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REVIEW

UHPLC-MS/MS Technique: Applications in Analytical Chemistry

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The ultra-high performance liquid chromatography-mass spectrometry/mass spectrometry (UHPLC-MS/MS) is becoming most advanced technique used for analysis of wide range of compounds in analytical chemistry. This technique has been effectively utilized for identifying and quantitatively determining substances in several pharmaceutical analysis fields. The UHPLC technique offers superior sensitivity, selectivity and peak shape in comparison to the conventional HPLC technique. The UHPLC coupled with various mass spectrometers gives accurate mass fragmentations which is ultimately helpful in structural identification and quantitative determination of compounds. The review provides brief introduction on development of UHPLC column packing materials and coupled mass detectors such as single quadrupole, triple quadrupole and time-of-flight mass. This review article also summarizes application of UHPLC-MS/MS technique in various fields of analytical chemistry.

Keywords: UHPLC-MS/MS, UPLC, Applications, Analytical chemistry.

INTRODUCTION

In the field of analytical chemistry, the UHPLC-MS/MS technique is becoming widely used technique for the structural identification and quantitative determination of compounds in almost every area of chromatographic and pharmaceutical analysis. The UHPLC systems assembled with hybrid material packed column which operates under 15000 psi pressure improves selectivity, sensitivity, speed of analysis and better peak shapes of compounds. The Waters Company manufactured its own UHPLC system under the trade name as ultra-performance liquid chromatography (UPLC) in 2004. Other companies such as Thermo and Agilent have also developed their UHPLC systems. The Waters Company manufactured HPLC columns with hybrid particle technology (HPT) in year 1999. The excellent mechanical strength, efficacy and pH stability for basic compounds towards HPT column are due to the combination of inorganic silica and organic polymeric packings. Thus, an innovative material for packing UHPLC columns has been created, which consists of particles with bridging ethylsiloxane hybrid (BEH) structures. This material offers better efficiency, strength and pH range. Recently charged surface hybrid technology (CSH) column developed for separations of compounds with entire ionic mobile phases. These different column technologies contain less than 2 µm particle size column materials [1-15]. Tolley *et al*. [16] built a UHPLC system that could reach pressures higher than 17,500 psi by adapting a commercially available pump. A capillary column was utilized, which was packed with non-porous silica particles that had been treated with C18. The UHPLC system, linked to a mass spectrometer in MS mode, was used to examine a bovine serum albumin (BSA) digest. In order to sequence peptides and identify proteins, the mass spectrometer was configured to execute data-dependent scanning, which involves automatically switching from MS to MS/MS mode upon detection of a peak.

Mass spectrometers: The UHPLC systems are coupled with various mass detectors such as single quadrupole, triple quadrupole or time-of-light (TOF) mass detectors for different analytical applications. Before understanding the applications of LC-MS/MS, we must know the various types of mass detectors coupled with UHPLC system. By applying scaling voltages across diagonally opposing quadrupole rods, a single quadrupole assembly Q1 scans and filters ionized molecules in a single quadrupole mass spectrometer. Full scan mass spectra,

also called multiple ion monitoring (MIM), can be obtained by completing a ramp. Because of this, one can quantitatively evaluate the constituents present in the sample. In SIM mode, only ions with a certain *m/z* ratio are allowed to enter the detector, while other ions are filtered away which is accomplished by supplying a constant voltage. Q1, Q2 and Q3 are the three quadrupoles that make up the triple quadrupole mass spectrometer. The middle quadrupole, Q2, serves as a collision cell, whereas quadrupoles Q1 and Q3 filter the mass. The collision cell uses collisions between chosen precursor ions and molecules of neutral gas to break them down into product ions. Third quadrupole assembly Q3 filters the product ions so that only those with a specific *m/z* ratio can reach the detector. When compared to devices with just one quadrupole, those with three can improve separation and ion resolution [17]. Time-of-flight (TOF) based on bombardment of sample by electron beam causes the fragmentation to form smaller groups of atoms or ions. The generated ions then measures the time for each ion takes to reach the detector. The TOF mass spectrometry provides accurate and reliable chemical fragmentations, which are ultimately helpful in structure elucidations of compounds [18-21]. Multiple reaction monitoring using LC-MS/MS offers many-fold selectivity improvements over single ion monitoring (SIM) using a single quadrupole LC-MS. The LC-MS/MS due to its superior performance in terms of higher accuracy and reproducibility of results has been applied in several areas such as pharmaceuticals, foods and cosmetics, sports medicines, *etc.* The applications are particularly promising in bioanalytical studies, therapeutic drug monitoring, clinical monitoring, forensic toxicology and proteomics. Rathod *et al.* [22] compiled a review on overview of medicinally important drugs and their analysis with UHPLC-MS/MS. A review on the applications of UHPLC in the pharmaceutical analysis are also reported [23]. Two review articles on applications of UHPLC reported by Khan & Ali [24,25] provided the brief introduction and applications of UHPLC/Q-TOF-MS with examples of some of the most advanced work in the pharmaceutical analysis.

The present review article summarizes applications of the UHPLC-MS/MS technique in various fields of analytical chemistry. The applications are described with special emphasis on recent examples of compounds analyzed by this technique. This review provides valuable information on the chromatographic and mass spectrometric settings used for analyzing the pharmaceutical and other substances. The various UHPLC-MS/MS applications are described as follows under the individual sub-titles.

Identification of impurities and degradation products: According to the ICH recommendations, drug products must undergo an essential and necessary impurity and degradation product determination process. The UHPLC-MS/MS is the most recent technique which has been applied for identification of impurities and degradation products of pharmaceuticals. The system provides changeable collision energy values allow the generation of mass information of the drugs and their related impurities. Identification of degradation products and degradation mechanisms can also be established. Recently, a UPLC-Q-TOF-MS method was developed for the simultaneous determination of aceclofenac and paracetamol with their known degradation products such as diclofenac and *p*-aminophenol [26]. The full scan Q-TOF mass spectra were obtained for aceclo-fenac, diclofenac, paracetamol and *p*-aminophenol. On the basis of the product ions spectra, detailed fragmentation mechanisms for each compound were also established. Other published research work also demonstrated the degradation of telmisartan and hydrochlorothiazide by applying the similar chromato-graphic and Q-TOF-MS conditions. Drugs were exposed to ICH stress testing conditions and analyzed by Q-TOF-MS detector. The possible degradation mechanisms were established on the basis of obtained mass spectra under stress testing [27]. The drugs analyzed along with their impurities and applied UHPLC conditions are presented in Table-1.

Pharmacokinetic studies: Identifying and measuring the amount of a drug in biological samples is a crucial aspect of drug development programs. The pharmacokinetic parameter such as T_{max}, C_{max}, AUC and $T_{1/2}$, has been evaluated for amount of drug reaching in blood. An effective method to pharmacokinetic studies is the use of LC/MS and LC/MS/MS techniques, which can examine complicated blood and plasma samples. UPLC-MS has high sensitivity and selectivity at low detection levels, providing precise and dependable data suitable for various

TABLE-1
DRUGS ANALYZED WITH THEIR IMPURITIES AND APPLIED UHPLC-MS/MS CONDITIONS

Drugs	Column	Mobile phase composition	Detection	Ref.
Aceclofenac & paracetamol	BEH C-18	Acetonitrile:ammonium acetate (50:50, % v/v)	Q-TOF-MS/MS	[26]
Telmisartan	LC C-8	Acetonitrile:ammonium acetate (50:50, % v/v)	Q-TOF-MS/MS	[27]
Telmisartan & hydrochlorothiazide	BEH C-18	Acetonitrile:ammonium acetate (50:50, % v/v)	Q-TOF-MS/MS	[28]
Valsartan	BEH C-18	Acetonitrile:ammonium acetate (50:50, % v/v)	Q-TOF-MS/MS	[29]
Aflatoxin	BEH C-18	0.1% FA in water & acetonitrile	Q-TOF-MS/MS	[30]
Famotidine	BEH C-18	Aqueous buffer:acetonitrile (92:8,%v/v)	Triple-Q-ESI-MS/MS	[31]
Sitagliptin, metformin	Hypersil gold C-18	0.2% FA in water:acetonitrile (50:50, % v/v)	Triple-Q-ESI-MS/MS	[32]
Illicit heroin samples	BEH C-18	Acetonitrile:methanol; ammonium formate (50:50, % v/v)	Q-TOF-MS/MS	[33]
Zolmitriptan	Hypersil BDS C-8	Acetonitrile:ammonium acetate (50:50, % v/v)	Triple-Q-ESI-MS/MS	[34]
Rivaroxaban	Agilent C-18	0.2% FA in water & acetonitrile	Q-TOF-MS/MS	[35]
Ciprofloxacin & norfloxacin	BEH C-18	Acetonitrile:0.2% FA in water (50:50, % v/v)	Triple-Q-ESI-MS/MS	[36]
Aripiprazole	ACE 3 C-18	0.1% FA in water & methanol (45:55, % v/v)	Triple-Q-ESI-MS/MS	[37]

applications, such as statistical pharmacokinetics (PK) study. Aceclofenac and paracetamol combination tablet pharmacokinetics in human plasma were reported by Khan & Ali [38,39]. The Q-TOF mass spectrometer was used for quantification in positive ionization mode, with MS/MS transitions *m/z* 354.07 to 215.07 for aceclofenac and 152.07 to 110.06 for paracetamol. The proposed method was sensitive enough to detect drugs in human plasma. The limit of detection and quantitation of drugs were obtained as 0.1 ng/mL and 1.0 ng/mL, respectively. The UPLC-Q-TOF-MS technique was also applied for the pharmacokinetic study of anti-hypertensive and anti-diabetic drugs in human plasma [40-42]. The pharmacokinetic study of drugs and applied UHPLC-MS/MS conditions are presented in Table-2.

Metabolite studies/metabonomics: Metabonomics refers to the metabolic alterations that occur in a drug when it interacts with the human system. Metabonomic investigations help in identifying novel drug metabolites. The MetaboLynx™ software, when combined with a UHPLC-MS system, simplifies the analysis of metabolites produced by drugs. By identify metabolites, their therapeutic and toxic aspects can be determined. The human metabolites of paracetamol were identified using HPLC monolithic column and sub-2 µm particle UPLC columns in conjunction with TOF-MS. The UHPLC system exhibited three times more sensitivity in detecting metabolites compared to the HPLC system [55]. Compounds are identified by the core structure they maintain from the original medication. Hence, the parent compound and its metabolites are likely to experience comparable fragmentations, resulting in mass spectra revealing the significant sub-structures. Drugs analyzed with their metabolites and applied UHPLC-MS/MS conditions are presented in Table-3.

Determination of phytoconstituents: Medicinal plants contain several different kinds of chemical constituents with many biological activities. Several analytical techniques have been used for the isolation and characterization of phytoconstituents. Natural products as well as traditional herbal medicines consist of extremely complex samples, but UPLC's high-quality separations and detection capabilities make it possible to iden-

TABLE-2
PHARMACOKINETIC STUDIES OF DRUGS AND APPLIED UHPLC-MS/MS CONDITIONS

Drugs	Column	Mobile phase composition	Detection	Ref.
Aceclofenac & paracetamol tablets	BEH C-18	Acetonitrile:2 Mm ammonium acetate (40:60, % v/v)	Q-TOF-MS/MS	[38,39]
Telmisartan & hydrochlorothiazide	BEH C-18	Acetonitrile:2 Mm ammonium acetate (40:60, % v/v)	Q-TOF-MS/MS	[40]
Metformin, glimepiride & pioglitazone	BEH C-18	Acetonitrile:2 Mm ammonium acetate (40:60, % v/v)	Q-TOF-MS/MS	[41]
SARTAN anti-hypertensive	BEH C-18	Acetonitrile:2 Mm ammonium acetate (40:60, % v/v)	Q-TOF-MS/MS	[42]
Nifedipine	BEH C-18	Acetonitrile:ammonium acetate (75:25, % v/v)	Triple-Q-ESI-MS/MS	[43]
Amlodipine	BEH C-18	Acetonitrile:0.3% FA in water	Triple-Q-ESI-MS/MS	[44]
Inflachromene	BEH C-18	0.1% FA in water:acetonitrile (Gradient)	Triple-Q-ESI-MS/MS	[45]
Cefaclor	BEH C-18	0.1% FA in water:acetonitrile (Gradient)	Triple-Q-ESI-MS/MS	[46]
Rhein	HSS T3	0.1% FA in water:acetonitrile (Gradient)	Triple-Q-ESI-MS/MS	[47]
Domeperidone	BEH C-18	Methanol-water & ammonium acetate and (60:40, %v/v)	Triple-Q-ESI-MS/MS	[48]
Terbinafine	BEH C-18	Acetonitrile-8.0 mM Ammonium formate (85:15, %v/v)	Triple-Q-ESI-MS/MS	[49]
Pentoxifylline	Phenyl-hexyl	5mM Ammonium formate & methanol (gradient)	Triple-Q-ESI-MS/MS	[50]
Gabapentin	Eclipse Plus C-18	Methanol:0.1% FA in Water (65:35, %v/v)	Triple-Q-ESI-MS/MS	[51]
Tamoxifen	BEH C-18	Acetonitrile:2 mM Ammonium formate (90:10,%v/v)	ESI-Q-TOF-MS/MS	[52]
Dipyridamole	HSS T3 C-18	10 mM Ammonium acetate & acetonitrile (Gradient)	ESI-Q-TOF-MS/MS	[53]
Amphetamine, ephedrine	HSS T3 C-18	5 mM Sodium formate in water:acetonitrile (50:50, %v/v)	ESI-Q-TOF-MS/MS	[54]

TABLE-3
DRUGS ANALYZED WITH THEIR METABOLITES AND APPLIED UHPLC-MS/MS CONDITIONS

Drugs	Column	Mobile phase composition	Detection	Ref.
Acetaminophen	Monolithic C-18	0.1% FA in water:acetonitrile (40:60, % v/v)	Q-TOF-MS/MS	[55]
Nicotine	BEH C-18	0.1% FA in water:acetonitrile	Triple-Q-ESI-MS/MS	[56]
Amoxicillin, ampicillin, cefuroxime, cefazolin, piperacillin, clavulanic acid & tazobactam	BEH C-18	0.1% FA in water:acetonitrile & (40:60, % v/v)	Triple-Q-ESI-MS/MS	[57]
Paclitaxel	BEH C-18	0.1% FA in water:methanol	Triple-Q-ESI-MS/MS	[58]
Methotrexate	BEH C-18	0.1% FA in water:acetonitrile (40:60, % v/v)	Triple-Q-ESI-MS/MS	[59]
Vincristine	HSS T3	Methanol-0.2% FA in water (30:70, %v/v)	Triple-Q-ESI-MS/MS	[60]
Atorvastatin and Ezetimibe	BEH C-18	0.1% FA in Water:acetonitrile (50:50, %v/v)	Triple-Q-ESI-MS/MS	[61]
Irbesartan	BEH C-18	Acetonitrile:methanol:ammonium acetate (70:30:v/v)	Triple-Q-ESI-MS/MS	[62]
Amlodipine, Benazeprile	BEH C-18	0.1% FA in water:acetonitrile (30:70, %v/v)	Triple-Q-ESI-MS/MS	[63]
Glipizide	BEH C-18	0.1% FA in water:acetonitrile (25:75, %v/v)	Triple-Q-ESI-MS/MS	[64]
Rifampicin, isoniazide, pyrazinamide, ethambutol	BEH C-18	Methanol-0.2% FA in water formic acid (gradient)	Triple-Q-ESI-MS/MS	[65]

tify active components in these samples. There is a strong relationship between bioactive compounds and their medicinal uses, and LC-MS can provide quantitative analysis in addition to coupled mass spectrum data. Mass spectrometry is a powerful tool that has been modified to analyze the structures of numerous phytoconstituents found in plant extracts. Lachowicz *et al*. [66] applied UPLC-PDA-Q/TOF-MS technique to find the bioactive chemicals in *Fallopia japonica* and *Fallopia sachalinensis* rhizomes and leaves, *viz*. polyphenolic, triterpenoids, carotenoids, chlorophyll and phytonutrients. Table-4 presented the other plant constituents that were subjected to UHPLC-MS/MS evaluation.

Determination of traditional Chinese medicines (TCM): Chinese system of medicines is the oldest system of medicines which provides the wide ranges of herbal drugs useful pharmacologically. Traditional Chinese Medicine (TCM) refers to an extensive variety of plant, animal or mineral-based therapies that have their roots in ancient Chinese medicine and are used all over the globe. More and more individuals throughout the world are incorporating traditional remedies, such as TCM, into their daily lives as a result of advancements in system science and modern industrial technology. Both solid and liquid forms of these medications are commercially available. These medications are gaining popularity in India as a means of treating a wide range of illnesses. To address the need of creating comprehensive quality standards of TCM, several aspects of TCM quality control are covered, such as origins, identification, testing and assays, sample preparation, marker selection and TCM processing. Wang *et al.* [73] proposed the TCM diagnosis and treatment within a systematic framework for TCM diagnosis and treatment. In the review of the methodologies and techniques used for TCM quality control in recent years, Chen *et al*. [74] covered all aspects of the Chinese medicine production cycle, including raw material sourcing, processing, effectiveness, metabolomics and pharmacokinetics. An extensive assessment summarizing TCM's background, health philosophy, primary treatment strategies and methodologies, present state of development and future prospects was also reported by Ma *et al*. [75]. In addition, they [76] further reviewed the TCM taking into consideration the applicability of UHPLC-HRMS techniques. A comparitive studies was conducted by Leong *et al*. [77] between the quality requirements that are mentioned in the European Pharmacopoeia and the Chinese Pharmacopoeia.

Rheumatism, tendon swelling, foot discomfort, athlete's foot, diuresis and gout are among the conditions that have responded positively to experimental investigations of the Chinese medicine prescription Ji-Ming-Shan (JMS). The seven herbs that made up JMS have a long history of usage in reducing the inflammatory responses. With the help of UPLC-Q-TOF-MS technique, the primary metabolites in rat serum from the JMS extract were analyzed, identified and categorized rutaecarpine as alkaloid, platycodin & narirutin as triterpenes and hesperidin & naringin as flavanoids [78]. A UPLC-MS/MS method was developed by Wang *et al*. [79] and applied to the pharmacokinetic studies of Naoshuantong granule in rats. The method simultaneously determined six bioactive components *viz.* danshensu, ferulic acid, astragaloside IV, naringin, neohesperidin and puerarinin rat plasma. Similarly, Yan *et al.* [80] developed a a UHPLC-MS/MS method for the simultaneous quantification of bioactive components in Chinese herbal drugs. Liu *et al.* [81] also determined 18 chemical constituents in the traditional Chinese medicine of anti-tussive by using UPLC-MS/MS method. Table-5 listed the details of traditional Chinese medicines analyzed by UHPLC-MS/MS.

Vitamin analysis: The water soluble and fat soluble vitamins have also been determined in food supplements by this technique. The electron-spray-ionization quadrupole-mass spectrometer (ESI-Q-MS/MS) changeable collision energy structurally identified the complex molecules of vitamins. For almost analysis of vitamins, the mobile phase composition was mixture of water and aceotnitrile with 0.1% formic acid of ammonium acetate used in gradient elution mode. The water soluble vitamins such as thiamin, rriboflavin, nicotinamide, pyridoxine, folate, niacin, pantothenic acid, biotin and vitamin C have been determined by UPLC-MS technique. Similarly, fat soluble vitamins such as vitamin A, D & K were also determined this technique [91-95]. The details of applied conditions for analysis of water and fat soluble vitamins are summarized in Table-6.

TABLE-4
ANALYSIS OF PLANTS CONSTITUENTS AND APPLIED UHPLC-MS/MS CONDITIONS

Plant	Chemical constituents	Column	Mobile phase composition	Detection	Ref.
Fallopia japonica	Phenolic acids, flavones, flavonols, stilbenes, carotenoids	BEH C-18	2.0% FA in water & acetonitrile	Q-TOF-MS/MS	[66]
Canarium pimela leaves	Flavonoids, phenolic acids, dianthrone, chlorogenic acid	BEH C-18	0.1% Acetic acid in water & methanol	Q-TOF-MS/MS	[67]
Salvia albimaculata	Phenolics, flavonoids	BEH C-18	1.0% FA in water:methanol	Triple-Q-ESI-MS/MS	[68]
Cocoa leaf	Procyanidins, theobromine, caffeine	HSS T3	Methanol & water/acetic acid (50/50, %v/v)	TQD-MS/MS	[69]
Theobroma cacao	Benzoic acid, cinnamic acids flavonoid, epicatechin, catechin, quercetin, isoquercitrin, naringenin, luteolin, apigenin	LC-18	1.0% FA in water :acetonitrile (gradient)	Ions Spray- Q-MS/MS	[70]
Catharanthus roseus	Vincristine, vinblastine, ajmalicine, catharanthine, serpentine & vindoline	BEH C-18	Ammonium acetate in water:acetonitrile (50/50, %v/v)	Triple-Q-ESI-MS/MS	[71]
Uncaria species	Oxindole alkaloids, indole alkaloids and flavone	BEH C-18	0.2% FA in water:acetonitrile (Gradient)	Triple-Q-ESI-MS/MS	[72]

TABLE-5
DETERMINATION OF CHINESE HERBAL MEDICINES AND APPLIED UHPLC-MS/MS CONDITIONS

Chinese herbal medicines	Column	Mobile phase	Detector	Ref.
Ji-Ming-Shan (JMS)	HSS T3	0.1% Formic acid (FA) in water:acetonitrile (gradient)	Q-TOF-MS/MS	[78]
Naoshuantong granules	BEH C-18	0.1% Formic acid (FA) in water:acetonitrile (gradient)	Triple-Q-ESI-MS/MS	[79]
Chinese medicinal wine	BEH C-18	0.1% Formic acid (FA) in water:acetonitrile (gradient)	Triple-Q-ESI-MS/MS	[80]
Traditional Chinese medicine of antitussive	HSS C18	0.1% Formic acid (FA) in water:methanol (gradient)	Triple-Q-ESI-MS/MS	[81]
QiShenYiQi Pill (QSYQ)	Zorbax SB C18	0.1% Formic acid (FA) in water:acetonitrile (gradient)	Triple-Q-ESI-MS/MS	[82]
Ligustri Lucidi Fructus	BEH C-18	0.1% Formic acid (FA) in water:acetonitrile (gradient)	Triple-Q-ESI-MS/MS	[83]
Dan-Deng-Tong-Nao-Capsule	BEH C-8	0.1% Formic acid (FA) in water:acetonitrile (gradient)	Q-Orbitrap MS	[84]
Sophora tonkinensis	BEH C-8	0.1% Formic acid (FA) in water:acetonitrile (gradient)	Q-TOF-MS/MS	[85]
Shuang-Huang-Lian	HSS T3	0.1% Formic acid (FA) in water:acetonitrile (gradient)	Q-TOF-MS/MS	[86]
Xuefu Zhuyu decoction (Phenolic acids, terpenoids, flavonoids, saponins)	BEH C-8	0.1% Formic acid (FA) in water:acetonitrile (gradient)	Q-TOF-MS/MS	[87]
Chinese Patent Medicines	BEH C-18	Ammonium acetate in water:acetonitrile (gradient)	Q-TOF-MS/MS	[88]
SiJunZiTang (Mixture of Radix Ginseng, & Glycyrrhiza uralensis)	BEH C-18	Ammonium acetate in water:acetonitrile (gradient)	Q-TOF-MS/MS	[89]
Bambusa chungii Leaves	ODS-AQ C-18	Ammonium acetate in water:acetonitrile (gradient)	Q-TOF-MS/MS	[90]

TABLE-6
DETERMINATION OF VITAMINS AND APPLIED UHPLC-MS/MS CONDITIONS

Vitamins	Column	Mobile phase composition	Detection	Ref.
Thiamin, rriboflavin, nicotinamide and pyridoxal	BEH C-18	Ammonium acetate in water:acetonitrile (50:50,% V/V)	Triple-Q-ESI-MS/MS	[91]
Folate, thiamine, riboflavin, niacin, pantothenic acid, biotin, B6, B12 & C	LC C-8	0.1% FA in Water:Acetonitrile (gradient)	Triple-Q-ESI-MS/MS	[92]
Four water-soluble vitamins & B5, B8, B9, B12	BEH C-18	0.1% FA in Water:Acetonitrile (gradient)	Triple-Q-ESI-MS/MS	[93]
Vitamin-D	LC-18	Acetonitrile:Methanol (75:25, % V/V)	Triple-Q-ESI-MS/MS	[94]
Vitamins A & E (α-,γ- and δ-tocopherol)	RP C-18	0.1% FA in Water: Acetonitrile (gradient)	Fluorescence	[95]

Toxicity studies: As per the ICH safety guidelines, toxicity study is essential part to prove safety profiles of drug product. During the drug development process, toxicity issues significantly impact drug candidates and result in financial losses for the firm. The toxicity studies *via* drug-drug interactions and generation of toxic metabolites has been done from this technique. An important bioactive component with broad anticancer activity, cantharidin is derived from the blister beetle and is used in traditional Chinese medicine. Due of its possible harmful effects, particularly hepatotoxicity, cantharidin is clinically limited. Recently, Zhu *et al*. [96] utilized a UPLC-Q-TOF/MS method based on a metabolomics approach to explore the mechanisms of cantharidin-induced hepatotoxicity. A total of 54 metabolites showed significant changes, along with 14 metabolic pathways that were disrupted. Similarly, Spagou *et al*. [97] explored the utility of HILIC-UPLC-TOF-MS technique in order to analyze the metabolic profiles of rat urine samples collected during a galactosamine hepatotoxicity experiment. Whereas Wang *et al*. [98] used the UPLC/ESI-QTOF-MS technique to study the triptolide toxicity and licorice detoxication. From the urine samples, eight distinct indicators for triptolide toxicity were found.

Analysis of alkaloids and glycosides: Alkaloids and glycosides are also extracted from different plants and have therapeutic properties due to their complex chemical compositions. The plant extracts containing alkaloids and glycosides have been successfully analyzed by UHPLC-MS/MS methods. The details of applied conditions for analysis of some alkaloids and glycosides are summarized in Table-7.

Analysis of amino acids, proteins, carbohydrates and lipids: The determination of biomolecules such as amino acids and proteins, carbohydrates and lipids have been successfully carried out by UHPLC-MS techniques. As the primary components of proteins and peptides and as intermediaries in numerous metabolic processes like the citric acid and urea cycles, amino acids play an essential role in biological activity. The peptide mapping is an approach utilized to identify the chemical structure of a peptide bound to a protein. The use of time-of-flight mass detection can facilitate the structural identification of proteins. Most of the applications for the analysis of amino acids and proteins were carried out by using UPLC BEH amide C-18 column, composition of water and acetonitrile, with 0.3% formic acid (in gradient elution mode) as mobile phase and ESI-QTOF-MS/MS detection technique [108-123]. Examples analyzed biomolecules and applied UHPLC-MS/MS conditions are presented in Table-8.

Screening of antibiotics and organic pollutants in wastewater: The identification of antibiotics in surface water and wastewaters has also been achieved successfully with the help of this approach. During the manufacturing process of pharmaceuticals, the compounds are transported *via* the cleaning of machinery and then transferred into the wastewater. Petrovic *et al*. [124] developed the UPLC-Q-TOF-MS method to screen the presence of 29 pharmaceutical compounds from various

TABLE-7
ANALYSIS OF AKALOIDS AND GLYCOSIDES AND APPLIED UPLC-MS/MS CONDITIONS

Plant (alkaloids)/(glycosides)	Column	Mobile phase	Detection	Ref.
Tobacco leaf (nicotine, anabasine, anatabine, nornicotine, nitrosonornicotine)	CHIRALPAK LUX-Cellulose	30 mM Ammonium formate with 0.3% NH_4OH & methanol (90:10; %v/v)	Triple-Q-ESI-MS/MS	[99]
Pyrrolizidines, monocrotaline, senkirkine, senecionine, seneciphylline	BEH C-18	Methanol:water & ammonium formate with formic acid (gradient)	Triple-Q-ESI-MS/MS	[100]
Tobacco leaves (nicotine, nornicotine, anabasine, anatabine, myosmine, nicotyrine, 2,3'-bipyridine & cotinine	BEH C-18	Methanol:ammonium acetate in water (40:60% v/v) (gradient)	Triple-Q-ESI-MS/MS	[101]
Opium alkaloids (morphine, codeine & thebaine)	BEH C-18	5 Mm Ammonium formate in water & methanol (75:25; v:v)	Ion trap-ESI-MS/MS	[102]
Phellodendri chinensis cortex (berberine, jateorhizine, palmatine, tetrahydropalmatine, phellodendrine, protopine)	Eclipse plus C-18	0.1% FA in Water & acetonitrile (gradient)	Triple-Q-ESI-MS/MS	[103]
Cardio glycoside (digoxin & digitoxin)	RP C-8	0.1% FA in water & acetonitrile (gradient)	Triple-Q-ESI-MS/MS	[104]
Curculigo orchioides (orcinol glucoside)	BEH C-18	0.1% FA in water & acetonitrile (gradient)	Triple-Q-ESI-MS/MS	[105]
Steviol glycosides (rebaudioside D, rebaudioside A, stevioside, dulcoside A, rubusoside, rebaudioside B & steviobioside)	RP C-18	0.05% FA in water & acetonitrile (gradient)	Triple-Q-ESI-MS/MS	[106]
Lemonade (flavonoid glycosides in lemonade (eriocitrin, narirutin, hesperidin, rutin)	BEH C-18	0.1% FA in water & acetonitrile (gradient)	TOF-MS/MS	[107]

TABLE-8
DETERMINATION OF BIOMOLECULES AND APPLIED UPLC-MS/MS CONDITIONS

Biomolecules (applications)	Column	Mobile phase	Detection	Ref.
Peptides- short chain of amino acids (peptide mapping)	BEH C-18	0.1% FA in water:acetonitrile (50:50% v/v)	ESI-TOF-MS/MS	[108]
Amino acids (amino acid anysis)	BEH C-18	Acetonitrile:water (60:40%)	TOF-MS/MS	[109]
Glycoproteins (glycoproteins anysis)	BEH C-18	Acetonitrile:water (50:50%)	TOF-MS/MS	[110]
Fructose & glucose, sucrose, in dates (carbohydrate analysis)	BEH Amide	Acetonitrile-water with gradient elution	Triple-Q-ESI-MS/MS	[111]
Glucose, fructose, galactose, xylose, glucoronic acid, galacturonic cid, arabinose, fucose, rhamnose, mannose, allose, ribose (carbohydrate analysis)	Agilent C-18	Acetonitrile-water & 25 mM ammonium acetate (95:5; %v/v)	MRM-Q-MS/MS	[112]
Cholestrol, triglycerides, steroids, fatty acids (lipid analysis)	BEH C-18	Methanol:water (99:1; %v/v) & ammonium acetate	Q-TOF-MS/MS	[113]
Glycine, alanine, proline, valine, leucine, lysine, methionine, phenyl alanine, arginine, tyrosine (amino acid analysis)	HILIC-amide	Acetonitrile:water ammonium acetate (40:60, %v/v)	Triple-Q-ESI-MS/MS	[114]
66 Amino acids in human plasma (amino acid analysis)	HSS T3	0.1% FA in water:acetonitrile (50:50% v/v)	Triple-Q-ESI-MS/MS	[115]
Glycerophospholipids (lipid analysis)	CSH C-18	0.1% FA in water:acetonitrile (40:60; % v/v)	Triple-Q-ESI-MS/MS	[116]
Phenylalanine, valine, histidine, tryptophan & methionine (hyperlipidemic analysis)	BEH C-18	0.1% FA in water:acetonitrile (20:80% v/v)	Triple-Q-ESI-MS/MS	[117]
Biopharmaceuticals (amino acid, peptides, protein analysis)	Cortecs C-18	0.1% FA in water:acetonitrile (gradient)	Single-Q-MS/MS	[118]
Protein biopharmaceuticals (protein analysis)	Peptide BEH C-18	0.1% FA in water:acetonitrile (gradient)	Q-Exactive-MS/MS	[119]
Amino acids in food samples (amino acid analysis)	BEH C-18	0.1% FA in water:acetonitrile (gradient)	Triple-Q-ESI-MS/MS	[120]
L-Ergothioneine (amino acid analysis)	XBridge C-18	0.1% FA in water:acetonitrile (gradient)	TOF-MS/MS	[121]
Glycerophospholipids (lipid analysis)	BEH C-18	Water:methanol (50:50, %v/v), phosphoric acid (8 µM), ammonium acetate (10 mM) and formic acid (0.1%)	Triple-Q-ESI-MS/MS	[122]
Lysophosphatidylcholine lysophosphatidylethanolamine phosphatidylcholine, phosphatidylethanolamine, cholesterol, diacylglyceride, triglyceride, sphingomyelin & ceramide (lipid analysis)	BEH C-18	Acetonitrile:water with 10 mM ammonium formate (60:40, %v/v)	Orbitrap-ESI-MS/MS	[123]

therapeutic classes, including anti-inflammatory and analgesics drugs, psychiatric medications, statins, antibiotics, histamine H2 receptor antagonists, lipid regulators and β-blockers. The method detection limits (MDLs) for wastewater treatment plant (WWTP) samples ranged from 10 to 500 ng/L, according to the analysis. Pharmaceutical residues in wastewater treatment plant samples were effectively analyzed using this method [124]. Ibanez *et al*. [125] also developed a UHPLC-Q-TOF-MS method to screen several drugs *e.g*. codeine, paracetamol, omeprazole and ciprofloxacin, as well as antibiotics such ofloxacin, ciprofloxacin, clarythromycin and erythromycin. To qualitatively screen for organic pollutants in both freshwater and wastewater, Diaz *et al*. [126] developed and validated the LC-QTOF-MS technique for screening the diverse types of water including surface water, groundwater and effluent urban wastewater. The samples were collected from various sources and had diverse matrix compositions. At the lowest measured concentration of 0.1 μg/L, all the chemicals were detectable. Furthermore, cocaine and its metabolite benzoylecgonine, triazine herbicides, fungicides such as thiabendazol, carbendazim, imazalil, and a number of antibiotics, anti-inflammatory, and analgesic medications were also identified using this method.

Iodinated byproducts in drinking water (IBP): Iodinated disinfection byproducts are typically more hazardous than their chlorinated counterparts. Ding & Zhang [127] developed a ESI-triple-quadrupole-MS technique to identify polar iodinated disinfection byproducts rapidly. The analytical quantification of several iodinated byproducts in water treated with chlorine and chlorine-ammonia has been conducted and their structures have been suggested.

Analysis of pesticides in fruits and vegetables: The approach is utilized for detecting pesticides in vegetables and fruits. The pesticide residue found at a very low concentration level on packaging materials used for fruit packaging, was also analyzed using this technique [128-132]. The analysis was conducted using UPLC BEH C-18 column with a mixture of water and acetonitrile containing 0.3% formic acid in gradient elution mode. Detection was done using ESI-MS/MS method. The details of applied conditions for the analysis of pesticides are summarized in Table-9.

Separations of isomers: The presence of chirality may have an effect on biological activity. Thus, it is necessary to be familiar with the structures of enantiomers and diasteriomers of chiral substances. The chirality of metabolites present in the biological fluids is being quantified and evaluated. For a wide variety of applications, including the measurement of optical purity and the purification of chiral compounds, several ultra-high-performance liquid chromatography (UHPLC) columns are utilized. Applications of some of the isomers analyzed in different sample matrix summarized in Table-10.

Screening of synthetic compounds: For the purpose of screening synthesized pharmaceutical compounds for quality control at high throughput, the approach has become an indispensable tool. Traditional methods, such nuclear magnetic resonance (NMR), are inadequate for meeting these demands for high throughput analytical results because of their low sensitivity, high sample purity requirements, operator competence requirements and solvent costs. It has been proven that automation, in conjunction with software for precise mass measurement, can simplify analytical procedures [139].

TABLE-9
DETAILS OF PESTICIDES DETERMINED USING LC-MS/MS CONDITIONS

Pesticides	Column	Mobile phase	Detector	Ref.
Diacylhydrazine (tebufenozide, methoxfenozide, chromafenozide, halofenozide) in fruits & vegetables	BEH C-18	water:acetonitrile, with 0.3% FA	Triple-Q-ESI-MS/MS	[128]
166 Pesticide residues in fresh fruits and vegetables	BEH C-8	Methanol:Acetonitrile mixture (25:75, %v/v)	ESI-Q-Orbitrap-MS	[129]
141 Pesticides in tea	BEH C-18	Water:acetonitrile, with 0.3% FA	Triple-Q-ESI-MS/MS	[130]
Imidacloprid, thiamethoxam, chlorpyrifos, dimethoate, monocrotophos, metalaxyl, methomyl, hexaconazole, myclobutanil, carbendazim) in fresh grape samples	BEH C-18	Water:acetonitrile, with 0.3% FA	Triple-Q-ESI-MS/MS	[131]
Chloronicotinyl pesticides (imidacloprid, acetamiprid, thiacloprid) in salad vegetables	LC C-18	Water:acetonitrile, with 0.3% FA	TOF-MS/MS	[132]

TABLE-10
SEPARATIONS OF ISOMERS USING LC-MS/MS CONDITIONS

Isomers (samples)	Column	Mobile phase (elution)	Detector	Ref.
Flavanone, naringenin and hesperetin (in spices samples)	Chiralpak AD-3R	Water:acetonitrile, with 0.1% FA (gradient)	Triple-Q-MS/MS	[133]
Trantinterol (in rat plasma)	BEH C-18	3 mM Ammonium acetate in water & acetonitrile (gradient)	Triple-Q-MS/MS	[134]
2-(2-Hydroxypropanamido)benzoic acid (in rat plasma)	Thermo C-18	Water:methanol, with 0.1% FA (gradient)	Triple-Q-MS/MS	[135]
60 Stimulants & their isomers (in urine sample)	BEH C-18	Water:acetonitrile, with 0.1% FA (50:50; %v/v)	ESI-Triple-Q-MS/MS	[136]
Vigabatrin & S-enantiomer (in mouse serum)	ZORBAX C-18	10 mM Ammonium formate in water & methanol (gradient)	Q-TOF-MS/MS	[137]
Zoxamide (in vegetables & fruits)	Lux Amylose chiral	Acetonitrile:water (70:30; %v/v) (Isocratic)	Triple-Q-ESI-MS/MS	[138]

Analysis of antioxidants and phenolic compounds: Antioxidants can combat free radicals, which are known to contribute to various diseases. Antioxidants are being used more in the food industry because of their antibacterial properties. Kivrak *et al*. [140] conducted the individual phenolic profiles of *S. potentillifolia*, *S. albimaculata* and *S. nydeggeri* and measured the antioxidant activity in salvia species using the UPLC-ESI-MS/MS technology in these medicinal plants collected from South West Anatolia, Turkey.

Therapeutic drug monitoring: Diagnostic testing that determines the concentration of specific medications in the blood is referred to as therapeutic drug monitoring. The study is heavily reliant on LC-MS/MS for the purpose of achieving rapid detection, excellent precision and reliable results. The use of UPLC-MS techniques has been utilized in order to do the high-throughput screening on antibiotics. Toxicological profiles are successfully determined *via* identification and characterization of byproducts such as toxic metabolites, degradation products, impurities and related isomers. Thomas *et al*. [141] developed a UPLC-MS/MS technique to monitor the etonogestrel levels in serum, which is beneficial for analyzing the drug's pharmacokinetics. Carlier [142] studied the therapeutic monitoring of plasma levels of β-lactam antibiotics. The analysis of seven β-lactam antibiotics and two β-lactamase inhibitors in human plasma was conducted using a validated UPLC-MS/MS method. The assay has effectively measured amounts of amoxicillin/clavulanic acid, cefuroxime and meropenem in plasma samples collected from the intensive care patients. Stolker *et al*. [143] also developed the UPLC-TOF-MS technique to detect over 100 veterinary medicines in milk. The analyzed veterinary drugs belong to several classes such as benzimidazoles, macrolides, penicillins, quinolones, sulphonamides, pyrimidines, tetracyclines, nitroimidazoles, tranquillizers, ionophores, amphenicols and non-steroidal anti-inflammatory agents (NSAIDs). This method appears to be robust for analyzing veterinary medications as well as organic pollutants such as pesticides, mycotoxins, and plant poisons in a single approach.

High-throughput screening (HTS): Systematic approach for screening, characterization and determination of synthetic, organic and pharmaceutical compounds is known as high-throughput screening. It allows swift testing of several compounds for their biological activities *via* an automated screening process such as UPLC-MS/MS instruments. By applying high-throughput screening steps pharmacokinetic, therapeutic, toxicological, analytical, degradation data of new drugs can be obtained. It reduces cost, time, materials and solvents during drug development. An overview of the high-throughput screening approaches employed in both academic and industrial research programs was outlined by Martis *et al*. [144]. Szymanski *et al.* [145] reviewed the utilization of HTS assays in the assessment of toxicity and drug development. They described the applications of HTS in determination of modulators of drug-metabolizing enzymes, pharmacological profiling and complex cellular toxicity and cytotoxicity assays. Whereas Armstrong reviewed [146] the assay adaptations, robotic equipment and implementation strategies that allow successful HTS programs. Kyranos *et al.* [147] also summarized and reviewed the high-throughput techniques for compound characterization and purification by mass spectrometry coupled with super-critical fluid chromatography.

Analysis of doping agents and prohibited compounds: Screening methods using LC-M/MS are rapidly expanding in the fields of clinical and forensic toxicology. Literature has been demonstrated the identification and quantitative determination of suspect drugs, emerging drugs of abuse and psychoactive substances [148-154]. Badoud *et al.* [155-157] described the analysis of doping agents in two steps *i.e.* rapid screening and confirmatory analysis. The method was based on UHPLC-Q-TOF-MS. Various 103 doping agents from different classes such as β blockers, stimulants, diuretics and narcotics were analyzed. Ventura *et al.* [158] analyzed 34 forbidden drugs by UPLC-MS/MS method using C-18 column and water & acetonitrile with formic acid as mobile phase in gradient elution. The identification was done by ESI-MS/MS in positive and negative ionization mode. The detection limits were 50 ng to 200 ng for all the compounds comply with quality standards established by world anti-doping agency. Analyses of doping agents/prohibited drugs are summarized in Table-11.

Conclusion

In this review article, the applications of UHPLC-MS/MS for the analysis of pharmaceuticals, synthetic compounds, pharmacokinetic and metabolite study, biochemical, vitamins, food, biomolecules (such as amino acids, peptides, proteins, carbohydrates and lipids) and pesticides analysis has been described. The technique has also been successfully applied for structural identification and quantitative determination of compounds analyzed in the field of analytical chemistry. The details of compounds analyzed along with applied chromatographic conditions such as column and mobile phase compositions along with various mass analyzers have been compiled. The uses of UHPLC-MS/MS in the study of doping substances in forensic and clinical toxicology have also been documented. The brief introduction on development of UHPLC column packing materials and different types of mass analyzers such as single quadrupole, triple quadrupole and time-of-flight mass also described. This review offers an in-depth understanding of the uses of UHPLC-MS/MS technology, assisting researchers in conducting their research in the field.

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CONFLICT OF INTEREST

The author declare that there is no conflict of interests regarding the publication of this article.

TABLE-11
ANALYSIS OF DOPING AGENTS/PROHIBITED DRUGS USING LC-MS/MS

Doping agents/prohibited drugs	Sample matrix	Limit of detection	Detector	Ref.
Synthetic glucocorticoids, stimulants (formoterol, modafinil and mesocarb), anti-oestrogens (finasteride, exemestane, anastrozole, letrozole and formestane) and synthetic anabolic steroids (stanozolol, gestrinone and tetrahydrogestrinone)	Urine	1-30 ng/mL for anti-oestrogens, glucocorticoids & steroids; 100-200 ng/mL for stimulants	Triple-Q-ESI-MS/MS	[159]
18 Narcotics drugs	Urine	0.5 and 10 ng/mL	Triple-Q-ESI-MS/MS	[160]
Salbutamol	Urine	200 ng/mL	ESI-MS/MS	[161]
Diuretics and stimulants	Urine	25-250 ng/mL (diuretics); 5-500 ng/mL (stimulants)	Orbitrap-MS/MS	[162]
Anabolic agents, β2-agonists, hormone antagonists, diuretics, stimulants, narcotics, glucocorticoids and β-blockers	Urine	Required limits of WADA	Triple-Q-ESI-MS/MS	[163]
Desmopressin (analogue of the endogenous peptide hormone arginine vasopressin)	Urine	25 pg/mL	Triple-Q-ESI-MS/MS	[164]
3-OH-stanozolol, methyl phenidate, mesocarb, clomiphene metabolite and carboxy finasteride	Urine	0.5 ng/mL for carboxy finasteride & 1-5 ng/mL for other drugs	Triple-Q-ESI-MS/MS	[165]
Anabolic agents, peptide hormones, β-2 agonists, hormones and metabolic modulators and diuretics, stimulants, narcotics, cannabinoids and glucocorticoids	Urine	Required limits of WADA	Triple-Q-ESI-MS/MS	[166,167]
Glucocorticosteroids	Urine	5-20 ng/mL	Triple-Q-ESI-MS/MS	[168]
Exogenous compounds, diuretics, β-blockers, stimulants & steroidal drugs	Urine	Required limits of WADA	Triple-Q-ESI-MS/MS	[169]
Stimulants and its isomeric compounds	Urine	50 ng/mL	Triple-Q-ESI-MS/MS	[170]
Amphetamines, opioids, cocaine, benzodiazepines (BZDs) and barbiturates	Urine	2-200 ng/mL	ESI-QTOF-MS	[171]
Illegal & therapeutic drugs, pesticides, alkaloids, other toxic chemicals and metabolites	Blood and urine	0.5-2 ng/mL for basic drugs & 2-20 ng/mL for benzodiazepines	QTOF-MS	[172]
4-Anilidopiperidine-related fentanyl analogues	Blood	0.0005-0.001 mg/kg	QTOF-MS	[173]
Diuretics, CNS stimulants and opiates	Urine	1 ng/mL to 50 ng/mL	ESI-MS/MS	[174]
Phenethylamine, amphetamine, cathinone, piperazine, ketamine & ritalinic acid	Urine	Under permitted limits	HRMS-QTOF	[175]
Anabolic and androgenic steroids (AASs) –testosterone & its epimers such as epitestosterone, boldenone and epiboldenone, nandrolone & epinandrolone	Human & equine plasma	50 pg/mL	Triple-Q-ESI-MS/MS	[176]
Illicit drugs, opiates, opioids, sedative, stimulants & γ-aminobutyric acid analogs	Urine	2 ng/mL	Triple-Q-ESI-MS/MS	[177]
Cannabinoids, opioids, cathinones, benzodiazepines (dBZDs), phenethylamines, & tryptamines	Blood	0.25-10 ng/mL for cannabinoids & 0.25-25 ng/mL for other drugs	Triple-Q-ESI-MS/MS	[178]
Testosterone androstenedione and 5α-dihydrotestosterone	Serum	50-500 pg/mL	Triple-Q-ESI-MS/MS	[179]
Endogenous steroids (blood steroid profiling)	Serum, plasma & DBS	Accepted limits	Triple-Q-ESI-MS/MS	[180]

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