 2006-2017

Table 4 Stability-indicating method UHPLC-MS/MS

Drug	Acid degradation	Base degradation	Photo-degradation	Oxidative degra.	Detection	Ref
Conditions	0.1 to 1 N	0.1 to 2 M	Light	H_2O_2 and KMnO4	–	–
Fluticasone Propionate	7 days	(50 °C) 24 h	–	–	Thioester, Carboxylic ester, alcohol, ketone, diol	[147]
Duloxetine	(50 °C) 24 h	7 days	–	–	Ether,1-naphthol	
Amlodipine	24 h	24 h	–	–	1,4-dihydropyridine ring	
Moxonidine	(0.5 M) HCl 80 min	2 M NaOH at 70 °C for 15 min	7 days at 80 °C	H_2O_2 5 h	Impurity-A and impurity-D	[148]
Rivaroxaban	(60 °C) 6–24 h	(60 °C) 1–6 h	2–5 h (254 nm)	–	Morpholinone moiety, oxazolidinone ring, chlorothiophene carbonyl.	[149]
Ciprofloxacin,Moxifloxacin, Norfloxacin, Ofloxacin	–	–	105–113 day	–	CP-1 - CP-6 and OP-1 - OP-6, NP-1 - NP-5 MP-1 and MP-10	[150]
Hexazinone	–	–	Degussa P25 and the nano-TiO_2. 40 min complete degradation	–	Methylamine, triazinone, urea, carbon dioxide.	[151]
Ciprofloxacin, Difloxacin, Lomefloxacin, Norfloxacin, and Ofloxacin	–	–	–	$KMnO_4$ in acidic pH (3–6)	N-1 and N-4 piperazine atoms and 3- monohydroxylated products 3-hydroxy-5-oxo derivatives	[152]
Ampicillin	(60 °C) 4 h	(60 °C) for 4 h	–	–	2-(acetamidomethyl)-5,5-dimethylthiazolidine-4-carboxylate 1, 1-dioxide	[153]

Table 5 Impurity profile of drug using UHPLC-MS/MS

Sr. no	Drug(s)	Detection wavelength	Name of impurity/number of impurities detected	References
1	Finasteride	210 nm	4	[154]
2	Famotidine	265 nm	Imines	[155]
3	Desloratadine	280 nm	5	[156]
4	Sitagliptin, vildagliptin, and metformin	210 nm	2	[157]
5	Heroin	–	Acidic and neutral impurity	[158]
6	Dabigatran Etexilate	220 nm	3	[159]
7	Zolmitriptan	–	4	[160]
8	Smokeless powder	210 nm	Nitroglycerin (NG), 2,4-dinitrotoluene (2,4-DNT), and 2,6-dinitrotoluene (2,6-DNT)	[161]
9	Ritonavir	240 nm	13	[162]
10	25-OCH_3-PPD	495 nm	3	[163]

reducing the retention of non-basic analytes due to the low ligand density and ionic repulsion [10].

Peptide separation technology

The separation or isolation of different peptides, the peptide-based peptide separation technology columns, was utilized for analysis of peptides. Developed peptide separation technology (PST) columns are C_{18} BEH Technology, in PST column particles sizes in the variety of 1.7 μm to 10 μm and the column dimension ranges from 75 μm to 30 mm internal diameter and column length from 50 to 250 mm. The PST columns demonstrate sharp-edged symmetrical peaks [7].

UHPLC, superior technique than HPLC

The UHPLC system is superior to HPLC system because the UHPLC system operates at high pressure up to 1000 bar or more than that, but a conventional HPLC system, compass a pressure up to 400 bars and it suffers problems like mobile phase swallowing and increases the time of analysis. But in UHPLC system, less solvent consumption and less time for analysis are required [13]. This could unlikely outstanding use of slighter particles less than 2.0 mm and also at tolerable flow up to 5 mL/min. The use of the lesser particle size shows better resolution of peaks, perform faster analysis, sharper, and higher peaks [14].

UHPLC-MS/MS detection

To detect and find out the amount of analyte, the mass spectrometry (MS) was widely used because of its selectively (Watson and Sparkman 2007; Chiu and Muddiman 2008). UHPLC-MS/MS method detection is considered as a method of choice for estimation of drugs in bulk and pharmaceutical formulations and their metabolites in biological fluids. In literature, there are several methods reported for analysis of drugs using UHPLC-MS/MS. In all ionization techniques, electrospray ionization (ESI) and atmospheric chemical ionization (APCI) ion source were extensively used [15]. Among all kinds of mass analyzers *viz* quadrupole, ion trap, and time of flight, the triple quadrupole was the most preferred one. The several mobile phases were used in UHPLC-MS/MS that includes many solvents such as water, ACN or MeOH, acetic acid, 0.1% formic acid, ammonium hydroxide/ammonia solution, and ammonium acetate (10 mM).

Mass spectrophotometer prominently consists of an ion source to construct gas phase ions and mass analyzers to separate these ions according to their mass to charge ratio; further, a detector to count the ions for every m/z ratios. The PC will change over the information from the analyzer and detector to a mass spectrum [16, 17]. The choice of detector is based on the necessary detection sensitivity and it is additionally controlled by other clear necessity; for example, the thermal, chemical, and required stability and the amount of space available. Ideal properties for detectors are high intensification, fast time analysis, low noise, high collection efficiency, minimal effort, narrow distribution of responses, and long life [18]. The MS-MS detectors are more advantageous over the other detectors with respective to the higher sensitivity to detect very small quantity, high selectivity to notify molecules apart in a mixture, and high time resolution and long lifetime. There are different detectors which are used in mass spectrophotometer such as electron multiplier, Faraday cup electrode, and photomultiplier. Electron multiplier is based on that the ion or electrons strikes on the first dynode, resulting in the emission of several electrons. These secondary electrons are then attracted to the second dynode, where

Table 6 Separation of isomers studies using UHPLC

Drugs/compounds	Column	Mobile phase system	Mode of analysis	Detector	Extraction method	Ref
Flavanone, Hesperetin, and Naringenin	Chiralpak AD-3R	Methanol	Isocratic	DAD	SPE	[165]
Flavanone, Naringenin, and Hesperetin	Chiralpak AD-3R	Methanol	Isocratic	Triple-quadrupoleMass spectrometer	SPE	[166]
Phenylethylamines and cathinones	BEH phenylCSH Fluro-phenyl	80 mM phosphate buffer (A) and acetonitrile or methanol (B)	Isocratic/gradient	PDA	–	[167]
Besifoxacin	Chiralpak IE-3	Dichloromethane: isopropyl alcohol: trifuoroacetic acid: diethylamine (90:10:0.3:0.05 *v/v/v/v*)	Isocratic	UV-Visible detector	-	[168]
Warfarin	ZORBAX RRHD Eclipse C18, SB-CN, SB-C8 and SB-Phenyl Hypersil Gold AQ and Gold PFP	0.1% Phosphoric acid in water (A) 10 mM ammonium acetate (pH 6.5) (B) and 5mM ammonium phosphate dibasic in water (pH 8.0) (C). 95:5 to 5:95 % A, B or C.	Gradient	PDA	---	[169]
Debenzazepine and Carbamazepine analogs,	Hypersil Gold PFP	2 mM Ammonium formate (A) and acetonitrile (B) 0-0.2 min, 80% (A): 20% (B); 0.2–0.8 min, 5% (A) :95% (B); and back to 80% (A): 20% (B) in 0.5 min	Gradient	PDA	–	[170]
Xanthine metabolites	SB-Phenyl	0.1 H_3PO_4 in water: acetonitrile	Gradient	PDA	–	
Steroid analogs	Eclipse Plus C_{18}	2 mM Ammonium formate in water (pH 3.5) and acetonitrile (65:35 to 5:95 in 2.0 min)	Gradient	PDA	–	
Nicotine analogs	SB-CN	5 mM Ammonium phosphate diabasic in water: acetonitrile	Gradient	PDA	–	
Glucuronide analogs	SB-CN	150 mM sodium percholrate in 0.02 % perchloric acid: acetonitrile	Gradient	PDA	–	
Rasagiline	Chiralpak AGP	Ammonium acetate: isopropyl alcohol (90:10, *v/v*)	Isocratic	PDA	--	[171]
Trantinterol	BEH C_{18}	3 mM ammonium acetate (A) and acetonitrile (B). 0–4 min, 80-20 %(A); maintained at 70% (A) for 2.5 min	Gradient	Triple-quadrupolemass spectrometer	LLE	[172]
SCH 503034	BEH C_{18}	A1-Methanol: water (5:95) with 40 mM PFPA and A2-methanol: water (95:5) with 40 mM PFPA. B1- Methanol: water (5/95) with 4 mM of ammonium acetate and B2-methanol: water (95/5) with 4 mM of ammonium acetate	Gradient	Triple-quadrupolemass spectrometer	PP	[173]
Ranolazine	BEH RP_{18}	(A) Acetonitrile: sodium dihydrogen phosphate (pH 7.3; 0.01 M)-Triethylamine (10:90:0.1, *v/v/v*). (B)- Acetonitrile-mobile phase-A (55:45, *v/v*).0.01 min, 17 % (B); 1.5 min, 17%(B); 3.5 min, 45%(B); 5.5 min, 60% (B); 8 min, 65 %(B); 12 min, 70% (B); 13 min, 95% (B); 15 min, 95 %(B); 15.5 min, 17% (B); and 18 min, 17%(B)	Gradient	PDA	–	[174]
Rivastigmine	BEH Phenyl	(A) Acetonitrile: disodium hydrogen orthophosphate (pH 7.5; 0.01 M)-Triethylamine (10:90:0.1 *v/v/v*). (B) Acetonitrile: water (80:20 *v/v*) 0.01 min, 5.0 %(B); 5.0 min, 35.0 % (B); 8.0 min, 60.0% (B);8.1 min, 5.0 % (B);10.0 min, 5.0%(B).	Gradient	PDA	–	[175]

Table 6 Separation of isomers studies using UHPLC *(Continued)*

Drugs/compounds	Column	Mobile phase system	Mode of analysis	Detector	Extraction method	Ref
Benzoic acid	Thermo Syncronis C_{18}	0.1% formic acid in water (A) and methanol (B) 0–1.5 min, 15–46 %(B); 1.5–1.9 min, 46% (B); 1.9–4.5 min, 15% (B)	Gradient	Triple-quadrupolemass spectrometer	LLE	[176]
Phenylmercapturic acid and Benzyl mercapturic acid	BEH C_{18}	0.1% acetic acid in water (A) and methanol (B). 0–1.0 min, 80% (A); 1.01–6.00 min, 80–70%(A); 6.00 min, 70–80 % (A)	Gradient	Triple-quadrupolemass spectrometer	LLE	[177]
Abacavir	BEH C_{18}	Water: Acetonitrile (90:10 *v/v*)	Isocratic	UV-Vis and PDA	–	[178]
Stimulants agents	BEH C_{18}	Water (A) and acetonitrile with 0.01% formic acid (B) (50:50 *v/v*) Four types of gradient program were used: 1. Gradient A/B: 0 min 1% B, increase to 3% B in 4.2 min, increase to 90%B in 3.8 min, 90% B for 0.5 min, decrease to 1% B in 0.1 min, and equilibration for 1.4 min. 2. Gradient C: 1% B for 1 min, increase to 15% B in 7 min, increase to 90% B in 1 min, 90% B for 1 min, decrease to 1% B in 0.1min, and equilibration for 1.9 min. 3. Gradient D: 5% B for 1.2 min, increase to 90% B in 16.8 min, 90% B for 0.7 min, decrease to 5% B in 0.1 min, and equilibration for 1.2 min. 4. Gradient E/F: 1% B for 1.2 min, increase to 90% B in 6.8 min, 90%B for 0.7 min, decrease to 1% B in 0.1 min, and equilibration for 1.2 min	Gradient	Triple-quadrupolemass spectrometer	–	[179]
Vigabatrin	Eclipse Plus C18 column	A-10 mM ammonium formate (pH 3.0 adjusted with formic acid and methanol (B), 0–1 min, 10–10% (B); 1–8 min, 10–16% (B), 8–9 min, 16–100% (B), 9–11 min, 100% (B)	Gradient	Triple-quadrupolemass spectrometer	LLE	[180]
Zoxamide	Lux Amylose-2	Acetonitrile: water (70:30 *v/v*)	Isocratic	Triple-quadrupolemass spectrometer	QuEChERS	[181]

every electron creates a few more electrons, and likewise the electrons are produced. The electron multiplier offers several advantages over the other detectors like low noise, high sensitivity, and typical gain of 106 and total life of electron multiplier 1–2 years. Faraday cup electrode is also known as cylinder electrode. The basic principle behind cylinder electrode is that the incident ion strikes the dynode surface which emits electrons and induces a current which is amplified and recorded. The dynode electrons which are used in faraday cup are made up of secondary emitting material like CsSb, GaP, or BeO. The cylinder electrode is very robust and it is generally used to isotope analysis and isotope-ratio mass spectrometry (IRMS). The photomultiplier are currently presumably the most widely recognized in mass spectrophotometer and it's also known as scintillation counter. The basic principle of scintillation counter or photomultiplier is that the ions at first strike a dynode which outcome in electron emission. These electrons then strike a phosphorous screen which thusly discharges a burst of photons. The photons then pass into the multiplier where amplification occurs in a cascade fashion. The main advantage of using photons is that the multiplier can be kept sealed in a vacuum preventing contamination and greatly extending the lifetime of the detector [16, 19].

Present perspective on UHPLC-MS/MS methods

The magnitude of the topic on a UHPLC-MS/MS can be learnt from the review articles published on the topics; to our knowledge, more than 11 [20–30] review articles on various facets of UHPLC-MS/MS have been published by different authors. The brief summary of review articles published in different journals on the topic "UHPLC-MS/MS" is depicted in Table 2.

Application of UHPLC-MS/MS

Bio-analytical method/metabolite studies

The sensitivity and selectivity of UHPLC at low detection levels produces precise dependable information that can be utilized for a wide range of purposes, including pharmacokinetics study, toxicity, and bioequivalence studies as the quantification of a medicinally active agent in biological samples is a crucial part of the development program of a bioanalytical method. The sample preparation techniques gained more significance in bioanalytical methods. UHPLC-MS has vital importance in metabolomics and proteomics [31]. A variety of sample preparation techniques have been applied in a bioanalytical method such as protein precipitation, liquid-liquid extraction, and solid-phase extraction [32]. Among these, the most widely used are protein precipitation and liquid-liquid extraction followed by solid-phase extraction which are used in different category such as antibiotic [33–40], anticancer [36, 41–45, 46–62], antiviral [63–67], antifungal [68–72], cardiovascular [73–86], analgesic [87–93], steroid [94, 95], NSAID [96–106], diabetes [107–110], antidepressant [111–114], antiepileptic [115–119], CNS [120, 121], proton pump inhibitor [122], anti-tubercular [123], vitamin [124, 125], immunosuppressant [126–128], anticoagulant [129, 130], expectorant [102], and multicomponent analysis of drug [131–145]. The simplest is protein precipitation by acetonitrile and centrifugation prior to analysis. The liquid-liquid extraction by ter-butyl methyl ether, chloroform, ethyl acetate, ethyl ether, etc., and solid-phase extraction techniques, disks, or cartridges are used to extract the sample by using methanol, formic acid, water, etc [146]. Bioanalytical studies using UHPLC-MS/MS is summarized in Table 3 and Fig. 2.

Stability-indicating method using UHPLC-MS/MS

It is performed at the preliminary stage in the process of drug development [7]. The research conditions force the drug compounds to degrade under tremendous conditions such as acid and base hydrolysis, peroxide oxidation, photo-oxidation, and thermal stability to identify the resultant degradation products. Stability indicating method using UHPLC-MS/MS is included in Table 4 [147–153]

Impurity profile of drug using UHPLC/MS/MS

For the medicine development and formulation process, profiling, detection, and evaluation of drug substances and their contamination in crude materials and finishing yield testing is an essential part which is summarized in Table 5 [3] [154–163].

UHPLC in separation of isomers

Chirality may influence biological activity; so, there is a necessity for the enantioseparation or diasterioseparation of these compounds. Therefore, sequentially to further examine the mechanisms of action of the enantiomers or diastereomers, it is necessary to understand which compounds are present at the site of action. Therefore, there is an increased demand for sensitive analytical methods to quantify and evaluate the chirality of metabolites present in biological fluids [96]. UHPLC is an incredible tool for the present rehearsing chromatographer, as it can essentially expand the output of a chromatographic separation. What is more, the more extensive scope of usable stream rates makes rapid partitions conceivable. Up till now, various UHPLC columns were employed for separation of structural analogs or for separation of isomers. These UHPLC columns are flexible column with excellent chemical durability and are suitable for quick analysis of samples containing hydrophobic compounds that are strongly retained

in columns or samples containing compounds with large differences in hydrophobicity. In addition, its high bonding density consent for excellent separation of compounds with minute structural differences. Furthermore, these UHPLC columns are used for a wide range of application areas such as measuring the optical purity wand purification of chiral materials [164]. The separations of isomers using UHPLC are summarized in Table 6.

Future direction

In the last decade, literature survey shows that several drugs and metabolites were separated, from their impurities and degradation product by implementing UHPLC-MS/MS technique. For separation or extraction of analytes or drugs and metabolites from the biological fluid with the help of organic solvents, but there are many problems associated with those organic solvents such as toxic nature, injurious to the environment, and dangerous. To overcome these problems, the green solvents are the choice for extraction of analytes. In the future, the more prominent result is also obtained with the help of green solvents because advantage green solvents are their high viscosity, high thermal stability, and low vapor pressure. They are also highly reusable and therefore considered efficient compared to organic solvents. In this survey, the column generally used is BEH C18. The green solvents with the help of increases; high-throughput, sensitivity, and resolution of drugs analysis and identify structures of compounds. Nonetheless, steady up gradation of UHPLC-MS/MS techniques besides data-handling routines are still obligatory for data preprocessing, statistical analysis, biomarker recognition impurity, and degrades products.

Discussion and conclusion

The presented review article gives a perspective on UHPLC-MS/MS in drug substance and medicine product. The current review article collects a simplified, fast, and selective UHPLC-MS/MS methods which were developed for the determination of drug in bulk and also in plasma. UHPLC-MS/MS technique holds out a very promising system for isolation, characterization, and identification of degradation products and impurities. This knowledge can create abundant information about drugs and guidance for its storage, increasing tools for quality control, and safer treatments.

Abbreviations

BEH: Ethylene-bridged hybrid; CSH: Charged surface hybrid; HETP: Height equivalent of theoretical plate; HILIC: Hydrophilic interaction chromatography; HPLC: High-performance liquid chromatography; HSS: High strength silica; IRMS: Isotope-ratio mass spectrometry; LC: Liquid chromatography; LLE: Liquid-liquid extraction; MPa: Megapascal; MS: Mass spectroscopy; NSAID: Nonsteroidal anti-inflammatory drug; PP: Protein precipitation; Psi: Per square inch; PST: Peptide separation technology; QuEChERS: Quick, easy, cheap, effective, rugged, and safe; RP: Reverse phase; SB: Selectivity for bases; SPE: Solid-phase extraction; UHPLC: Ultra high-performance liquid chromatography; UPLC-MS/MS: Ultra performance liquid chromatography-mass spectroscopy

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References

1. Walter TH, Andrews RW (2014) Recent innovations in UHPLC columns and instrumentation. Trends Anal Chem 63:14–20. https://doi.org/10.1016/j.trac.2014.07.016
2. Singh S, Prasad L, Kumar V, Roy S, Patnaik SK (2016) Ultra performance liquid chromatography: high throughput analysis over high performance liquid chromatography. Int J Eng Allied Sci 2:19–25
3. Samatha Y, Srividya A, Ajitha A, Rao VUM (2015) Ultra performance liquid chromatography (UPLC). World J Pharm Pharm Sci 8:356–367
4. Swartz ME (2005) UPLC: an introduction and review. J Liq Chromatogr Relat Technol 28:1253–1263. https://doi.org/10.1081/JLC-200053046
5. Ht Quantitative Analysis for a drug mixture by LC/MS/MS: UPLC-MS/MS and HPLC-MS/MS Compared (2005) water. http://www.water.com.
6. Novakova L, Matysova L, Solich P (2006) Advantages of application of UPLC in pharmaceutical analysis. Talanta 68:908–918. https://doi.org/10.1016/j.talanta.2005.06.035
7. Chawla G, Ranjan C (2016) Principle, instrumentation, and applications of UPLC: A novel technique of liquid chromatography. Open Chem J 3:1–16. https://doi.org/10.2174/1874842201603010001
8. Phalke P, Kavade S (2013) Review on hyphenated techniques. Int J Chem Stud1:157–165
9. UPLC columns and consumables. https://www.waters.com//UPLCColumns 2014.
10. Acquity UPLC column by water. https://www.waters.com/waters/acquitycolumns 2015.
11. Acquity UPLC column solution. https://www.waters.com//UPLCColumns 2009.
12. Acquity UPLC columns by waters. https://www.waters.com 2008.
13. Roge AB, Firke SN, Dhane RM, Gunjkar VJ, Vadvalkar SM (2011) Novel achievement of HPLC: UPLC. Int JPharm Tech Res 3:1423–1429
14. Narwate BM, Ghule PJ, Ghule AV, Darandale AS, Wagh JG (2014) Ultra performance liquid chromatography: A new resolution in chromatography. Int J Pharm Drug Anal 2:25–34
15. Principles and applications of LC-MS/ (2012) MS for the quantitative bioanalysis of analytes in various biological samples. In: tandem mass spectrometry-applications and principles. http://www.intechopen.com
16. Khatri N, Gupta A, Taneja R, Bilandi A, Beniwal P (2012) A review on mass spectrophotometry detectors. Int Res J Pharm 3:33–42

17. De Hoffmann E (2000) Mass spectrometry. Kirk-Othmer Encyclopedia of Chemical Technology.
18. Mass Spectrometry Detectors. https://www.colorado.edu/mass spectrophotmetry detector/. 2009 .
19. Mass Spectrometry detectors. http://www.chm.bris.ac.uk/ms/detectors. Accessed 28 Nov 2018.
20. Higashi T, Shimada K, Toyooka T (2010) Advances in determination of vitamin D related compounds in biological samples using liquid chromatography–mass spectrometry: a review. JChromatogr B 878:1654–1661. https://doi.org/10.1016/j.jchromb.2009.11.026
21. Roux A, Lison D, Junot C, Heilier JF (2011) Applications of liquid chromatography coupled to mass spectrometry-based metabolomics in clinical chemistry and toxicology. Clin Biochem 44:119–135. https://doi.org/10.1016/j.clinbiochem.2010.08.016
22. Zoerner AA, Gutzki FM, Batkai S, May M, Rakers C, Engeli S, Jordan J, Tsikas D (2011) Quantification of endocannabinoids in biological systems by chromatography and mass spectrometry: a comprehensive review from an analytical and biological perspective. Biochim Biophys Acta 1811:706–723. https://doi.org/10.1016/j.bbalip.2011.08.004
23. Gosetti F, Mazzucco E, Gennaro MC, Marengo E (2013) Ultra high performance liquid chromatography tandem mass spectrometry determination and profiling of prohibited steroids in human biological matrices. A review. J Chromatogr B 927:22–36. https://doi.org/10.1016/j.jchromb.2012.12.003
24. Bantscheff M, Lemeer S, Savitski MM, Kuster B (2012) Quantitative mass spectrometry in proteomics: critical review update from 2007 to the present. Anal Bioanal Chem 404:939–965. https://doi.org/10.1007/s00216-012-6203-4
25. Viant MR, Sommer U (2013) Mass spectrometry based environmental metabolomics: a primer and review. Metabolomics 9:144–158. https://doi.org/10.1007/s11306-012-0412-x
26. Motilva MJ, Serra A, Macia A (2013) Analysis of food polyphenols by ultra high-performance liquid chromatography coupled to mass spectrometry: an overview. J Chromatogr A 1292:66–82. https://doi.org/10.1016/j.chroma.2013.01.012
27. Pratima NA, Shraddha B, Zibran S (2013) Review of ultra performance liquid chromatography and its applications. Int J Res Pharm Sci 3:1–42
28. Gouveia MJ, Brindley PJ, Santos LL, da Costa JMC, Gomes P, Vale N (2013) Mass spectrometry techniques in the survey of steroid metabolites as potential disease biomarkers: a review. Metabolism 62:1206–1217. https://doi.org/10.1016/j.metabol.2013.04.003
29. Kailemia MJ, Ruhaak LR, Lebrilla CB, Amster IJ (2013) Oligosaccharide analysis by mass spectrometry: a review of recent developments. Anal Chem 86:196–212. https://doi.org/10.1021/ac403969n
30. Kortz L, Dorow J, Ceglarek U (2014) Liquid chromatography–tandem mass spectrometry for the analysis of eicosanoids and related lipids in human biological matrices: a review. J Chromatogr B 964:1–11. https://doi.org/10.1016/j.jchromb.2014.01.046
31. Desai TK, Mahajan AA, Thaker A (2012) Ultra performance liquid chromatography: a step ahead to HPLC. Int J Pharm Res Rev 2:61–68
32. Kole PL, Venkatesh G, Kotecha J, Sheshala R (2011) Recent advances in sample preparation techniques for effective bioanalytical methods. Biomed Chromatogr 25(1–2):199–217. https://doi.org/10.1002/bmc.1560
33. Carlier M, Stove V, Roberts JA, Van de VE, De WJJ, Verstraete AG (2012) Quantification of seven β-lactam antibiotics and two β-lactamase inhibitors in human plasma using a validated UPLC-MS/MS method. Int J Antimicrob Agents 40:416–422. https://doi.org/10.1016/j.ijantimicag.2012.06.022
34. Zhao L, Zhao Y, Li Q, Chen X, Xiao F, He B, Wang J, Bi K (2012) A fast, sensitive, and high throughput method for the determination of cefuroxime lysine in dog plasma by UPLC–MS/MS. Talanta 89:84–90. https://doi.org/10.1016/j.ijantimicag.2012.06.022
35. Wang YJ, Wu YT, Lin JY, Chu CH, Huang HY, Wang YC, Chen JK, Yang CS (2012) Rapid quantitative analysis of clarithromycin in rat plasma by UPLC–MS/MS after intravenous injection of the clarithromycin-loaded ultrafine PLGA nanoparticles. J Chromatogr B 895:178–181. https://doi.org/10.1016/j.jchromb.2012.03.022
36. Oufir M, Sampath C, Butterweck V, Hamburger M (2012) Development and full validation of an UPLC-MS/MS method for the determination of an anti-allergic indolinone derivative in rat plasma, and application to a preliminary pharmacokinetic study. J Chromatogr B 902:27–34. https://doi.org/10.1016/j.jchromb.2012.06.009
37. Marca GL, Giocaliere E, Villanelli F, Malvagia S, Funghini S, Ombrone D, Filippi L, Gaudio MD, Martino MD, Galli L (2012) Development of an UPLC–MS/MS method for the determination of antibioticertapenem on dried blood spots. J Pharm Biomed Anal 61:108–113. https://doi.org/10.1016/j.jpba.2011.12.018
38. Chahbouni A, Dungen FAVD, Vos RM, den Burger JC, Sinjewel A, Wilhelm AJ, Veldkamp AI, Swart EL, van Weissenbruch MM (2015) An UPLC–MS detection method for the quantification of five antibiotics in human plasma. Bioanalysis 7:2321–2329. https://doi.org/10.4155/bio.15.121
39. Wang XS, Sun JC, Yang RN, Ren J, Liang S, Sun M, Wang YF, Gao SG (2014) Determination of cephalomannine in rat plasma by gradient elution UPLC–MS/MS method. J Chromatogr B 963:70–74. https://doi.org/10.1016/j.jchromb.2014.05.045
40. Yu HC, Pan CW, Xie QP, Zheng Y, Hu YZ, Lin YM (2016) Simultaneous determination of tedizolid and linezolid in rat plasma by ultra performance liquid chromatography tandem mass spectrometry and its application to a pharmacokinetic study. J Chromatogr B 1011:94–98. https://doi.org/10.1016/j.jchromb.2015.12.056
41. Li Y, Sun Y, Du F, Yuan K, Li C (2008) Pulse gradient, large-volume injection, high-throughput ultra-performance liquid chromatographic/tandem mass spectrometry bioanalysis for measurement of plasma amrubicin and its metabolite amrubicinol. J Chromatogr A 1193:109–116. https://doi.org/10.1016/j.chroma.2008.04.014
42. Chen Y, Zhang S, Chen D, Zhou M, Zheng J, Xiang Z (2015) An UPLC-MS/MS method for determination of solasonine in rat plasma and its application of a pharmacokinetic and bioavailability study. J Chromatogr B 985:1–5. https://doi.org/10.1016/j.jchromb.2015.01.017
43. Wang X, Wang S, Ma J, Ye T, Lu M, Fan M, Deng M, Hu L, Gao Z (2015) Pharmacokinetics in rats and tissue distribution in mouse of berberrubine by UPLC-MS/MS. J Pharm Biomed Anal 115:368–374. https://doi.org/10.1016/j.jpba.2015.07.031
44. Iqbal M, Ezzeldin E, Al-Rashood KA, Shakeel F (2015) A validated UPLC–MS/MS assay using negative ionization mode for high-throughput determination of pomalidomide in rat plasma. J Chromatogr B 983:76–82. https://doi.org/10.1016/j.jchromb.2014.12.036
45. Du P, Li N, Wang H, Yang S, Song Y, Han X, Shi Y (2013) Development and validation of a rapid and sensitive UPLC–MS/MS method for determination of total docetaxel from a lipid microsphere formulation in human plasma. J Chromatogr B 926:101–107. https://doi.org/10.1016/j.jchromb.2013.02.006
46. Iqbal M, Wani TA, Khalil NY, Darwish IA (2013) Development and validation of ultra-performance liquid chromatographic method with tandem mass spectrometry for determination of lenalidomide in rabbit and human plasma. Chem Cent J 7:1–9. https://doi.org/10.1186/1752-153X-7-7
47. Zhang SQ, Chen GH (2008) Determination of paclitaxel in human plasma by UPLC-MS-MS. J Chromatogr Sci 46:220–224. https://doi.org/10.1093/chromsci/46.3.220
48. Goldwirt L, Lemaitre F, Zahr N, Farinotti R, Fernandez C (2012) A new UPLC-MS/MS method for the determination of irinotecan and 7-ethyl-10-hydroxycamptothecin (SN-38) in mice: application to plasma and brain pharmacokinetics. J Pharm Biomed Anal 66:325–333. https://doi.org/10.1016/j.jpba.2012.04.003
49. Ju P, Liu Z, Jiang Y, Zhao S, Zhang L, Zhang Y, Gu L, Tang X, Bi K, Chen X (2015) Determination of a novel anticancer c-Met inhibitor LS-177 in rat plasma and tissues with a validated UPLC-MS/MS method: application to pharmacokinetics and tissue distribution study. Biomed Chromatogr 29:1103–1111. https://doi.org/10.1002/bmc.3397
50. Lin H, Zhao Y, Men L, Yang M, Liu SY, Wang P, Tang X, Yu Z (2015) Development of a rapid and sensitive UPLC-MS/MS assay for the determination of TM-2 in beagle dog plasma and its application to a pharmacokinetic study. Biomed Chromatogr 29:110–114. https://doi.org/10.1002/bmc.3246
51. Haandel LV, Becker ML, Williams TD, Leeder JS, Stobaugh JF (2011) Measurement of methotrexate polyglutamates in human erythrocytes by ion-pair UPLC–MS/MS. Bioanalysis 3:2783–2796. https://doi.org/10.4155/bio.11.288
52. Hubicka U, Żmudzki P, Talik P, Żuromska WB, Krzek J (2013) Photodegradation assessment of ciprofloxacin, moxifloxacin, norfloxacin and ofloxacin in the presence of excipients from tablets by UPLC-MS/MS and DSC. Chem Cent J7:133. https://doi.org/10.4155/bio.11.288
53. Goldwirt L, Zahr N, Farinotti R, Fernandez C (2013) Development of a new UPLC-MSMS method for the determination of temozolomide in mice:

application to plasma pharmacokinetics and brain distribution study. Biomed Chromatogr 27:889–893. https://doi.org/10.1002/bmc.2877
54. Wang S, Wu H, Geng P, Lin Y, Liu Z, Zhang L, Ma L, Zhou Y, Wang X, Wen C (2016) Pharmacokinetic study of dendrobine in rat plasma by ultra-performance liquid chromatography tandem mass spectrometry. Biomed Chromatogr 30:1145–1149. https://doi.org/10.1002/bmc.3641
55. Li N, Han X, Du P, Song Y, Hu X, Yang S, Shi Y (2014) Development and validation of a UPLC-MS/MS assay for the quantification of simotinib in human plasma. Anal Bioanal Chem 406:1799–1805. https://doi.org/10.1007/s00216-013-7570-1
56. Lin D, Qiao LM, Zhang N, Liu Y, Liu XS (2016) Simultaneous determination of nintedanib and its metabolite by UPLC–MS/MS in rat plasma and its application to a pharmacokinetic study. J Pharm Biomed Anal 117:173–177. https://doi.org/10.1016/j.jpba.2015.08.024
57. CAO G, ZHANG Q, YANG X (2015) Determination of Letrozole in rat plasma by UPLC-MS/MS and its application to a pharmacokinetic study. Lat Am J Pharm 34:45–50
58. Zhao AQ, Zhao JH, Zhang SQ, Pan YY, Huo XL (2016) Determination of parthenolide in rat plasma by UPLC-MS/MS and its application to a pharmacokinetic study. J Pharm Biomed Anal 119:99–103. https://doi.org/10.1016/j.jpba.2015.11.039
59. Dahmane E, Mercier T, Zanolari B, Cruchon S, Guignard N, Buclin T, Leyvraz S, Zaman K, Csajka C, Decosterd LA (2010) An ultra performance liquid chromatography–tandem MS assay for tamoxifen metabolites profiling in plasma: first evidence of 4′-hydroxylated metabolites in breast cancer patients. J Chromatogr B 878:3402–3414. https://doi.org/10.1016/j.jchromb.2010.10.027
60. Yang F, Wang H, Hu P, Jiang J (2014) Validation of an UPLC–MS-MS method for quantitative analysis of vincristine in human urine after intravenous administration of vincristine sulfate liposome injection. J Chromatogr Sci 53:974–978. https://doi.org/10.1093/chromsci/bmu164
61. Yang S, Qin F, Wang D, Li N, Li F, Xiong Z (2012) Determination of palonosetron in human plasma by ultra performance liquid chromatography–tandem mass spectrometry and its application to a pharmacokinetic study. J Pharm Biomed Anal 57:13–18. https://doi.org/10.1016/j.jpba.2011.08.038
62. Zhang WM, Li RF, Qiu JF, Zhang ZY, Wang HB, Bian L, Lei JH (2015) Determination of kurarinone in rat plasma by UPLC–MS/MS. J Chromatogr B 986:31–34. https://doi.org/10.1016/j.jchromb.2015.02.005
63. Liu H, Xu H, Song W, Zhang Y, Yu S, Huang X (2016) Validated UPLC/MS/MS assay for quantitative bioanalysis of elbasvir in rat plasma and application to pharmacokinetic study. J Chromatogr B 1015:150–156. https://doi.org/10.1016/j.jchromb.2016.02.025
64. Rezk MR, Bendas ER, Basalious EB, Karim IA (2016) Development and validation of sensitive and rapid UPLC–MS/MS method for quantitative determination of daclatasvir in human plasma: application to a bioequivalence study. J Pharm Biomed Anal 128:61–66. https://doi.org/10.1016/j.jpba.2016.05.016
65. Shi X, Zhu D, Lou J, Zhu B, Hu AR, Gan D (2015) Evaluation of a rapid method for the simultaneous quantification of ribavirin, sofosbuvir and its metabolite in rat plasma by UPLC–MS/MS. J Chromatogr B 1002:353–357. https://doi.org/10.1016/j.jchromb.2015.08.038
66. Mishra T, Shrivastav PS (2014) Validation of simultaneous quantitative method of HIV protease inhibitors atazanavir, darunavir and ritonavir in human plasma by UPLC-MS/MS. Sci World J:1–12. https://doi.org/10.1155/2014/482693
67. Li TX, Chu CS, Zhu JY, Yang TY, Zhang J, Hu YT, Yang XH (2016) A rapid UPLC-MS/MS method for the determination of oleanolic acid in rat plasma and liver tissue: application to plasma and liver pharmacokinetics. Biomed Chromatogr 30:520–527. https://doi.org/10.1002/bmc.3577
68. Jiménez GM, Contreras-Zavala L, Maggi-Castellanos M, Ángeles-Moreno AP, García-González A (2012) Development of a method by UPLC–MS/MS for the quantification of tizoxanide in human plasma and its pharmacokinetic application. Bioanalysis 4:909–917. https://doi.org/10.4155/bio.12.41
69. Wang Z, Huang CK, Sun W, Xiao C, Wang ZS (2015) UPLC-MS/MS determination of voriconazole in human plasma and its application to a pharmacokinetic study. Biomed Chromatogr 29:188–193. https://doi.org/10.1002/bmc.3257
70. Al-Quadeib BT, Radwan MA, Siller L, Mutch E, Horrocks B, Wright M, Alshaer A (2014) Therapeutic monitoring of amphotericin B in Saudi ICU patients using UPLC MS/MS assay. Biomed Chromatogr 28:1652–1659. https://doi.org/10.1002/bmc.3198
71. Decosterd LA, Rochat B, Pesse B, Mercier T, Tissot F, Widmer N, Bille J, Calandra T, Zanolari B, Marchetti O (2010) Multiplex ultra-performance liquid chromatography-tandem mass spectrometry method for simultaneous quantification in human plasma of fluconazole, itraconazole, hydroxyitraconazole, posaconazole, voriconazole, voriconazole-N-oxide, anidulafungin, and caspofungin. Antimicrob Agents Chemother 54:5303–5315. https://doi.org/10.1128/AAC.00404-10
72. Rochat B, Pascual A, Pesse B, Lamoth F, Sanglard D, Decosterd LA, Bille J, Marchetti O (2010) Ultra-performance liquid chromatography mass spectrometry and sensitive bioassay methods for quantification of posaconazole plasma concentrations after oral dosing. Antimicrob Agents Chemother 54:5074–5081. https://doi.org/10.1128/AAC.00022-10
73. Abdelbary G, Nebsen M (2013) Application of a novel UPLC–MS/MS method for the pharmacokinetic/bioequivalence determination of atorvastatin and ezetimibe in human plasma. J Pharm Res 7:24–32. https://doi.org/10.1016/j.jopr.2013.01.010
74. Patel DP, Sharma P, Sanyal M, Singhal P, Shrivastav PS (2013) UPLC-MS/MS assay for the simultaneous quantification of carvedilol and its active metabolite 4′-hydroxyphenyl carvedilol in human plasma to support a bioequivalence study in healthy volunteers. Biomed Chromatogr 27:974–986. https://doi.org/10.1002/bmc.2889
75. Zoerner AA, Schroeder C, Kayacelebi AA, Suchy MT, Gutzki FM, Stichtenoth DO, Tank J, Jordan J, Tsikas D (2013) A validated, rapid UPLC–MS/MS method for simultaneous ivabradine, reboxetine, and metoprolol analysis in human plasma and its application to clinical trial samples. J Chromatogr B 927:105–111. https://doi.org/10.1016/j.jchromb.2013.01.016
76. Pidpruzhnykov YV, Sabko EV, Iurchenko VV, Zupanets IA (2012) UPLC-MS/MS method for bioequivalence study of oral drugs of Meldonium. Biomed Chromatogr 26:599–605. https://doi.org/10.1002/bmc.1703
77. Singh B, Lokhandae RS, Dwivedi A, Sharma S, Dubey N (2014) Improved simultaneous quantitation of candesartan and hydrochlorthiazide in human plasma by UPLC–MS/MS and its application in bioequivalence studies. J Pharm Anal 4:144–152
78. Al-Dirbashi OY, Aboul-Enein HY, Jacob M, Al-Qahtani K, Rashed MS (2016) UPLC-MS/MS determination of doxazosine in human plasma. Anal Bioanal Chem 38:1439–1443. https://doi.org/10.1007/s00216-006-0553-8
79. Kalovidouris M, Michalea S, Robola N, Koutsopoulou M, Panderi I (2006) Ultra-performance liquid chromatography/tandem mass spectrometry method for the determination of lercanidipine in human plasma. Rapid Commun Mass Spectrom 20:2939–2946
80. Ebeid MW, Elkady EF, El-Zaher AA, El-Bagary RI, Patonay G (2015) Simultaneous Determination of Aliskiren Hemifumarate, Amlodipine Besylate and Hydrochlorothiazide in Spiked Human Plasma Using UPLC-MS/MS. J Chromatogr Sci 53:178–1184. https://doi.org/10.1093/chromsci/bmu213
81. Wani TA, Zargar S (2015) New ultra-performance liquid chromatography-tandem mass spectrometry method for the determination of irbesartan in human plasma. J Food Drug Anal 23:569–576. https://doi.org/10.1016/j.jfda.2015.02.008
82. Rezk MR, Badr KA (2014) Development, optimization and validation of a highly sensitive UPLC–ESI-MS/MS method for simultaneous quantification of amlodipine, benazeprile and benazeprilat in human plasma: application to a bioequivalence study. J Pharm Biomed Anal 98:1–8. https://doi.org/10.1016/j.jpba.2014.05.005
83. Prajapati ST, Patel PK, Chauhan VB, Patel CN, Patel M (2011) Development and validation of the liquid chromatography-tandem mass spectrometry method for quantitative estimation of candesartan from human plasma. Pharm Methods 2:130–134. https://doi.org/10.4103/2229-4708.84460
84. Favreto WAJ, Pugens Pinto AM, Manfio JL, Fiametti KG, Percio MF, Santos MBD (2012) Development and validation of a UPLC-ESI-MS/MS method for the determination of N-butylscopolamine in human plasma: application to a bioequivalence study. Drug Test Anal 4:215–221. https://doi.org/10.1002/dta.40
85. Bae SK, Kang MJ, Yeo CW, Kim MJ, Shon JH, Liu KH, Shin JG (2008) Simultaneous determination of udenafil and its active metabolite, DA-8164, in human plasma and urine using ultra-performance liquid chromatography–tandem mass spectrometry: application to a pharmacokinetic study. Biomed Chromatogr 22:939–946. https://doi.org/10.1002/bmc.1011
86. Lin X, Zhang Y, Cui Y, Wang L, Wang J, Tang X (2009) Determination of alprostadil in rat plasma by ultra performance liquid chromatography–electrospray ionization–tandem mass spectrometry after intravenous administration. J Pharm Biomed Anal 49:983–988. https://doi.org/10.1016/j.jpba.2009.01.019
87. Kumbhar AB, Galgatte UC, Warkad S, Santhakumari B (2013) Development and validation of a sensitive bioanalytical method for the determination of sumatriptan in rat plasma by UPLC-MS. Int J Pharm Pharm Sci 5:78–82

88. Liang L, Wan S, Xiao J, Zhang J, Gu M (2011) Rapid UPLC–MS/MS method for the determination of sufentanil in human plasma and its application in target-controlled infusion system. J Pharm Biomed Anal 54:838–844. https://doi.org/10.1016/j.jpba.2010.11.016
89. Vuppala K, Boddu SP, Furr EB, McCurdy (2011) A Simple, sensitive, high-throughput method for the quantification of mitragynine in rat plasma using UPLC-MS and its application to an intravenous pharmacokinetic study. Chromatographia 74:703–710. https://doi.org/10.1007/s10337-011-2128-x
90. Hillewaert V, Pusecker K, Sips L, Verhaeghe T, Vries RD, Langhans M, Terlinden R, Timmerman P (2015) Determination of tapentadol and tapentadol-O-glucuronide in human serum samples by UPLC–MS/MS. J Chromatogr B 981:40–47. https://doi.org/10.1016/j.jchromb.2014.12.013
91. Inoue K, Sakamoto T, Fujita Y, Yoshizawa S, Tomita M, Min JZK, Todoroki K, Sobue T, Toyo'oka (2013) Development of a stable isotope dilution UPLC-MS/MS method for quantification of dexmedetomidine in a small amount of human plasma. Biomed Chromatogr 27: 853-858. doi:https://doi.org/10.1002/bmc.2870.
92. Huang PW, Liu HT, Hsiong CH, Pao LH, Lu CC, Ho ST, Hu OYP (2013) Simultaneous determination of nalbuphine and its prodrugsebacolydinalbuphine ester in human plasma by ultra-performance liquid chromatography–tandem mass spectrometry and its application to pharmacokinetic study in humans. Biomed Chromatogr 27:831–837. https://doi.org/10.1002/bmc.2867
93. Lüthi G, Blangy V, Eap CB, Ansermot N (2013) Buprenorphine and norbuprenorphine quantification in human plasma by simple protein precipitation and ultra-high performance liquid chromatography tandem mass spectrometry. J Pharm Biomed Anal 77:1–8. https://doi.org/10.1016/j.jpba.2012.12.023
94. Licea-Perez H, Wang S, Szapacs ME, Yang E (2008) Development of a highly sensitive and selective UPLC/MS/MS method for the simultaneous determination of testosterone and 5α-dihydrotestosterone in human serum to support testosterone replacement therapy for hypogonadism. Steroids 73:60–610. https://doi.org/10.1016/j.steroids.2008.01.018
95. Liu H, Yang M, Wu P, Guan J, Men L, Lin H, Tang X, Zhao Y, Yu Z (2015) Simultaneous determination of triamcinolone acetonidepalmitate and triamcinolone acetonide in beagle dog plasma by UPLC-MS/MS and its application to a long-term pharmacokinetic study of triamcinolone acetonidepalmitate lipid emulsion injection. J Pharm Biomed Anal 104:105–111. https://doi.org/10.1016/j.jpba.2014.11.028
96. Leveques A, Actis-Goretta L, Rein MJ, Williamson G, Dionisi F, Giuffrida F (2012) UPLC–MS/MS quantification of total hesperetin and hesperetin enantiomers in biological matrices. J Pharm Biomed Anal 57:1–6. https://doi.org/10.1016/j.jpba.2014.11.028
97. Wong KC, Law MC, Wong MS, Chan TH (2014) Development of a UPLC–MS/MS bioanalytical method for the pharmacokinetic study of (−)-epiafzelechin, a flavan-3-ol with osteoprotective activity, in C57BL/6J mice. J Chromatogr B 967:162–167. https://doi.org/10.1016/j.jchromb.2014.07.028
98. Mano Y, Ishii T, Hotta K, Kusano K (2015) Validation of a UPLC–MS/MS method for the simultaneous determination of E6005, a phosphodiesterase 4 inhibitor, and its metabolite in human plasma. J Chromatogr B 998:31–39. https://doi.org/10.1016/j.jchromb.2015.06.023
99. Li X, Xiong Z, Lu S, Zhang Y, Li F (2010) Pharmacokinetics of naringin and its metabolite naringenin in rats after oral administration of RhizomaDrynariae extract assayed by UPLC-MS/MS. Chin J Nat Med 8:40–46. https://doi.org/10.3724/SP.J.1009.2010.00040
100. Szeitz A, Edginton AN, Peng HT, Cheung B, Riggs KW A validated enantioselective assay for the determination of ibuprofen in human plasma using ultra performance liquid chromatography with tandem mass spectrometry (UPLC-MS/MS). Am J Anal Chem 2(210):47–58. https://doi.org/10.4236/ajac.2010.12007
101. Zhang WM, Li RM, Sun M, Hu DM, Qiu JE, Yan YH (2014) UPLC–MS/MS method for determination of avicularin in rat plasma and its application to a pharmacokinetic study. J Chromatogr B 965:107–111. https://doi.org/10.1016/j.jchromb.2014.06.015
102. Wen C, Wang S, Huang X, Liu Z, Lin Y, Yang S, Ma J, Zhou Y, Wang X (2005) Determination and validation of hupehenine in rat plasma by UPLC-MS/MS and its application to pharmacokinetic study. Biomed Chromatogr 29:1805–1810. https://doi.org/10.1002/bmc.3499
103. He X, Zhang Y, Gao H, Li K, Zhang Y, Sun L, Tao G (2016) Simultaneous quantification of picfeltarraenins IA and IB in rat plasma by UPLC–MS/MS: application to a pharmacokinetic study. J Pharm Biomed Anal 120:32–37. https://doi.org/10.1016/j.jpba.2015.11.031
104. Cui Y, Lin X, Guan TT, Zhang Y, Tang X (2010) A new rapid ultra-performance liquid chromatography method for the pharmacokinetic and bioavailability study of diclofenac sodium aqueous injection and lipid microsphere injection in rats. Biomed Chromatogr 24:406–412. https://doi.org/10.1002/bmc.130.
105. Patel DP, Sharma P, Patel BM, Sanyal M, Singhal P, Shrivastav PS (2013) Analysis of 21-hydroxy deflazacort in human plasma by UPLC–MS/MS: Application to a bioequivalence study in healthy volunteers. J Pharm Biomed Anal 85:213–217. https://doi.org/10.1016/j.jpba.2013.07.035
106. Qiu X, Lou D, Su D, Liu Z, Gao P, Zhang NS (2015) Simultaneous determination of acetaminophen and dihydrocodeine in human plasma by UPLC–MS/MS: Its pharmacokinetic application. J Chromatogr B 992:91–95. https://doi.org/10.1016/j.jchromb.2015.04.031
107. Qiu X, Zheng SL, Wang Y, Wang R, Ye L (2014) A Rapid and Simple UPLC–MS-MS Method for Determination of Glipizide in Human Plasma and Its Application to Bioequivalence Study. J Chromatogr Sci 53:85–89. https://doi.org/10.1093/chromsci/bmu023
108. Cai S, Huo T, Li N, Xiong Z, Li F (2009) Lysophosphatidylcholine—biomarker of metformin action: studied using UPLC/MS/MS. Biomed Chromatogr 23: 782–786. https://doi.org/10.1002/bmc.1185
109. Jain R, Lukram O, Dwivedi A (2011) Ultra-performance liquid chromatography electrospray ionization–tandem mass spectrometry method for the estimation of miglitol in human plasma using metformin as the internal standard. Drug Test Anal. 3:255–262
110. Zhang JF, Sha CF, Sun Y, Gai YY, Sun JY, Han JB, Shao X, Sha CN, Li YX, Liu WH (2013) Ultra-high-performance liquid chromatography for the determination of exenatide in monkey plasma by tandem quadrupole mass spectrometry. J Pharm Anal 3:235–240. https://doi.org/10.1016/j.jpha.2012.12.007
111. Gu EM, Huang C, Liang B, Yuan L, Lan T, Hu G, Zhou H (2015) An UPLC–MS/MS method for the quantitation of vortioxetine in rat plasma: application to a pharmacokinetic study. J Chromatogr B 997:70–74. https://doi.org/10.1016/j.jchromb.2015.05.010
112. Denooz R, Mercerolle M, Lachâtre G, Charlier C (2010) Ultra-performance liquid chromatography-tandem mass spectrometry method for the determination of bupropion and its main metabolites in human whole blood. J Anal Toxicol 34:280–286
113. Qin F, Li N, Qin T, Zhang Y, Li F (2010) Simultaneous quantification of venlafaxine and O-desmethylvenlafaxine in human plasma by ultra performance liquid chromatography–tandem mass spectrometry and its application in a pharmacokinetic study. J Chromatogr B. 878:689–694. https://doi.org/10.1016/j.jchromb.2010.01.007
114. Bhatt M, Shah S (2010) Solid-phase extraction and analysis of paroxetine in human plasma by ultra-performance liquid chromatography–electrospray ionization mass spectrometry. Biomed Chromatogr 24:209–215. https://doi.org/10.1002/bmc.1275.
115. Karinen R, Vindenes V, Hasvold I, Olsen KM, Christophersen AS, Oiestad E (2015) Determination of a selection of anti-epileptic drugs and two active metabolites in whole blood by reversed phase UPLC-MS/MS and some examples of application of the method in forensic toxicology cases. Drug Test Anal 7:634–644
116. Proença P, Franco JM, Mustra C, Monteiro C, Costa J, Real FC, Vieira DN (2013) UPLC-MS/MS determination in blood of a mixed-drug fatal intoxication: a case report. Forensic Sci Int 227:85–89. https://doi.org/10.1016/j.forsciint.2012.10.038
117. Bhatt M, Shah S (2015) Rapid ultra-performance liquid chromatography-tandem mass spectrometry method for quantification of Oxcarbazepine and its metabolite in human plasma. Biomed Chromatogr 25:751–759
118. Marin SJ, Roberts M, Wood M, McMillin GA (2012) Sensitive UPLC–MS-MS assay for 21 benzodiazepine drugs and metabolites, zolpidem andzopiclone in serum or plasma. J AnalToxicol 36:472–476. https://doi.org/10.1093/jat/bks059
119. Liang F, Terry AV, Bartlett MG (2012) Determination of aripiprazole in rat plasma and brain using ultra-performance liquid chromatography/electrospray ionization tandem mass spectrometry. Biomed Chromatogr 26: 1325–1332. https://doi.org/10.1002/bmc.2698
120. Junnotula V, Licea-Perez H (2013) Development and validation of a simple and sensitive method for quantification of levodopa and carbidopa in rat and monkey plasma using derivatization and UPLC–MS/MS. J Chromatogr B 926:47–53. https://doi.org/10.1016/j.jchromb.2013.03.004
121. Zhang Y, Tingley FD, Tseng E, Tella M, Yang X, Groeber E, Liu J, Li W, Schmidt CJ, Steenwyk R (2012) Development and validation of a sample

stabilization strategy and a UPLC–MS/MS method for the simultaneous quantitation of acetylcholine (ACh), histamine (HA), and its metabolites in rat cerebrospinal fluid (CSF). J Chromatogr B 879:2023–2033. https://doi.org/10.1016/j.jchromb.2011.05.030
122. Chunduri RHB, Dannana GS (2016) Development and validation of a high throughput UPLC–MS/MS method for simultaneous quantification of esomeprazole, rabeprazole and levosulpiride in human plasma. J Pharm Anal 6:190–198
123. Baietto L, Calcagno A, Motta I, Baruffi K, Poretti V, Di PG, Bonora S, D'avolio A (2015) A UPLC-MS-MS method for the simultaneous quantification of first-line antituberculars in plasma and in PBMCs. J Antimicrob Chemother 70: 2572–2575. https://doi.org/10.1093/jac/dkv148
124. Hampel D, York ER, Allen LH (2012) Ultra-performance liquid chromatography tandem mass-spectrometry (UPLC–MS/MS) for the rapid, simultaneous analysis of thiamin, riboflavin, flavin adenine dinucleotide, nicotinamide and pyridoxal in human milk. J Chromatogr B 903:7–13. https://doi.org/10.1016/j.jchromb.2012.06.024
125. Jacobs BA, Rosing H, Vries ND, Meulendijks D, Henricks LM, Schellens JH, Beijnen JH (2016) Development and validation of a rapid and sensitive UPLC–MS/MS method for determination of uracil and dihydrouracil in human plasma. J Pharm Biomed Anal 126:75–82. https://doi.org/10.1016/j.jpba.2016.04.039
126. Upadhyay V, Trivedi V, Shah G, Yadav M, Shrivastav PS (2012) Rapid and sensitive UPLC–MS-MS determination of Tacrolimus in Wistar rats and human blood. J Chromatogr Sci 52:59–67. https://doi.org/10.1093/chromsci/bms205
127. Cao S, Ni B, Feng L, Yin X, Dou H, Fu J, Lin J, Ni J (2014) Simultaneous Determination of Typhaneoside and Isorhamnetin-3-O-Neohesperidoside in rats after oral administration of pollen Typhae extract by UPLC–MS/MS. J Chromatogr Sci 53:866–871. https://doi.org/10.1093/chromsci/bmu132.
128. Upadhyay V, Trivedi V, Shah G, Yadav M, Shrivastav PS (2014) Determination of mycophenolic acid in human plasma by ultra performance liquid chromatography tandem mass spectrometry. J Pharm Anal 4:205–216
129. Radwan MA, Bawazeer GA, Aloudah NM, AlQuadeib BT, Aboul-Enein HY (2012) Determination of free and total warfarin concentrations in plasma using UPLC MS/MS and its application to a patient samples. BiomedChromatogr 26:6–11. https://doi.org/10.1002/bmc.1616
130. Yang X, Liu S, Sun J, Liu X, Sun Y, He Z (2009) UPLC for the determination of clopidogrel in dog plasma by tandem quadrupole MS: application to a pharmacokinetic study. Chromatographia 70:259–263. https://doi.org/10.1365/s10337-009-1109-9
131. Xiong Z, Sun X, Huo T, Li N, Zheng Y, Sun Y (2010) Development and validation of UPLC-MS/MS method for simultaneous determination of gestodene and ethinyl estradiol in rat plasma. Biomed Chromatogr 24:160–168. https://doi.org/10.1002/bmc.1265.
132. Hu G, Xu RA, Dong YY, Wang YY, Yao WW, Chen ZC, Chen D, Bu T, Ge RS (2015) Simultaneous determination of liensinine, isoliensinine and neferine in rat plasma by UPLC–MS/MS and application of the technique to pharmacokinetic studies. J Ethno Pharmacol 163:94–98. https://doi.org/10.1016/j.jep.2015.01.020
133. Rodríguez OP, Zapata-Morales JR, Moratilla AE, León-Cabrero MDD, Roque IT, Urizar JP (2015) Determination of Pinaverium bromide in human plasma by a sensitive and robust UPLC–MS-MS method and application to a pharmacokinetic study in Mexican subjects. J Chromatogr Sci 53:1373–1378. https://doi.org/10.1093/chromsci/bmv027
134. Liu Z, Jiang M, Lu X, Qin F, Song Y, Wen J, Li F (2012) Simultaneous determination of pimpinellin, isopimpinellin and phellopterin in rat plasma by a validated UPLC–MS/MS and its application to a pharmacokinetic study after administration of Toddaliaasiatica extract. J Chromatogr B 891:102–108. https://doi.org/10.1016/j.jchromb.2012.02.022
135. Zoerner AA, Batkai S, Suchy MT, Gutzki FM, Engeli S, Jordan J, Tsikas D (2012) Simultaneous UPLC–MS/MS quantification of the endocannabinoids 2-arachidonoyl glycerol (2AG), 1-arachidonoyl glycerol (1AG), and anandamide in human plasma: Minimization of matrix-effects, 2AG/1AG isomerization and degradation by toluene solvent extraction. J Chromatogr B 883:161–171. https://doi.org/10.1016/j.jchromb.2011.06.025
136. Huang X, Su S, Cui W, Liu P, Duan JA, Guo J, Li Z, Shang E, Qian D, Huang Z (2014) Simultaneous determination of paeoniflorin, albiflorin, ferulic acid, tetrahydropalmatine, protopine, typhaneoside, senkyunolide I in Beagle dogs plasma by UPLC–MS/MS and its application to a pharmacokinetic study after Oral Administration of ShaofuZhuyu Decoction. J Chromatogr B 962:75–81. https://doi.org/10.1016/j.jchromb.2014.05.032
137. Liu Y, Li X, Yang C, Tai S, Zhang X, Liu G (2012) UPLC–MS-MS method for simultaneous determination of caffeine, tolbutamide, metoprolol, and dapsone in rat plasma and its application to cytochrome P450 activity study in rats. J Chromatogr Sci 51:26–32. https://doi.org/10.1093/chromsci/bms100
138. Colón RK, Martínez MA, Silva-Torres LA, Chavez-Arias C, Negrón MM, Conte-Miller MS, Oquendo JB (2012) Simultaneous determination of Xylazine, free morphine, codeine, 6-acetylmorphine, cocaine and benzoylecgonine in postmortem blood by UPLC–MS-MS. J Anal Toxicol 36:319–326. https://doi.org/10.1093/jat/bks024
139. Ma J, Wang S, Zhang M, Zhang Q, Zhou Y, Lin C, Lin G, Wang X (2015) Simultaneous determination of bupropion, metroprolol, midazolam, phenacetin, omeprazole and tolbutamide in rat plasma by UPLC-MS/MS and its application to cytochrome P450 activity study in rats. Biomed Chromatogr 29:1203–1212. https://doi.org/10.1002/bmc.3409
140. Chen X, Gu E, Wang S, Zheng X, Chen M, Wang L, Hu G, Cai JP, Zhou H (2015) Evaluation of the effects of Ketoconazole and Voriconazole on the pharmacokinetics of Oxcarbazepine and its main metabolite MHD in rats by UPLC–MS-MS. J Chromatogr Sci 541:334–342. https://doi.org/10.1093/chromsci/bmv146.
141. Wang Y, Wen J, Zheng W, Zhao L, Fu X, Wang Z, Xiong Z, Li F, Xiao W (2015) Simultaneous determination of neochlorogenic acid, chlorogenic acid, cryptochlorogenic acid and geniposide in rat plasma by UPLC-MS/MS and its application to a pharmacokinetic study after administration of Reduning injection. Biomed Chromatogr 29:68–74. https://doi.org/10.1002/bmc.3241
142. Zhao J, Chen X, Wang C, Wang Y, Ma C, Li W, Bi K (2010) Simultaneous determination of Evodiamine and Rutaecarpine in rat plasma by UPLC-MS-MS and its application in a pharmacokinetics study. Chromatographia 72: 187–191. https://doi.org/10.1365/s10337-010-1633-7
143. Qiu X, Zhao J, Wang Z, Xu Z, Xu RA (2014) Simultaneous determination of bosentan and glimepiride in human plasma by ultra performance liquid chromatography tandem mass spectrometry and its application to a pharmacokinetic study. J Pharm Biomed Anal 95:207–212. https://doi.org/10.1016/j.jpba.2014.03.011
144. Li H, Xia X, Xue Y, Tang S, Xiao X, Li J, Shen J (2012) Simultaneous determination of amoxicillin and prednisolone in bovine milk using ultra-high performance liquid chromatography tandem mass spectrometry. J Chromatogr B 900:59–63. https://doi.org/10.1016/j.jchromb.2012.05.031
145. Li G, Yang F, Liu M, Su X, Zhao M, Zhao L (2016) Development and application of a UPLC-MS/MS method for simultaneous determination of fenofibric acid and berberine in rat plasma: application to the drug–drug pharmacokinetic interaction study of fenofibrate combined with berberine after oral administration in rats. Biomed Chromatogr 30:1075–1082. https://doi.org/10.1002/bmc.3652.
146. Pan J, Zhang C, Zhang Z, Li G (2014) Review of online coupling of sample preparation techniques with liquid chromatography. Analytica chimica acta 815:1–15. https://doi.org/10.1016/j.aca.2014.01.017
147. Ludvigsson JW, Andersson T, Kjellberg V (2016) A new method to identify hydrolytic degradants in drug substances with UPLC-MS using 18O-labelled water. J Pharm Biomed Anal 122:9–15. https://doi.org/10.1016/j.jpba.2016.01.041
148. Otasevic B, Milovanović S, Zečević M, Golubović J, Protić A (2014) UPLC method for determination of moxonidine and its degradation products in active pharmaceutical ingredient and pharmaceutical dosage form. Chromatographia 1:109–118. https://doi.org/10.1007/s10337-013-2580-x
149. Wingert NR, dos Santos NO, Nunes MA, Gomes P, Müller EI, Flores EM, Steppe M (2016) Characterization of three main degradation products from novel oral anticoagulant rivaroxaban under stress conditions by UPLC-Q-TOF-MS/MS. J Pharm Biomed Anal 123:10–15. https://doi.org/10.1016/j.jpba.2016.01.053
150. Hubicka U, Żmudzki P, Talik P, Żuromska-Witek B, Krzek J (2013) Photodegradation assessment of ciprofloxacin, moxifloxacin, norfloxacin and ofloxacin in the presence of excipients from tablets by UPLC-MS/MS and DSC. Chem Cent J 7:133. https://doi.org/10.1186/1752-153X-7-133
151. Mei MK, Du Z, Xu R, Chen Y, Zhang H, Qu S (2012) Photocatalytic degradation of hexazinone and its determination in water via UPLC–MS/MS. J Hazard Mater 221:100–108. https://doi.org/10.1016/j.jhazmat.2012.04.018
152. Hubicka U, Żmudzki P, Żuromska-Witek B, Zajdel P, Pawłowski M, Krzek J (2012) Separation and characterization of ciprofloxacin, difloxacin, lomefloxacin, norfloxacin, and ofloxacin oxidation products under potassium permanganate treatment in acidic medium by UPLC-MS/MS. Talanta 109:91–100. https://doi.org/10.1016/j.talanta.2013.01.055
153. Siddiqui MR, Alothman ZA, Wabaidur SM (2014) Ultra performance liquid chromatography–mass spectrometric method for determination of

ampicillin and characterization of its forced degradation products. J Chromatogr Sci 52:1273–1280
154. Reddy YK, Reddy GS, Veera KJ, Hotha KK (2012) A Stability Indicating UPLC Method for Finasteride and Its Related Impurities. Am J Anal Chem 3:737–745. https://doi.org/10.4236/ajac.2012.311098P
155. Hotha KK, Patel T, Roychowdhury S, Subramanian V (2015) Identification, synthesis, and characterization of unknown impurity in the famotidine powder for oral suspension due to excipient interaction by UPLC-MS/MS and NMR. J Liq Chromatogr Rela Technol 38:977–985. doi:org/https://doi.org/10.1080/10826076.2014.999201.
156. Rao DD, Satyanarayana NV, Reddy AM, Sait SS, Chakole D, Mukkanti K (2010) A validated stability-indicating UPLC method for desloratadine and its impurities in pharmaceutical dosage forms. J Pharm Biomed Anal 51:736–742. https://doi.org/10.1016/j.jpba.2009.09.016
157. Mowaka S, Mohamed D (2015) Novel contribution to the simultaneous analysis of certain hypoglycemic drugs in the presence of their impurities and degradation products utilizing UPLC-MS/MS. RSC Adv 5:60467–60481. https://doi.org/10.1039/C5RA11448A
158. Liu C, Hua Z, Bai Y (2015) Classification of illicit heroin by UPLC–Q-TOF analysis of acidic and neutral manufacturing impurities. Forensic Sci Int 257:196–202. https://doi.org/10.1016/j.forsciint.2015.08.009
159. Bapatu HR, Maram RK, Cho WH, Pasagadugula VBR (2016) QbD Approach method development for estimation of Dabigatran Etexilate along with its impurities and identification of degradants in capsule dosage form. Am J Anal Che 7:494–524. https://doi.org/10.4236/ajac.2016.76047
160. Reddy AVB, Venugopal N, Madhavi G, Reddy KG, Madhavi V (2013) A selective and sensitive UPLC–MS/MS approach for trace level quantification of four potential genotoxic impurities in zolmitriptan drug substance. J Pharm Biomed Anal 84:84–89. https://doi.org/10.1016/j.jpba.2013.05.047
161. Thomas JL, Lincoln D, McCord BR (2013) Separation and detection of smokeless powder additives by ultra performance liquid chromatography with tandem mass spectrometry (UPLC/MS/MS). J Forensic Sci 58:609–615. https://doi.org/10.1111/1556-4029.12096
162. Koppala S, Panigrahi B, Raju SVN, Reddy KP, Reddy VR, Anireddy JS (2014) Development and validation of a simple, sensitive, selective and stability-indicating RP-UPLC Method for the quantitative determination of ritonavir and its related compounds. J Chromatogr Sci 53:662–675. https://doi.org/10.1093/chromsci/bmu097
163. Ding M, Lu J, Zhao C, Zhang S, Zhao Y (2016) Determination of 25-OCH 3-PPD and the related substances by UPLC–MS/MS and their cytotoxic activity. J Chromatogr B 1022:274–280. https://doi.org/10.1016/j.jchromb.2016.04.031
164. Chrial columns. http://www.ymc.co.jp/en/columns/chiral_art/ Accessed 30 November 2018.
165. Baranowska I, Hejniak J, Magiera S (2016) Simultaneous Chiral Separation of Flavanone, Naringenin, and Hesperetin Enantiomers by RP-UHPLC-DAD. Chirality 28:147–152. https://doi.org/10.1002/chir.22559
166. Baranowska I, Hejniak J, Magiera S (2016) Development and validation of a RP-UHPLC-ESI-MS/MS method for the chiral separation and determination of flavanone, naringenin and hesperetin enantiomers. Talanta 1(159):181–188. https://doi.org/10.1016/j.talanta.2016.06.020
167. Li L, Lurie IS (2015) Regioisomeric and enantiomeric analyses of 24 designer cathinones and phenethylamines using ultra high performance liquid chromatography and capillary electrophoresis with added cyclodextrins. Forensic Sci Int 1(254):148–157. https://doi.org/10.1016/j.forsciint.2015.06.026
168. Ramisetti NR, Arnipalli MS, Nimmu NV, Bondigalla R (2017) UHPLC determination of besifloxacin enantiomers on immobilized amylose tris (3, 5-dichlorophenylcarbamate) chiral stationary phase. Chromatographia 80:1509–1515. https://doi.org/10.1007/s10337-017-3346-7
169. Regalado EL, Schafer W, McClain R, Welch CJ (2013) Chromatographic resolution of closely related species: separation of warfarin and hydroxylated isomers. J Chromatogr A1 1314:266–275. https://doi.org/10.1016/j.chroma.2013.07.092
170. Regalado EL, Helmy R, Green MD, Welch CJ (2014) Chromatographic resolution of closely related species: drug metabolites and analogs. J Sep Sci 37:1094–1102. https://doi.org/10.1002/jssc.201400038
171. Balaji N, Sultana S (2017) Reversed-phase UHPLC enantiomeric separation of rasagiline salts using a Chiralpak® AGP Column. Sci Pharm 85:26. https://doi.org/10.3390/scipharm85030026
172. Yang J, Wang Y, Pan L, Li N, Lu X, Guan J, Cheng M, Li F (2009) Enantioselective determination of trantinterol in rat plasma by ultra performance liquid chromatography–electrospray ionization mass spectrometry after derivatization. Talanta 79:1204–1208. https://doi.org/10.1016/j.talanta.2009.03.036
173. Wang G, Hsieh Y, Cheng KC, Morrison RA, Venkatraman S, Njoroge FG, Heimark L, Korfmacher WA (2007) Ultra-performance liquid chromatography/tandem mass spectrometric determination of diastereomers of SCH 503034 in monkey plasma. J Chromatogr B 852:92–100. https://doi.org/10.1016/j.jchromb.2006.12.038
174. Malati V, Reddy AR, Mukkanti K, Suryanarayana MV (2012) A novel reverse phase stability indicating RP-UPLC method for the quantitative determination of fifteen related substances in Ranolazine drug substance and drug product. Talanta 97:563–573. https://doi.org/10.1016/j.talanta.2012.03.067
175. Raju TS, Kalyanaraman L, Reddy VV, Swamy PY (2012) Development and validation of an UPLC method for the rapid separation of positional isomers and potential impurities of rivastigmine hydrogen tartrate in drug substance and drug product. J Liq Chromatogr Relat Technol 35(7):896–911. https://doi.org/10.1080/10826076.2011.613143
176. Zhang Q, Wang D, Zhang M, Zhao Y, Yu Z (2017) The determination of 2-(2-hydroxypropanamido) benzoic acid enantiomers and their corresponding prodrugs in rat plasma by UHPLC–MS/MS and application to comparative pharmacokinetic study after a single oral dose. J Chromatogr B 1041:175–182. https://doi.org/10.1016/j.jchromb.2016.11.017
177. Jin H, Thangadurai TD, Jo SC, Jin D, Cui S, Lee YI (2012) On-line chiral analysis of benzylmercapturic acid and phenylmercapturic acid in human urine using UPLC-QToF mass spectrometry with the kinetic method. Microchem J 103:170–176. https://doi.org/10.1016/j.microc.2012.03.003
178. Reyes-Reyes ML, Roa-Morales G, Melgar-Fernández R, Reyes-Pérez H, Gómez-Oliván LM, Gonzalez-Rivas N, Bautista-Renedo J, Balderas-Hernández P (2015) Chiral recognition of abacavir enantiomers by (2-hydroxy) propyl-β-cyclodextrin: UHPLC, NMR and DFT studies. J InclPhenomMacrocyclChem 82:373–382. https://doi.org/10.1007/s10847-015-0499-6
179. Monfort N, Martínez L, Bergés R, Segura J, Ventura R (2015) Screening method for stimulants in urine by UHPLC-MS/MS: identification of isomeric compounds. Drug Test Anal 7:819–830. https://doi.org/10.1002/dta.1776
180. Zhao J, Shin Y, Jin Y, Jeong KM, Lee J (2017) Determination of enantiomericvigabatrin by derivatization with diacetyl-L-tartaric anhydride followed by ultra-high performance liquid chromatography-quadrupole-time-of-flight mass spectrometry. J Chromatogr B 1040:199–207. https://doi.org/10.1016/j.jchromb.2016.11.016
181. Pan X, Dong F, Chen Z, Xu J, Liu X, Wu X, Zheng Y (2017) The application of chiral ultra-high-performance liquid chromatography tandem mass spectrometry to the separation of the zoxamide enantiomers and the study of enantioselective degradation process in agricultural plants. J Chromatogr A 1525:87–95. https://doi.org/10.1016/j.chroma.2017.10.016

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