A Comprehensive Review on Developed Pharmaceutical Analysis Methods by Iranian Analysts in 2018

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Abstract
This article summarizes the publishing activities including bioanalytical and pharmaceutical analyses carried out in Iran in 2018 in order to connect academic researchers to those in industry, medical care units and hospitals. A wide spectrum of analytical methods has been used to determine and/or evaluate drug levels in the biological samples, based on physical, chemical and biochemical principles. We have compiled a concise survey of the literature covering 125 reports and tabulated the relevant analytical parameters. Chromatographic and electrochemical methods were found to be the technique of choice for many workers and almost 83% studies were performed by using these methods. This is the first annual review of the literature searching in SCOPUS database for published bioanalytical and pharmaceutical analysis researches in Iran.

Introduction
Iran (also known as Persia in the West) has a very long history of civilization and the Iranian scientists played a significant role in the scientific findings in the past. Geographically, Iran is located in the Silk Road connecting Asia to Europe and had scientific interactions with the ancient civilizations of Greece, India, and China beside the economic and cultural interactions. Great scientists have emerged from Iran who contributed substantially in expanding medicine, chemistry, physics, mathematics, astronomy, philosophy etc. They played an essential role to keep alive the scientific approaches in the Dark Ages and handing over these approaches to the pionners of Renaissance.

The history of higher education in Iran goes back to centuries before the birth of Jesus, as examples schools of Nisibis, Sarouyeh, Reishahr. The first educational complex in the form of university was Academy of Gundeshapur or Jundishapur in Alvaz in the 3rd century CE and was attracted scientists and scholars from Rome, China, and India. Various books were written in Pahlavi script in Jundishapur. After spread of Islam to Iran in the mid 7th century CE, the Islamic world entered to the Golden age of learning. The Abbasi caliphate invited the scientists (from different origins including Iranian, Jewish, Syrian, Greek etc.) to the new capital of Islamic empire, Baghdad. Many Pahlavi books were translated into Arabic. A number of Iranian scientists are well-known in the West includes; Razes (865-925 CE), Majusi which was called as Haly Abbas in the Western literature (930-994 CE) and Avicenna (980-1037 CE). The Rab' e Rashidi (Rabi Rashidi) complex in Tabriz (Tauris) was the next comprehensive university established ~ 700 years ago which consist of various faculties, libraries, production units for medicine and also farms for herbas production. The updated and Western style higher education institution was found by Amir Kabir in the form of Dar ul-Funun in Tehran on 1851 which is continued the academic jobs as the University of Tehran later on.14

The first paper with Iran affiliation under subject of chemistry indexed in Scopus data base goes to back to 1840 and was published by Zinin3 in German language. Figure 1 depicts the number of publications per year indexed in Web of science since 1983 and searched using “AFFILCOUNTRY (Iran)”. Then the reported publications are limited to the subject of “Chemistry” and the sub-category of “Analytical chemistry” and “Pharmaceutical analysis”. Concerning the number of publications, there is an obvious increase in the all research activities in Iran after year 2000 and continuously increasing patterns in the number of articles was observed for articles published by Iranian researchers in the field of chemistry and analytical chemistry. Until now, the maximum numbers of articles

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published per year (i.e. in 2018) was 53624 which 7819 of them are in chemistry subject and 939 of chemistry articles is related to analytical chemistry. From citation viewpoint, the highest number of citations for the articles until now is related to Assadi et al. published in Journal of Chromatography A with 2339 citations.

Pharmaceutical research encompasses a wide array of researches, extending from “basic research” to “clinical research” conducted to expand knowledge in the field of drug manufacturing, drugs and pharmaceutical analysis including therapeutic drug monitoring (TDM) and or medication concentrations control in the biological fluids. Analytical chemistry as an inseparable part of pharmaceutical analysis employs various instruments and methods to identify, and quantify pharmaceutical compounds in different stages of drug development and clinical application. Bioanalytical methods as subset of analytical methods can be used for the quantification of drugs, their metabolites and also biomarkers in various biological matrices. The applicability of bioanalytical methods in the pharmaceutical research for analysis of the biological samples became the mainstay of pharmaceutical analysis development. The main aim in the pharmaceutical analysis is selecting the appropriate methodology to drug monitoring, and developing valid analytical schemes that are performed with suitable quality. So far, various analytical methods including spectrophotometric, fluorometric methods, high-pressure liquid chromatography (HPLC) in combination with different detection methods, such as UV detection, fluorescence detection (FD), or mass spectrometry (MS), gas chromatography (GC) in combination with flame ionization detector (FID) and MS and capillary electrophoresis were developed for analysis of pharmaceutical compounds in the biological samples. As many different types of analytical methods are reported for pharmaceutical analysis, the selection of an appropriate assay for a given drug will be easy if the respective merits of each method are documented.

To the best of our knowledge, this is the first annual review to summarize Iran's published pharmaceutical analysis studies which covers the bioanalytical researches conducted in Iran for determination of pharmaceuticals in various biological samples in 2018. In order to find the reported studies, SCOPUS database search are limited to year of 2018 with the keyterms of: 'drug determination, pharmaceutical determination, drug analysis, pharmaceutical analysis, drugs level in biological samples and pharmaceuticals level in biological samples'. A total of 125 studies were identified for the given keywords. Since this review is limited to the determination methods of drug/pharmaceutical compounds in the biological samples, other sample matrices such as food and environmental samples are excluded and the literature search was restricted to the biological samples only.

Reported Analytical Methods for Determination of Drug/pharmaceutical Compounds in the Biological Samples

According to methodological aspects, the selected literature on the determination of pharmaceutical compounds in the biological samples were classified into several categories.

Optical methods
Spectrophotometry
Spectrophotometric methods are the commonly used methods for analysis due to their fast, available and
simple instrumentation. The reported spectrophotometric studies in Iran in 2018 are summarized here and the analytical properties of each method are given in Table 1. Barkat Rezaei et al. developed a poly (vinyl alcohol)/chitosan (PVA/CS) nanofiber decorated with Ag ions as a smart spectrophotometric probe for determination of azathioprine in spiked serum samples. In the absence of azathioprine, Ag ions reduce by ascorbic acid and result in the formation of decorated silver nanoparticles (AgNPs) on to the surface of nanofibers. The presence of azathioprine during reduction process leads to a decrease in the formation of AgNPs on to the surface, consequently decreasing plasmon resonance intensity of nanoparticles. Hashemi et al. reported a combination of dispersive liquid-liquid microextraction (DLLME) method and surface plasmon of silver nanoparticles for determination of captopril in spiked serum and urine samples. The presence of captopril affected the AgNPs synthesis and results in enhancement in plasmon absorbance intensity of nanoparticle. Shahrouei et al. also employed a gold nanoparticle's aggregation for direct determination of ceftriaxone in spiked urine and serum samples. The suggested mechanism for aggregation of nanoparticles in the presence of ceftriaxone molecules are given in Figure 2. Farahmand et al. developed a spectrophotometric method for determination of atenolol, propanolol and carvedilol in plasma and urine samples after extraction with an air assisted liquid–liquid microextraction (AA-LLME) by applying the solidification of a floating organic droplet method for simultaneous extraction of drugs. Hamid et al. used a surfactant ion pair-switchable solvent dispersive liquid–liquid microextraction (SIP-SS-DLLME) for extraction/pre-concentration of phenazopyridine prior to spectrophotometry measurement in spiked urine and plasma samples. Protonated triethylamine bicarbonate and Aliquat 336 are used as a protonated switchable solvent and ion-pair agent in this study, respectively. Nezhadali et al. used a solid phase extraction (SPE) method based on molecularly imprinted polymers (MIPs) prior to spectrophotometry determination for fluoxetine. The MIPs were synthesized using pyrrole as a functional monomer and fluoxetine as a template molecule. Mehrabifar et al. described a spectrophotometric method for the determination of penicillamine based on analyte derivatization with 6-dichlorophenolindophenol as the chromogenic agent. They used Fe$_3$O$_4$ nanoparticles for pre-concentration of penicillamine from spiked serum samples. Kamari et al. used a Fe$_3$O$_4$ @SiO$_2$-MIP for magnetic SPE of amitriptyline in spiked plasma and urine samples, Sadat Alaei used a photoresponsive molecularly imprinted polymers conjugated hyperbranched polymers based on functionalized magnetic nanoparticles (PMIP@HBPM) for determination of azathioprine in spiked urine and plasma prior to analyte determination and Amraei et al. reported a direct spectrophotometric determination of cefixime in spiked urine and plasma using parallel factor analysis (PARAFAC) and partial least squares (PLS). As mentioned in all reports, the spiked biological samples were used to demonstrate the application of the methods on real samples. Due to relatively poor selectivity of spectrophotometric methods and presence of drug's metabolites with very similar spectroscopic properties, application of the developed methods on real samples and also reporting the selectivity and also interference results are highly recommended.

Figure 2. Suggested mechanism for the nanoparticles aggregation in the presence of ceftriaxone molecules in aqueous and micellar media. Adapted with permission from Shahrouei et al. Copyright (2018) Elsevier.
Fluorimetric methods are usually more selective and sensitive than absorbance methods. This is due to the fact that fluorescence emission is detected against a low background isolated from the excitation source. Soleimani et al. reported a validated spectrofluorometry method for determination of rizatriptan in urine samples after its extraction with the aid of a Fe$_3$O$_4$@SiO$_2$-MIP. In their work, adsorption equilibrium behaviors were studied and the results showed that rizatriptan adsorption on the nanosorbent is monolayer and is compatible with Langmuir assumptions. Some similar works were performed for determination of ofloxacin in plasma and urine samples after extraction by Fe$_3$O$_4$@SiO$_2$@mSiO$_2$–NH$_2$ nanosorbent. Other similar works were performed for determination of furosemide in serum samples after extraction by a DLLME with methanol and chloroform solvent mixture and for determination of ofloxacin in spiked plasma samples after extraction by using CoFe$_2$O$_4$ nanoparticles grafted multi-walled carbon nanotubes (MWCNTs).

Eskandari et al. used a fluorometric probe based on the MIP capped terbium metal-organic frameworks (MIP@TbMOF-76) for the measurement of cefixime in urine samples. The synthesized composite had an intense fluorescence emission related to the terbium emission which undergo a decrease in the presence of cefixime. The cefixime extraction procedure was performed by Fe$_3$O$_4$/GO before analysis. Amjadi et al. synthesized a dual-emission molecularly imprinted mesoporous silica embedded with carbon dots and CdTe quantum dots (mMIP@CDs/CdTe QDs) and used it for determination of celecoxib in spiked serum samples. Detection mechanism is quenching of green emissive QDs in the presence of celecoxib. Other similar works were performed for determination of atropine by using a MIP capped GQDs in spiked plasma samples, and for determination of tetracycline using fluorescent nano-sensor based on oxidized starch polysaccharide biopolymer-capped CdTe/ZnS quantum dots. Rahbar et al. synthesized a graphitic carbon nitride nanosheet (g-C$_3$N$_4$) as nano fluoroprobe and used for determination of metformin in spiked serum samples. Nanosheets were synthesized by direct pyrolysis of melamine at 600°C. Cu (II) is used as a quencher for g-C$_3$N$_4$ nanosheets; addition of metformin to the solutions leads to fluorescence restoring proportional to its concentration which indicating that metformin molecule as a strong ligand participates in complex formation reaction with Cu (II) ions. A similar work was performed by Amin et al. for determination of zoledronic acid in serum samples in the presence of a nitrogen doped carbon dots (N-CDs) - Fe$_3$$^{+}$ as a label free fluorescence platform. An illustration of fluorescence sensing strategy for zoledronic acid detection are shown in Figure 3. Najafi et al. used a thioglycolic acid (TGA)-capped Au: CdTe quantum dots (QDs) for determination of gemcitabine in plasma and urine samples. The response of probe is result of quenching in fluorescence of nanoprobe due to the formation of a TGA-capped Au: CdTe QDs– gemcitabine complex and Bahrami et al. used a combined unfolded principal component analysis and artificial neural network (UPCA-AN) for determination of ibuprofen in serum by three-dimensional excitation–emission matrix fluorescence spectroscopy. Analytical performance of each reported study are summarized at Table 1.

**Resonance light scattering method**

Resonance light scattering (RLS) is an optical method based on elastic light-scattering and occurs when an incident beam in energy is close to an absorption band. Maleki et al. synthesized a polyacrylonitrile nano fibers decorated with magnetic carbon dots (MCDs@NFs) nanocomposite for determination of famotidine in spiked serum samples. Possible mechanism for RLS enhancement is this fact that the RLS properties is related to morphology of the particles and the molecular volume. So, the higher RLS intensity observed for nanocomposite in the presence of famotidine is due to the bigger molecular volume after assembling of famotidine on the nanoparticle's surface.

![Figure 3](https://example.com/figure3.png)

**Figure 3.** A schematic mechanism for zoledronic acid detection with N-CDs/Fe$_3$$^{+}$ system. Adapted with permission from Amin et al. Copyright (2018) Elsevier.
Table 1. Analytical details of optical methods used for pharmaceutical analysis in biological samples conducted in Iran (year 2018).

| Method               | Analyte             | Sample | Linear range          | Detection limit | Remarks                                                                 | Ref. |
|----------------------|---------------------|--------|-----------------------|-----------------|--------------------------------------------------------------------------|------|
| Spectrophotometry    | Azathioprine        | Serum  | 0.14 – 2.88 µmol L⁻¹  | 0.09 µmol L⁻¹   | PVA/CS nanofiber decorated with Ag-NPs as a smart probe                 | 10   |
| Spectrophotometry    | Captopril           | Serum  | 0.77 – 22.5 nmol L⁻¹  | 0.51 nmol L⁻¹   | -                                                                        | 11   |
| Spectrophotometry    | Ceftriaxone         | Urine  | 5 – 300 ng mL⁻¹       | 3 ng mL⁻¹       | Gold nanoparticles as a nanoprobe                                        | 12   |
| Spectrophotometry    | Atenolol            | Urine  | 0.3 – 6 µg mL⁻¹       | 0.09 µg mL⁻¹    | Using floating organic droplet solidification for simultaneous extraction of drugs | 13   |
| Spectrophotometry    | Propanolol          | Urine  | 0.3 – 1.4 µg mL⁻¹     | 0.08 µg mL⁻¹    |                                                                         |      |
| Spectrophotometry    | Carvedilol          | Urine  | 0.3 – 2 µg mL⁻¹       | 0.1 µg mL⁻¹     |                                                                         |      |
| Spectrophotometry    | Phenazopyridine     | Plasma | 5 – 180 µg L⁻¹        | 0.88 µg L⁻¹     | Using a SIP-SS-DLLME method for analyte extraction                      | 14   |
| Spectrophotometry    | Fluoxetine          | Plasma | 10⁻⁷ – 10⁻⁴ mol L⁻¹   | 6.56×10⁻⁵ mol L⁻¹ | Using a MIP based on pyrrole for SPE of fluoxetine                      | 15   |
| Spectrophotometry    | Penicillinamide     | Serum  | 50 – 3000 µg L⁻¹      | -               | Using Fe₃O₄ NPs for analyte pre-extraction                              | 16   |
| Spectrophotometry    | Amitriptyline       | Plasmm | 0.05 – 250 mg L⁻¹     | 0.01 mg L⁻¹     | Using a Fe₃O₄@SiO₂-MIP for analyte extraction                           | 17   |
| Spectrophotometry    | Azathioprine        | Plasma | 0.1 – 80 µg mL⁻¹      | 1.77 ng mL⁻¹    | Using of PMIP@HBPM for analyte extraction                               | 18   |
| Spectrophotometry    | Cefixime            | Urine  | 0.5 – 9.0 µg mL⁻¹     | -               | Using PARAFAC and PLS                                                  | 19   |
| Spectrofluorometry   | Rizatriptan         | Urine  | 2.5 – 200 ng mL⁻¹     | 1.1 ng mL⁻¹     | Using a Fe₃O₄@SiO₂-MIP for analyte extraction                           | 20   |
| Spectrofluorometry   | Ofloxacin           | Plasma | 1 – 500 µg L⁻¹        | 0.21 µg L⁻¹     | Using Fe₃O₄@gsiO₂@msiO₂–NH₂ for analyte extraction                      | 21   |
| Spectrofluorometry   | Furosemide          | Serum  | 0.3 – 20 µg mL⁻¹      | 0.12 µg mL⁻¹    | Using DLLME with methanol and chloroform solvent mixture for analyte extraction | 22   |
| Spectrofluorometry   | Ofloxacin           | Plasma | 100 – 750 ng mL⁻¹     | 23 ng mL⁻¹      | Using CoFe₃O₄/MWCTNs for analyte extraction                             | 23   |
| Spectrofluorometry   | Cefixime            | Urine  | 0.8 – 90 ng mL⁻¹      | 0.34 ng mL⁻¹    | Using Fe₃O₄@GQ for SPE of cefixime and MIP@TbMOF-76 as a fluorometric probe | 24   |
| Spectrofluorometry   | Celecoxib           | Serum  | 0.08 – 0.90 µmol L⁻¹ | 57 nmol L⁻¹     | Using mMIP@CDs/CdTe QDs as a nanoprobe                                 | 25   |
| Spectrofluorometry   | Atropine            | Plasma | 0.5 – 300 ng mL⁻¹     | 0.22 ng mL⁻¹    | Using MIP capped GQDs as a nanoprobe                                    | 26   |
| Spectrofluorometry   | Tetracycline        | Urine  | 9.14 – 7230 nmol L⁻¹  | 2.74 nmol L⁻¹   | Using oxidized starch polysaccharide biopolymer-capped CdTe/ZnS quantum dots as nanoprobe | 27   |
| Spectrofluorometry   | Metformin           | Serum  | 0.01 – 20 µmol L⁻¹    | 3 nmol L⁻¹      | Using of gC₃N₄/Cu(II) as a nano fluorochrome                           | 28   |
| Spectrofluorometry   | Zoledronic acid     | Serum  | 0.1 – 10 µmol L⁻¹     | 0.04 µmol L⁻¹   | Using a N-CDs - Fe⁺⁺ system as a fluorescence platform                   | 29   |
| Spectrofluorometry   | Gemcitabine         | Plasma | 0.3 – 100 µmol L⁻¹    | 0.1 µmol L⁻¹    | TGA-capped Au: CdTe QDs as a nanoprobe                                  | 30   |
| Spectrofluorometry   | Ibuprofen           | Serum  | 0.043 – 0.43 µmol L⁻¹ | 0.519 nmol L⁻¹  | Using UPCA-AN method                                                   | 31   |
| RLS                  | Famotidine          | Serum  | 0.15 – 50 µmol L⁻¹    | 0.04 µmol L⁻¹   | Using MCDs@NFs nanocomposite as a sensor                                | 32   |

**Electrochemical methods**

Electrochemical methods are regarded as more sensitive method in compared with optical methods. In electrochemical techniques, the potential, current, or charge in an electrochemical cell serves as the analytical signal. Almost all electrochemical studies performed in Iran in 2018 are summarized in Table 2. As can be seen from Table 2, different types of electrochemical techniques...
Table 2. Analytical details of electrochemical methods used for pharmaceutical analysis in biological samples conducted in Iran (year 2018).

| Method                          | Analyte                  | Sample       | Linear range                        | Detection limit          | Remarks                                                                 | Ref. |
|--------------------------------|--------------------------|--------------|-------------------------------------|--------------------------|--------------------------------------------------------------------------|------|
| DPV                            | Levodopa, Carbidopa Methyldopa, Benserazide, Tolcapone, Entacapone | Serum        | 10 – 320 µmol L⁻¹ 0.5 – 600 µmol L⁻¹ 2 – 380 µmol L⁻¹ 1 – 36 µmol L⁻¹ 0.1 – 178 µmol L⁻¹ 2 – 85 µmol L⁻¹ | -                        | Ag/AgCl as reference electrode, a Pt wire as auxiliary electrode and a gold electrode as a working electrode. | 35   |
| Voltammetry                    | Sulfasalazine            | Serum        | 0.009 – 1.6 µmol L⁻¹ 0.0017 µmol L⁻¹ | Ag/AgCl as a reference electrode, NiO NPS modified CPE as working electrode | 36   |
| Voltammetry                    | Fluconazole              | Serum, Urine | 0.01 – 400 µmol L⁻¹ 3.5 nmol L⁻¹ | A yolk shell Fe₃O₄@PA-Ni@Pd/Chitosan nanocomposite -modified CILE as working electrode | 37   |
| Voltammetry                    | Trazosin                 | Serum, Urine | 2 – 250 µmol L⁻¹ 0.3 µmol L⁻¹ | Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and MIP/AuNPs/SPCE as working electrode | 38   |
| DPV and Square wave voltammetry (SWV) | Alprazolam, Chlordiazepoxide, Clonazepam, Diazepam, Oxazepam | Serum, Urine | 0.05 – 0.42 µmol L⁻¹ 0.28 – 0.65 µmol L⁻¹ 0.075 – 0.4 µmol L⁻¹ 0.02 – 1.0 µmol L⁻¹ 0.063 – 1.39 µmol L⁻¹ | Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and poly (DA-CS)-AuNPs- modified GCE as working electrode | 39   |
| SWV                            | Raloxifene               | Serum        | 0.03 – 520 µmol L⁻¹ 7.0 nmol L⁻¹ | Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and CPE/NiO/SWCNTs/ 1B4MPTFB as working electrode | 40   |
| SWV Amperometry                | Epinephrine              | Serum        | 0.36 – 380 µmol L⁻¹ 0.3 nmol L⁻¹ | Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and GQD-CS modified CPE electrode as working electrode | 41   |
| DPV                            | Nifedipine, Dehydronifedipine | Urine       | 0.1 – 100 µmol L⁻¹ 0.015 µmol L⁻¹ 0.017 µmol L⁻¹ | Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and MWCNT modified GCE as working electrode | 42   |
| Voltammetry                    | Epirubicin               | Serum        | 0.02 – 700 µmol L⁻¹ 7.0 nmol L⁻¹ | Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and Fe₃O₄-SWCNTs/ MOCTICl/ CPE as working electrode | 43   |
| DPV                            | Didanosine               | Urine        | 0.02 – 60 µmol L⁻¹ 8 nmol L⁻¹ | Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and PGE/PPy/rGO as working electrode | 44   |
| SWV                            | Midazolam                | Urine        | 0.5 – 1000 nmol L⁻¹ 0.177 nmol L⁻¹ | Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and MIP nanoparticles modified CPE as working electrode | 45   |
| SWV                            | Trimipramine             | Urine, Serum | 0.1 – 25 nmol L⁻¹ 0.045 nmol L⁻¹ | Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and CPE modified with MWCNTs and a nano-structured MIP as working electrode | 46   |
| SWV                            | Mephedrone               | Plasma, Urine | 1 – 100 nmol L⁻¹ 0.8 nmol L⁻¹ | Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and MIP/polytyramine/f-MWCNT@ AuNPs nanocomposite/GCE as working electrode | 47   |
| CV                             | Tramadol                 | Urine        | 3.5 nmol L⁻¹ – 0.01 mol L⁻¹ 2.04 nmol L⁻¹ | Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and GNS@Ag NPs/ MIPNPs/[BMP] Ti2N RTIL/CPE as working electrode | 48   |
| CV                             | Dopamine                 | Serum        | 0.8 – 800 µmol L⁻¹ 0.62 µmol L⁻¹ | Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and MWCNT/TOAı₃ /CIL as working electrode | 49   |
| DPV                            | Methimazole              | Serum        | 5.2 – 50 µmol L⁻¹ 2 µmol L⁻¹ | Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and CuNPs-P-L-Arginine/MWCNTs/GC as working electrode | 50   |
| DPV                            | Meloxicam                | Plasma       | 9.0 – 8500 nmol L⁻¹ 1.008 nmol L⁻¹ | Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and AuNPs-ChCl-GO/CPE as working electrode | 51   |
### Table 2 Continued.

| Method                      | Drug          | Matrix     | Concentration Range | Electrode Details                                                                                                                                                                                                 |
|-----------------------------|---------------|------------|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| DPV                          | Celecoxib     | Plasma     | 9.6 – 7400 nmol L⁻¹ | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and AgNPs-ChCl-GO/CPE as working electrode                                                                                                         |
| Differential pulse anodic stripping voltammetry (DPASV) | Acyclovir     | Serum      | 0.03 – 1.0 µmol L⁻¹ | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and GCE / MWCNTs / Ag NPs as working electrode                                                                                                 |
| Linear sweep voltammetry (LSV) | Isosuxprine  | Serum      | 0.04 – 5.0 µmol L⁻¹ | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and GCE / MWCNTs / Ag NPs as working electrode                                                                                                 |
| DPV                          | Theophylline  | Urine      | 1.0 – 700 µmol L⁻¹ | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and GCE / MWCNTs / Ag NPs as working electrode                                                                                                 |
| DPV                          | Methyldopa    | Urine      | 0.5 – 800 µmol L⁻¹ | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and GCE / MWCNTs / Ag NPs as working electrode                                                                                                 |
| DPV                          | Epinephrine   | Serum      | 7 – 560 µmol L⁻¹   | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and Ni-LFONRCPE as working electrode                                                                                            |
| DPV                          | Acyclovir     | Urine      | 0.03 – 1.0 µmol L⁻¹ | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and Ni-LFONRCPE as working electrode                                                                                            |
| DPV                          | Paracetamol   | Serum      | 0.04 – 5.0 µmol L⁻¹ | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and Ni-LFONRCPE as working electrode                                                                                            |
| DPV                          | Trypsphan     | Serum      | 7 – 560 µmol L⁻¹   | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and Ni-LFONRCPE as working electrode                                                                                            |
| DPV                          | Favoxatehydrochloride | Urine | 7.8 – 1200 µmol L⁻¹ | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and FMCPE as working electrode                                                                                                         |
| DPV                          | Meclizine     | Urine      | 0.33 – 29.13 µmol L⁻¹ | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and bare GSPE as working electrode                                                                                                          |
| Voltammetry                  | L-Carnitine   | Serum      | 24 – 312 µmol L⁻¹ | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and anodized Ni/Cu alloy electrode as working electrode                                                                               |
| DPV                          | Rituxan       | Serum      | 7 – 300 µmol L⁻¹   | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and PA-MAM/RGO/PGE as working electrode                                                                                                 |
| DPV                          | Azithromycin  | Serum      | 0.3 – 920 nmol L⁻¹ | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and MIP/GNU/GO/GCE as working electrode                                                                                                 |
| Voltammetry                  | Estradiol valerate | Blood | 0.1 – 10000 ng mL⁻¹ | CPE modified with Tb₂(CO₃)₃ nanoparticles as working electrode                                                                                                                |
| DPV                          | Methimazole   | Serum      | 0.007 – 6 nmol L⁻¹ | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and MIP-GCE as working electrode                                                                                                            |
| DPV                          | Diclofenac sodium | Urine | 0.23 – 12.95 µmol L⁻¹ | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and PGPE as working electrode                                                                                                                   |
| DPV                          | Rapaglinide   | Serum      | 0.005 – 1 µmol L⁻¹ | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and MIP-GCE as working electrode                                                                                                            |
| LSV                          | Tizanidine    | Serum      | 0.01 – 1.0 µmol L⁻¹ | Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode, and OPPY/CNT/GCE as working electrode                                                                                                 |
| DPV                          | Propythiouracil | Urine | 0.05 – 5 µg mL⁻¹ | Using a copper nanoparticles-decorated hollow fibers for analyte extraction                                                                                                                                             |
| DPV                          | Nitrazepam    | Urine      | 0.03 – 20 ng mL⁻¹ | Using a HLLME procedure for extraction of nitrazepam. Ag/AgCl as a reference electrode, a Pt wire as auxiliary electrode and modified CPE by b-CD/MWCNTs / Co₃O₄ NPs/CPE as working electrode |
| Adsorptive stripping voltammetry | Warfarin     | Serum Urine | 0.05 – 150 µmol L⁻¹ | A saturated calomel electrode as a reference electrode, a Pt wire as auxiliary electrode and modified CPE by b-CD/MWCNTs / Co₃O₄ NPs/CPE as working electrode |
| Fast Fourier transform SWV    | Estradiol valerate | Blood | 0.1 – 10000 ng mL⁻¹ | CPE modified with Tb₂(CO₃)₃ nanoparticles as working electrode                                                                                                                |

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e.g. differential pulse voltammetry (DPV), adsorptive stripping voltammetry, square wave voltammetry (SWV), amperometry, adsorptive stripping differential pulse voltammetry (ASDPV), differential pulse anodic stripping voltammetry (DPASV), cyclic voltammetry (CV) and linear sweep voltammetry (LSV) were used for pharmaceutical analysis. The common characteristic of all voltammetric methods is the application of a potential to an electrode and the monitoring of the resulting current flowing through the electrochemical cell. Among of these methods, SWV and DPV can offer better sensitivity with higher signal-to-noise ratios, and can be employed as a powerful techniques for determination of trace levels of compounds. So, mostly these methods were used for determination of pharmaceutical compounds in biological samples.

Mohammadi et al. developed a DPV method by using an unmodified gold electrode for simultaneous determination of levodopa, carbidopa, methyldopa, benserazide, tolcapone and entacapone in the presence of dopamine as uncalibrated interference in spiked serum samples. Amani-Beni et al. validated a voltammetric method for determination of sulfasalazine by using NiO nanoparticles modified carbon paste electrode (CPE) in spiked serum samples. Some other electrochemical works were developed and validated for determination of flucloxacillin in serum and urine samples by using a yolk shell Fe₃O₄@PA-Ni@Pd/Chitosan nanocomposite -modified carbon ionic liquid electrode (CILE), for determination of terazosin by using MIP with disposable gold nanoparticles modified screen printed carbon electrode (MIP/AuNPs/SPCE), for simultaneous determination

| Table 2 Continued. |
|---------------------|
| Adsorptive strip-  |
| ping differential   |
| pulse voltammetry   |
| (ASDPV)             |
| Metformin           |
| Urine               |
| 0.1 – 80 µmol L⁻¹  |
| 14 nmol L⁻¹        |
| Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and CPE modified with γ-Fe₂O₃@HAp/Cu (II) as working electrode |
| T1                  |
| Ceftizoxime         |
| Plasma              |
| 0.001 – 1 nmol L⁻¹  |
| 0.00035 nmol L⁻¹    |
| Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and HGNPs/rGO/PGE as working electrode |
| T2                  |
| Docetaxel           |
| Urine               |
| 0.3 – 3.3 µmol L⁻¹  |
| 90 nmol L⁻¹         |
| Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and Au-MWCNTs/GCE as working electrode |
| T3                  |
| Dopamine            |
| Acetaminophen       |
| Xanthine            |
| Urine               |
| 0.3 – 60 µmol L⁻¹   |
| 20 nmol L⁻¹         |
| Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and GCE/PDA-MWCNTs as working electrode |
| T4                  |
| Acetaminophen       |
| Codeine             |
| Urine               |
| 0.01 – 1.5 µmol L⁻¹ |
| 0.007 µmol L⁻¹      |
| Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and CuO-CuFe₂O₄ nanoparticles /CPE as working electrode |
| T5                  |
| Acetaminophen       |
| Pramipexole Carba-  |
| mazepine            |
| Plasma              |
| 2.5 – 110 µmol L⁻¹  |
| 0.58 µmol L⁻¹       |
| Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and ZSM-5 nanozeolite and TiO₂ NPs modified CPE as working electrode |
| T6                  |
| Dopamine            |
| Acetaminophen       |
| Xanthine            |
| Serum               |
| 25 – 3000 pg mL⁻¹   |
| 2 pg mL⁻¹           |
| Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and the modified Au electrode with spindle-shaped gold nanostructure as working electrode |
| T7                  |
| Diclofenac          |
| Morphine            |
| Mefenamic acid      |
| Serum               |
| 0.04 – 1200 µmol L⁻¹|
| 0.008 µmol L⁻¹      |
| Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and NiO-SWCNTs/DDPM/CPE as working electrode |
| T8                  |
| Diclofenac          |
| Urine               |
| 5 – 80 mg L⁻¹       |
| 1.1 mg L⁻¹          |
| A saturated calomel electrode as a reference electrode, a Pt wire as auxiliary electrode and MIP-CPE as working electrode |
| T9                  |
| Flutamide           |
| Urine               |
| 0.05 – 200 nmol L⁻¹ |
| 14 pmol L⁻¹         |
| Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and CPE modified with CuO/GO/PANI as working electrode |
| T10                 |
| Flutamide           |
| Plasma              |
| 0.1 – 110 µmol L⁻¹  |
| 0.029 µmol L⁻¹      |
| Ag/AgCl as a reference electrode a Pt wire as auxiliary electrode and HF/HBP-GO/PGE as working electrode |
| T11                 |
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Figure 4. Illustration of the phase behavior of water and N,N-dipropylamine in HLLME of nitrazepam (a) primary separated water and N,N-dipropylamine phases (b) homogeneous solution of water and N,N-dipropylamine after the addition of HCl (c) cloudy mixture of water and N,N-dipropylamine after the addition of NaOH (d) phase separation. Adapted with permission from Shahraki et al.48

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of alprazolam, chlordiazepoxide, clonazepam, diazepam, and oxazepam in spiked serum samples by using a poly(dopamine-chitosan) (DA-CS)-AuNPs organic-inorganic hybrid – modified glassy carbon electrode (GCE),49 for determination of raloxifene in spiked serum samples by using CPE modified with NiO/SWCNTs and 1-butyl-4-methylpyridinium tetra-fluoroborate (1B4MPTFB),50 for determination of epinephrine in serum by using graphene quantum dots - chitosan (GQD-CS) modified CPE electrode,51 for determination of nifedipine and dehydrofenedipine by using MWCNT modified glassy carbon electrode (GCE),52 for determination of epirubicin in spiked serum samples by using both 3D Fe3O4 decorated single wall carbon nanotubes (Fe3O4-SWCNTs) nanocomposite and 1-methyl-3-octylimidazlium chloride (MOCTICl) as amplifier into CPE,53 for determination of didanosine in spiked serum samples by using pencil graphite electrode modified with polypyrrole and reduced graphene oxide (PGE/PPy/rGO),54 for determination of midazolam in spiked serum samples by using MIP nanoparticles modified CPE,55 for determination of trimipramine in spiked urine and serum samples by using CPE modified with MWCNTs and a nano-structured MIP,56 for determination of mephedrone in spiked urine and plasma samples by using MIP/polytyramine/1-MWCNT@AuNPs nanocomposite/GCE,57 for determination of tramadol by using CPE modified with nanographene/tramadol-MIP/ionic liquid (GNS@Ag NPs/ MIPNPs/ [BMP]T2N RTIL) with measured concentration between 45.2 – 51.0 μmol L⁻¹ in urine sample of patients receiving tramadol,58 for determination of dopamine in spiked serum samples by using a MWCNT/ionic liquid paste electrode / tetra-n-octylammonium triiodide (MWCNT/TOA/+/CIL),59 for determination of methimazole in serum samples by using CuNPs-P-L-Argenine/MWCNTs/GCE,60 for determination of meloxicam in the spiked plasma samples by using CPE modified with gold nanoparticles modified choline chloride functionalized graphene oxide (AuNPs-ChCl-GO),61 for detection of celecoxib in the spiked plasma samples by using CPE modified with AgNPs modified ChCl-GO,62 for determination of acyclovir in spiked serum and urine samples by using GCE modified with a polymeric chitosan film decorated with MWCNTs + TiO2 NPs,63 for determination of isoxsuprine in spiked serum samples by using GCE modified with MWCNTs decorated with Ag NPs,64 for determination of theophylline in spiked urine samples by using GQD modified SPE,65 for determination of methylidopa in spiked urine samples by using a GCE modified with Cu/TiO2 nanocomposite,66 for simultaneous determination of epinephrine, paracetamol and tryptophan in spiked urine and serum samples by using modified CPE with Ni-doped Lewatit FO36 nano ion exchange resin,67 for determination of favoxate hydrochloride and tolterodine tartrate in spiked urine samples by using ferrocene modified carbon paste electrode (FMCP),68 for determination of meclizine in spiked urine samples by using bare graphite screen-printed electrode (GSPE),69 for determination of L-carnitine in spiked serum samples by using anodized Ni/Cu alloy electrode,70 for determination of rituxan in spiked serum samples by using PAMAM dendrimer/RGO nanocomposite modified PGE,71 for determination of azithromycin in serum samples by using GCE modified with MIP / gold nanourchin (GNU) / GO,72 for determination of estradiol valerate in spiked blood samples by using CPE modified with terbium carbonate (Tb3+(CO3)2) nanoparticles,73 for determination of methimazole in the spiked serum samples by using MIP- PGE,74 for determination of diclofenac sodium in spiked serum samples by using pretreated pencil graphite electrode (PPGE),75 for determination of repaglinide in spiked serum and urine samples by using a MIP-GCE,76 and for determination of tizanidine in spiked serum samples by using GCE modified with a thin film of MWCNTs coated with an electro-polymerized layer of titan yellow-doped overoxidized polypyrrole (OPPY).77

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Tahmasebi et al.\textsuperscript{68} reported a DPV method for determination of propylthiouracil in spiked urine samples after electromembrane extraction (EME) by copper nanoparticles-decorated hollow fibers and Shahraei et al.\textsuperscript{69} used a homogeneous liquid–liquid microextraction (HLLME) method (Figure 4) before DPV measurement of nitrazepam in spiked urine samples by using GCE.

It should be noted that the stripping analyses have the lowest limits of detection of any of the commonly used electroanalytical techniques. Gholivand et al.\textsuperscript{70} developed an ASV method for simultaneous determination of warfarin and mycophenolic acid by using CPE modified with b-cyclodextrin/multi-walled carbon nanotubes/cobalt oxide nanoparticles (b-CD/MWCNTs/CuO\textsubscript{4} NPs/CPE) as working electrode. LOD of reported method for warfarin and mycophenolic acid in serum and urine samples were 0.02 and 0.03 µmol L\textsuperscript{-1}, respectively. Mirzajani et al.\textsuperscript{71} used a ASDPV for determination of metformin with LOD of 14 nmol L\textsuperscript{-1} by using CPE modified with γ-Fe\textsubscript{3}O\textsubscript{4}@hydroxyapatite/Cu (II) nanocomposite (γ-Fe\textsubscript{3}O\textsubscript{4}@HAp/Cu (II)). The average found amount in urine samples 6 h after taking a 500 mg metformin hydrochloride tablet was reported to be of 6.7 µmol L\textsuperscript{-1}. A similar work was also performed by Azadmehr et al.\textsuperscript{72} for determination of ceftriaxone using PGE modified by hollow gold nanoparticles (HGNPs)/rGO in plasma samples with a very low LOD of 0.35 pmol L\textsuperscript{-1}. Najari et al.\textsuperscript{73} developed a DPASV method for determination of docetaxel by using Au-MWCNTs/GCE as working electrode in spiked serum and urine samples with LOQ and LOD of 0.3 µmol L\textsuperscript{-1} and 90 nmol L\textsuperscript{-1}, respectively. In some reports, an identical pharmaceutical compound is also measured dopamine in the spiked serum and urine samples without any preconcentration procedures. Ramezani et al.\textsuperscript{74} developed a micellar HPLC-UV method for isocratic determination of dopamine in plasma and cerebrospinal fluid of patients addicted to opiates undergoing surgery.

In our researches, it is found that more than half of the studies reported different methods in compared with other methods. The reported works are classified in the following sections and details of each study are given in Table 3.

**Chromatographic methods**

Chromatographic methods which are physical methods for the separation of mixture based on the concept of partition coefficient, have always been a more specialized approach than optical and electrochemical methods. In our researches, it is found that more than half of the studies in 2018 were performed by these methods. It can be related to high selectivity and specificity of chromatographic methods in compared with other methods. The reported works are classified in the following sections and details of each study are given in Table 3.

**High-performance liquid chromatography (HPLC)-UV detector**

Rezaee et al.\textsuperscript{82} validated a HPLC-UV method for determination of thiopental in spiked plasma samples without any preconcentration procedures. Haghhin et al.\textsuperscript{83} used a HPLC-UV method for determination of morphine in plasma and cerebrospinal fluid of patients addicted to opiates undergoing surgery. Ramezani et al.\textsuperscript{84} developed a micellar HPLC-UV method for isocratic isolation of some cardiovascular drugs including losartan, hydrochlorothiazide and triamterene with different polarities in spiked plasma samples. They used a green mobile phase additive i.e. deep eutectic solvent (DES) to improve the chromatographic behavior of the drugs. As a new type of solvent, DESs have been attracted great attention because of its excellent physical and chemical properties. They can also be used as an extractor solvent in various sample preparation procedures. Rajabiet al.\textsuperscript{85} used an air agitated-emulsification microextraction (AA-EME)-HPLC-UV for simultaneous extraction/determination of amphetamine and methamphetamine by using a DES comprising choline chloride and phenylethanol (ChCl:...
Ph-EtOH). A similar work was performed by Ghoochani et al. for simultaneous determination of escitalopram, desipramine and imipramine in spiked plasma samples. Khataei et al. used a three-phase hollow fiber liquid phase microextraction (HF-LPME) based on two immiscible organic phases by using DES for determination of dydrogesterone and cyproterone acetate in spiked plasma and urine samples. However, other extractor solvents (other than DESs) had also been used before HPLC methods in sample preparation step. For example: Rezaee Moghadam et al. used a DLLME coupled with HPLC-UV method for simultaneous determination of enrofloxacin and ciprofloxacin in tissue samples. Mirparizi et al. used a tandem dispersive liquid–liquid microextraction (TDLLME) followed by HPLC-UV for determination of rivastigmine and donepezil in spiked plasma samples. Similar works were performed for determination of duloxetine in plasma after extraction by using 1-butyl-3-methylimidazolium hexafluoroborate-based ultrasound-assisted in situ solvent formation microextraction (IL-UA-ISFME) procedure, and for determination of sodium closantel in spiked blood and urine samples after extraction by a UA-DLLME.

As has been already described a sample preparation step is often required before chromatographic analysis. In addition to LLME methods, solid phase extraction (SPE) methods have also been used to separate the analytes of interest from possible interferences of biological samples. Asiabi et al. used an electrochemically controlled in-tube solid phase microextraction (EC-IT-SPME) method (modified with nanostructured polypyrrole film), followed by HPLC-UV for simultaneous determination of diclofenac and mefenamic acid in spiked samples of urine and plasma.

Figure 5. Schematic diagram of the packed column preparation for the packed EC-IT-SPME system. Adapted with permission from Asiabi et al. Copyright (2018) Elsevier.
supported liquid membrane and an aqueous receiving phase (pH = 3.1), for simultaneous determination of oxazepam, flurazepam, and diazepam in hair, nail and blood samples after extraction by using a vortex assisted dispersive solid phase extraction approach based on crab shell powder as micro-sorbent, for determination of rizatriptan in spiked plasma and urine samples after extraction by using SBME technique, for determination of diclofenac, ibuprofen, and mefenamic acid in spiked plasma and urine samples after extraction with centrifugeless ultrasound-assisted dispersive micro solid-phase extraction with Zn-Al-LDH-MWCNT nanohybrid as a nanosorbent coupled with salting-out ultrasound-assisted liquid-liquid microextraction based on solidification of a floating organic droplet, for determination of zolpidem in spiked plasma and serum samples after an EME procedure, for determination of phenazopyridine after an extraction procedure by coupling EME and packing a sorbent (a cation exchanger) with reported value of 33 µg L\(^{-1}\) and 237.3 µg L\(^{-1}\) for phenazopyridine in urine sample of patients treated with it respectively after 9 and 12 hour, for determination of diclofenac in spiked plasma and urine samples after extraction by HF-LPME, for determination of valproic acid in spiked plasma samples after extraction by using HF-EME method, and for determination of exemestane, letrozole and paclitaxel in spiked urine samples after extraction by using three-phase HF-LPME based on two immiscible organic solvents (acetonitrile and n-dodecane).

Magnetic solid phase extraction (MSPE) as an alternative method for SPE have mostly been used for sample preparation before HPLC-UV. Safari et al. synthesized a magnetic framework composites (Fe\(_3\)O\(_4\)@TMU-10) microspheres for simultaneous MSPE of some tricyclic antidepressants including amitriptyline and imipramine in plasma and urine samples prior to HPLC-UV determination. The value for imipramine concentration in the investigated urine samples was reported to be 55 µg L\(^{-1}\). A similar work was reported by Baimani et al. for determination of methylprednisolone acetate after extraction with an allyl glycidyl ether/acrylic acid grafted on modified magnetite nanoparticles with functionalized dendrimer conjugated β-CD (AA@MNP-β-CD) from spiked plasma and urine samples (see Figure 6). Similar works were performed for simultaneous extraction of morphine and codeine in the serum and blood samples after extraction by using magnetite (Fe\(_3\)O\(_4\))/rGO/silver nano-composite (Ag NC) (with reported level of 0.610 – 1.075 µg L\(^{-1}\) for morphine and 0.746 – 1.124 µg L\(^{-1}\) for codeine in blood samples of addicted person to opium), for determination of baclofen in spiked urine samples after extraction with superparamagnetic molecularly imprinted biopolymer (SMIBP), for simultaneous determination of dasatinib, erlotinib, and nilotinib in spiked plasma, serum and urine samples after extraction by using bio-inspired magnetic sorbent doped melamine-phenylate supermolecular aggregate (Fe\(_3\)O\(_4\)/MPA) applied for UA-DMSPE, for determination of buprenorphine and norbuprenorphine in spiked plasma samples after extraction by poly (para-phenylenediamine)-modified Fe\(_3\)O\(_4\) nanoparticles (PpPDAM/Fe\(_3\)O\(_4\)), for determination of rivaroxaban in spiked plasma and urine samples after extraction with a high generation thermo-sensitive dendrimer of magnetic nanoparticles/ poly(N-isopropylacrylamide)/G10 4-amino-2,3-dimethyl-1-phenyl-3-pyrazoline-5-one (MNP/PIPAAmG10-ADMPhP) nanocomposite, for
determination of chlordiazepoxide in spiked urine samples after extraction with a magnetic MIP,\textsuperscript{115} for determination of letrozole in spiked plasma and urine after extraction with magnetic nanoparticles (MNP)\textsuperscript{(s)}/ polyethylene glycol (PEG)ylated dendrimer,\textsuperscript{116} and for determination of amphetamine in spiked urine samples after extraction by using a magnetic block copolymer (poly ethylene glycol-b-poly (N,N-dimethylaminoethylethacrylate-co-maleic acid) (magnetic PEG-b-P(DMAEMA-co-MA)).\textsuperscript{117}

**HPLC- diode array detector (DAD)**

DAD as a multi-wavelength detector is used for obtaining spectral profiles of molecular mixtures or chromatographically separated samples providing a facility to check peak purity. The spectrum can be employed to show the optimal wavelength for the detection within one run. Ghorbani et al.\textsuperscript{118} used an ultrasonic assisted magnetic dispersive solid phase microextraction method coupled with HPLC-DAD for determination of some serotonin–norepinephrine reuptake inhibitor drugs such as duloxetine, venlafaxine and atomoxetine in urine samples. They used a magnetic p-phenylenediamine functionalized reduced graphene oxide quantum dots@ Ni nanocomposites (MrGOQDs–PD@ Ni) as a nanosorbent for preconcentration of investigated analytes. Jalilian et al.\textsuperscript{119} developed a similar method for determination of nortriptyline, cetirizine, naproxen, diclofenac and ibuprofen after simultaneous extraction with MWCNT/ MNP@poly(2-aminopyrimidine) composite (MWCNTs/Fe\textsubscript{3}O\textsubscript{4}@PAPy). Alahyari et al.\textsuperscript{120} used a DLLME coupled with HPLC-DAD method with chloroform and acetone as extraction and disperser solvents for determination of some opioids such as morphine, codeine and methadone in urine sample. The concentration of morphine, codeine and methadone in three postmortem urine samples are reported to be in the range of 2.5 – 17.8 µg mL\textsuperscript{-1}, 0.9 – 5.3 µg mL\textsuperscript{-1}, 1.9 – 10.4 µg mL\textsuperscript{-1}, respectively. Rezaei et al.\textsuperscript{121} developed a HPLC-DAD method for simultaneous determination of prednisolone and methylprednisolone and mycophenolic acid in spiked plasma samples. They used a fast-elution protocol and smart methodology based on multivariate curve resolution-alternating least square (MCR-ALS) modeling for this analysis. A similar work was performed for determination of three immunosuppressant drugs including tacrolimus, everolimus and cyclosporine A in whole blood samples using intelligent chemometrics resolving of coeluting peaks in the presence of blood interferences.\textsuperscript{122}

**HPLC-fluorescence detector (FD)**

Fluorescence detectors are the most sensitive and low cost among the existing HPLC detectors. Typically, fluorescence sensitivity is 10 -1000 times higher than that of the UV detector for strong UV absorbing materials. Some of the chromatographic studies are performed by HPLC-FD methods. For example: Rastkari et al.\textsuperscript{123} developed a HPLC-FD method for determination of lisinopril. They used a magnetic polydimethylsiloxane/OH-functionalized multiwalled carbon nanotubes nanocomposite (PDMS/MWCNT-OH-NC) for extraction of lisinopril from spiked plasma samples and 4-fluoro-7-nitro-2,1,3-benzoxadiazole for precolumn derivatization.

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**Figure 7.** Schematic illustration of the developed DSPE-DES-AALLME preconcentration procedure. Adapted with permission from Mohebbi et al.\textsuperscript{109} Copyright (2018) Elsevier.
Table 3. Analytical details of chromatographic methods used for pharmaceutical analysis in biological samples conducted in Iran (year 2018).

| Method     | Analyte          | Sample       | Linear range | Detection limit | Remarks                                                                                     | Ref. |
|------------|------------------|--------------|--------------|-----------------|---------------------------------------------------------------------------------------------|------|
| HPLC-UV    | Thiopeptal       | Plasma       | -            | 0.001 µg mL⁻¹   | Mixture of acetonitrile: methanol: potassium di-hydrogen phosphate buffer (10 mM, pH 2.7) (40:10:50) as mobile phase, Drug monitoring at 280 nm. | 82   |
| HPLC-UV    | Morphine         | Plasma Cerebral-spinal Fluid | -       | -               | -                                                                                           | 83   |
| Micellar HPLC-UV | Losartan Hydrochlorothiazide | Plasma | 7 – 20 µg mL⁻¹ | 0.6 µg mL⁻¹ | 0.12 mol L⁻¹ SDS, 5% acetonitrile, 4% DES, and 2% acetic acid as mobile phase, monitoring at 254 nm | 84   |
| HPLC-UV    | Amphetamine      | Plasma       | 15 – 2000 ng mL⁻¹ | 5.0 ng mL⁻¹ | 0.05 mol L⁻¹ phosphate buffer solution (pH 5.5) and acetonitrile (20:80) as mobile phase, Drug monitoring at 210 nm. Using AA-EME for analyte extraction. | 85   |
| HPLC-UV    | Escitalopram     | Plasma       | 10 – 5000 ng mL⁻¹ | 3.0 ng mL⁻¹ | Acetonitrile and 0.05 mol L⁻¹ phosphate buffer solution (pH 3.0) as mobile phase, Drug monitoring at 220 nm. Using AA-EME-LD-DES for analyte extraction. | 86   |
| HPLC-UV    | Dydrogesterone   | Urine        | 1.0 – 500 µg L⁻¹ | 0.5 µg L⁻¹ | Water: acetonitrile (38:62) as mobile phase, analyte monitoring at 282 nm, Using HF-LPME with DES for analyte preconcentration. | 87   |
| HPLC-UV    | Enrofloxacin     | Tissue       | -            | 5.3 µg kg⁻¹    | Acetonitrile and phosphoric acid buffer (0.01 M, pH 3) (25:75% v/v) as mobile phase, Drug monitoring at 278 nm, Using a DLLME method for analyte extraction. | 88   |
| HPLC-UV    | Rivastigmine     | Plasma       | 2 – 1100 ng mL⁻¹ | 0.5 ng mL⁻¹ | A mixture of 0.05 mol L⁻¹ phosphate buffer (pH 4.0) and acetonitrile (70:30) as mobile phase, Drug monitoring at 210 nm. Using TDLLME for analyte extraction. | 89   |
| HPLC-UV    | Duloxetine       | Plasma       | 2.0 – 1500 µg L⁻¹ | 0.8 µg L⁻¹ | A mixture of ammonium formate (10 mmol L⁻¹) and acetonitrile (40:60) with pH of 3.8 as mobile phase, Drug monitoring at 230 nm, Using IL-UA-ISFME for analyte extraction. | 90   |
| HPLC-UV    | Sodium closantel | Blood, Urine | 10 – 3000 µg L⁻¹ | 1 µg L⁻¹ | A mixture of acetonitrile, water and ammonium acetate buffer of pH 4.3 (45:45:10, v/v) as mobile phase, Drug monitoring at 240 nm. | 91   |
| HPLC-UV    | Phenobarbital    | Urine        | 1 – 300 µg L⁻¹ | 0.35 µg L⁻¹ | 40% acetonitrile and 60% water as mobile phase, Drug monitoring at 220 nm, Using DLPME-SI-SFOD for analyte extraction. | 92   |
| HPLC-UV    | Amitriptyline    | Urine        | 1 – 800 µg L⁻¹ | 0.35 – 0.7 µg L⁻¹ | A mixture of 60% buffer containing 50.0 mmol L⁻¹ sodium dihydrogen phosphate with pH 4.2 containing 0.50 mmol L⁻¹ sodium dodecyl sulfate (SDS) and 40% acetonitrile as mobile phase, Drug monitoring at 210 nm, Using CLPME for analyte extraction. | 93   |
| HPLC-UV    | Diclofenac       | Urine        | 1.3 – 200 µg L⁻¹ | 1.0 µg L⁻¹ | 10 mmol L⁻¹ phosphate buffer (pH= 4.5) and acetonitrile (40:60) as mobile phase, Drug monitoring at 210 nm, Using in-tube SPE for extraction of analyte | 94   |
| HPLC-UV    | Mefenamic acid   | Plasma       | 4 – 1000 µg L⁻¹ | 1.0 µg L⁻¹ | 10 mmol L⁻¹ phosphate buffer (pH= 4.5) and acetonitrile (40:60) as mobile phase, Drug monitoring at 210 nm, Using in-tube SPE for extraction of analyte | 95   |
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Table 3 Continued.

| Method         | Compound         | Matrix | Concentration                  | Mobile Phase                                      | Detection Wavelength | Analyte Extraction Method |
|----------------|------------------|--------|--------------------------------|---------------------------------------------------|-----------------------|---------------------------|
| HPLC-UV        | Diclofenac       | Plasma | 1 – 200 µg L⁻¹                 | Methanol-water (60:40 v/v)                         | 276 nm               | Using LDH/GO               |
|                |                  |        | 2 – 200 µg L⁻¹                 |                                                   |                       |                           |
|                |                  |        | 0.23 µg L⁻¹                    |                                                   |                       |                           |
| HPLC-UV        | L-cysteine       | Urine  | 4 – 1000 µg L⁻¹                | Water-methanol (95:5, v/v; pH 7.0)                | 230 nm               | Using Zn-MOP              |
|                |                  |        | 0.76 µg L⁻¹                    |                                                   |                       |                           |
| HPLC-UV        | Losartan         | Plasma | 24 – 1000 ng mL⁻¹              | Mixture of acetonitrile and acetate buffer (pH 3.8; 10 mM) | 220 nm               | Using SBSE                |
|                |                  |        | 7 ng mL⁻¹                      |                                                   |                       |                           |
| HPLC-UV        | Vincristine      | Plasma | 0.05 – 5 mg L⁻¹                | Mixture of acetonitrile-water (60:40 v/v) as mobile phase, Drug monitoring at 297 nm, Using SBME for analyte extraction | 297 nm               |                           |
|                |                  |        | 0.015 mg L⁻¹                   |                                                   |                       |                           |
| HPLC-UV        | Oxazepam Flurazepam | Hair | 0.79 – 20 µg mL⁻¹              | Mixture of acetonitrile–methanol–pure water optimized on (80:10:10, v/v/v) as mobile phase, drug monitoring at 238 nm, Using crab shell powder as micro-sorbent for analyte extraction | 238 nm               |                           |
|                |                  |        | 0.22 µg mL⁻¹                   |                                                   |                       |                           |
|                |                  | Nail   | 0.04 – 10 µg mL⁻¹              | Methanol, potassium hydrogen phosphate (pH 2.5) (70:30, v/v) as mobile phase, Drug monitoring at 254 nm, Using HF-LPME for analyte extraction | 254 nm               |                           |
|                |                  |        | 0.011 µg mL⁻¹                  |                                                   |                       |                           |
|                |                  | Blood  | 3.15 – 20 µg mL⁻¹              | Methanol, potassium hydrogen phosphate (pH 2.5) (70:30, v/v) as mobile phase, Drug monitoring at 254 nm, Using HF-LPME for analyte extraction | 254 nm               |                           |
|                |                  |        | 0.94 µg mL⁻¹                   |                                                   |                       |                           |
|                |                  |        | 2.11 – 20 µg mL⁻¹              | Methanol, potassium hydrogen phosphate (pH 2.5) (70:30, v/v) as mobile phase, Drug monitoring at 254 nm, Using HF-LPME for analyte extraction | 254 nm               |                           |
|                |                  |        | 0.61 µg mL⁻¹                   |                                                   |                       |                           |
|                |                  |        | 1.07 – 20 µg mL⁻¹              | Methanol, potassium hydrogen phosphate (pH 2.5) (70:30, v/v) as mobile phase, Drug monitoring at 254 nm, Using HF-LPME for analyte extraction | 254 nm               |                           |
|                |                  |        | 0.31 µg mL⁻¹                   |                                                   |                       |                           |
|                |                  |        | 0.3 – 15 µg mL⁻¹               | Methanol, potassium hydrogen phosphate (pH 2.5) (70:30, v/v) as mobile phase, Drug monitoring at 254 nm, Using HF-LPME for analyte extraction | 254 nm               |                           |
|                |                  |        | 0.1 µg mL⁻¹                    |                                                   |                       |                           |
|                |                  |        | 3.38 – 15 µg mL⁻¹              | Methanol, potassium hydrogen phosphate (pH 2.5) (70:30, v/v) as mobile phase, Drug monitoring at 254 nm, Using HF-LPME for analyte extraction | 254 nm               |                           |
|                |                  |        | 1.1 µg mL⁻¹                    |                                                   |                       |                           |
|                |                  |        | 3.8 – 15 µg mL⁻¹               | Methanol, potassium hydrogen phosphate (pH 2.5) (70:30, v/v) as mobile phase, Drug monitoring at 254 nm, Using HF-LPME for analyte extraction | 254 nm               |                           |
|                |                  |        | 1.2 µg mL⁻¹                    |                                                   |                       |                           |
| HPLC-UV        | Oxazepam Flurazepam | Plasma | 50 – 10000 ng mL⁻¹            | 10 mM sodium dihydrogen phosphate, methanol, and acetonitrile (40:40:20) as mobile phase, Drug monitoring at 226 nm, Using solvent bar microextraction for analyte extraction | 226 nm               |                           |
|                |                  |        | 15 ng mL⁻¹                     |                                                   |                       |                           |
| HPLC-UV        | Diclofenac Ibuprofen | Plasma | 0.8 – 2000 ng mL⁻¹            | Acetonitrile and 0.05 mol L⁻¹ phosphate buffer solution (pH 3.0) (65:35) as mobile phase, Drug monitoring at 220 nm, Using UA-Dµ-SPE-S-UA-LLME-SFO for analyte extraction | 220 nm               |                           |
|                |                  |        | 0.2 ng mL⁻¹                    |                                                   |                       |                           |
| HPLC-UV        | Zolpidem         | Urine  | 10 – 1000 ng mL⁻¹             | Mixture of methanol and 50 mmol L⁻¹ ammonium acetate buffer containing 0.1 % v/v triethylamine at a pH = 3.7 as mobile phase, Drug monitoring at 300 nm, Using an EME method for analyte extraction | 300 nm               |                           |
|                |                  |        | 3 ng mL⁻¹                      |                                                   |                       |                           |
| HPLC-UV        | Phenazopyridine  | Urine  | 10 – 1000 µg L⁻¹               | A mixture of acetonitrile and a 10 mmol L⁻¹ acetate buffer with the pH of 5.5 (60:40, v/v), Drug monitoring in 395 nm, analyte extraction by coupling of EME and SPE procedure | 395 nm               |                           |
|                |                  |        | 0.2 µg L⁻¹                     |                                                   |                       |                           |
| HPLC-UV        | Diclofenac       | Plasma | 50 – 2000 ng mL⁻¹             | Methanol- potassium hydrogen phosphate (pH 2.5) (70:30, v/v) as mobile phase, Drug monitoring at 254 nm, Using HF-LPME for analyte extraction | 254 nm               |                           |
|                |                  |        | 2.8 µg mL⁻¹                    |                                                   |                       |                           |
| HPLC-UV        | Valproic acid    | Plasma | 0.5 – 10 µg mL⁻¹              | A mixture of acetonitrile and 80 mM sodium dihydrogen phosphate buffer (pH = 3.5) in the ratio 43:57 (v/v) as mobile phase, Drug monitoring at 210 nm, Using a HF-EME for analyte extraction | 210 nm               |                           |
|                |                  |        | 0.2 µg mL⁻¹                    |                                                   |                       |                           |
| HPLC-UV        | Exemestane       | Urine  | 1.8 – 200 µg L⁻¹               | A mixture of acetonitrile and ultra-pure water (50:50) as mobile phase, Drug monitoring at 240 nm, Using HF-LPME for analyte extraction | 240 nm               |                           |
|                | Letrozole        |        | 0.9 – 200 µg L⁻¹               |                                                   |                       |                           |
|                | Paclitaxel       |        | 0.3 µg L⁻¹                     |                                                   |                       |                           |
|                |                  |        | 1.2 – 200 µg L⁻¹               |                                                   |                       |                           |
|                |                  |        | 0.4 µg L⁻¹                     |                                                   |                       |                           |
| MSPE-HPLC/UV   | Amitriptyline    | Plasma | 8 – 800 ng mL⁻¹                | 10 mmol L⁻¹ phosphate buffer (pH 4.0) containing 25 mmol L⁻¹ KCIO₄ and acetonitrile (65:35) as mobile phase. Monitoring at 220 nm. Using magnetic framework Fe₃O₄@TMU-10 as a nanosorbent for analyte extraction | 220 nm               |                           |
|                | Imipramine       |        | 5 ng mL⁻¹                      |                                                   |                       |                           |
|                |                  |        | 10 µmol L⁻¹                    |                                                   |                       |                           |
| HPLC-UV        | Methylprednisolone | Plasma | 0.01 – 80 µg mL⁻¹             | n-Butyl chloride, water-saturated n-butyl chloride, tetrahydrofuran, methanol, and glacial acetic acid (95:95:14:7:6) as mobile phas, Drug monitoring at 254 nm, Using AA@MNP–D/β-CD for analyte extraction | 254 nm               |                           |
|                | acetae           |        | 0.75 ng mL⁻¹                   |                                                   |                       |                           |
| HPLC-UV        | Morphine         | Urine  | 0.01 – 10 µg L⁻¹               | 40% acetonitrile and 60% (v/v) phosphate buffer (0.01 mol L⁻¹, pH 8.5) as mobile phase, Drug monitoring at 285 nm, Using Fe₃O₄/GO/Ag NC for analyte extraction | 285 nm               |                           |
|                | Codeine           |        | 0.0018 – 0.0021 µg L⁻¹         |                                                   |                       |                           |
Table 3 Continued.

| Method | Compound | Solvent | Lower Limit | Peak Area | Description |
|--------|----------|---------|-------------|-----------|-------------|
| HPLC-UV | Most of these pharmaceuticals were studied at 200 mmol L\(^{-1}\) or 100 mmol L\(^{-1}\) sodium dihydrogenphosphate buffer (pH 2.3–7.5) and acetonitrile (45:55, v/v) as mobile phase, drug monitoring at 210–230 nm, Using MWCNTs/Fe\(_{3}\)O\(_{4}\)@PAPy for analyte extraction. | |
| HPLC-UV | Morphine Codeine Methadone | 0.5 – 100 µg mL\(^{-1}\) | 25 µg L\(^{-1}\) | 9 µg L\(^{-1}\) | 10 µg L\(^{-1}\) | A 60:40 (v/v) mixture of acetonitrile and water (0.02 mol L\(^{-1}\) phosphate buffer at pH 2.3) with gradient elution mode: 0–7 min, A% 0 and B % 100; 7–8 min, A% 100 and B % 0; 8–15 min, A% 100 and B % 0; 15–16 min, A% 0 and B % 100; 16–20 min, A% 0 and B % 100; 20–21 min, A% 0 and B % 100. Using a DLLME for analyte extraction. |
| HPLC-DAD | Duloxetine Venlafaxine Atomoxetine | 2.9 – 560 ng mL\(^{-1}\) | 1.0 ng mL\(^{-1}\) | 0.7 ng mL\(^{-1}\) | 1.1 ng mL\(^{-1}\) | 20 mmol L\(^{-1}\) phosphate buffer solution (pH7.5), acetonitrile and methanol (65:12:23 v/v) as mobile phase, drug monitoring at 217 nm. Using MrGOQDs–PD@ Ni nanocomposite as nanosorbent for analyte extraction |
| HPLC-DAD | Noritriptyline Cetodizine Naproxen Di-clofenac Ibuprofen | 0.25 – 1500 µg L\(^{-1}\) | 0.07 – 3.5 µg L\(^{-1}\) | Na\(_{2}\)HPO\(_{4}\) buffer (10 mmol L\(^{-1}\); pH 2.5) and acetonitrile (45:55, v/v) as mobile phase, Drug monitoring at 210 – 230 nm, Using MWCNTs/Fe\(_{3}\)O\(_{4}\)@PAPy for analyte extraction. |
| HPLC-DAD | Prednisolone Methylprednisolone Mycophenolic acid | 2.8 – 400 µg L\(^{-1}\) | 0.9 µg L\(^{-1}\) | 1.3 µg L\(^{-1}\) | 0.03 µg L\(^{-1}\) | A 60:40 (v/v) mixture of acetonitrile and water (0.02 mol L\(^{-1}\) KH\(_{2}\)PO\(_{4}\) (pH=3.7) buffer solution as mobile phase, Drug monitoring at 210 – 400 nm. |
| HPLC-DAD | Tacrolimus, Everolimus Cyclosporine A | 2.1 – 6.3 µg L\(^{-1}\) | 0.56 µg L\(^{-1}\) | 0.08 µg L\(^{-1}\) | 7.6 µg L\(^{-1}\) | 90% acetonitrile and 10% phosphate buffer (pH = 3.5) as mobile phase, Drug monitoring at 210 – 400 nm. |
| HPLC-FD | Lisinopril | 3 – 1000 ng mL\(^{-1}\) | 1 ng mL\(^{-1}\) | A mixture of methanol–sodium dihydrogen phosphate (pH 3.0; 0.005 mol L\(^{-1}\); 75:25, v/v), Drug monitoring at ex/em 470/530 nm, Using PDMS/MWCNT-OH-NC as sorbent. |
| HPLC-FD | Bisphosphonates | 5 – 2500 µg L\(^{-1}\) | 1.4 µg L\(^{-1}\) | A mixture of acetonitrile and water with the ratio of 10:90 (v/v), Drug monitoring at ex/em 335/470 nm, Using ZNPs as a DMSPE sorbent for analyte extraction. |
| HPLC-FD | Buprenorphine | 1 – 1000 ng mL\(^{-1}\) | 0.21 ng mL\(^{-1}\) | A mixture of acetate buffer (50 mM; pH 5); acetonitrile: triethylamine (52:47:95:0.05; v/v/v), Drug monitoring at ex/em: 210 / 354 nm. Using magnetic MIP for analyte extraction. |
| GC - FID | Imipramine Desipramine | 0.005 – 5 µg mL\(^{-1}\) | 0.003 µg mL\(^{-1}\) | 0.007 µg mL\(^{-1}\) | Temperature program: Detector temperature, 270 °C; splitless injection (1 µl) at 270 °C; initial oven temperature was 80 °C for 1 min and then increased to 280 °C with the rate of 30 °C min\(^{-1}\) and held for 5 min. |
Table 3 Continued.

| Method  | Analyte(s)          | Sample(s) | Concentration(s) | Temperature Program                                                                 | Extraction Method |
|---------|---------------------|-----------|------------------|-------------------------------------------------------------------------------------|-------------------|
| GC - FID | Nicotine            | Hair      | 0.01 – 30 µg g⁻¹ | 0.002 µg g⁻¹ | Temperature program was started at 100 °C (held 1 min) and then raised to 280 °C at a rate 20 ºC min⁻¹ and held constant for 2 min. Both injector and FID detector were set at 280 °C. Using HS-SPME for analyte extraction. |
| GC - FID | valproic acid       | Plasma    | 0.25 – 100 mg L⁻¹ | 0.065 mg L⁻¹ | Temperature program: The oven temperature was programmed from 70 °C held (for 2 min) to 200 °C at a rate of 15 °C min⁻¹ and then increased to 300 °C at a rate of 20 °C min⁻¹ for cleaning column. Using a DLLME for analyte extraction. |
| GC - FID | Sodium valproate    | Plasma    | 0.5 – 500 µg mL⁻¹ | 0.22 µg mL⁻¹ | Temperature program: The oven temperature was programmed from 50 °C (held for 2 min) to 210 °C at a rate of 10 °C min⁻¹ and held at 210 °C for 3 min; then, the temperature was raised with a rate of 15 °C min⁻¹ to a final temperature of 290 °C that was held for 1 min. Using AA-LLME for analyte extraction. |
| GC - FID | Amitriptyline       | Plasma    | 0.003 – 1.5 µg mL⁻¹ | 0.001 µg mL⁻¹ | Temperature program: initial temperature 70°C (held for 2 min), then increased to 300°C at a rate of 20°C min⁻¹ and held for 2 min. Using LLLE coupled with DLLME method |
| GC - FID | Amitriptyline       | Plasma    | 10 – 3000 ng mL⁻¹ | 1.0 ng mL⁻¹ | Temperature program: The GC oven was initially held at temperature of 100 °C for 1 min, programmed to 240 °C at 20 °C min⁻¹, further programmed to 260 °C at a rate of 2 °C min⁻¹. The injector and detector temperatures were 280 °C and 290 °C, respectively. Using AA-LLME for analyte extraction. |
| GC-FID  | Clomipramine        | Urine     | 0.5 – 750 ng mL⁻¹ | 0.15 ng mL⁻¹ | Temperature program: The initial column oven temperature was adjusted at 150 °C then increased by 30 °C min⁻¹ to 300 °C and held for 1 min. The temperature of injection port and FID were 280 and 300 °C, respectively. The splitless mode of injection was used for 1 min and then split valve was opened at the split ratio of 10:1. Ultrapure nitrogen gas at 20 psi constant pressure was applied as carrier gas. Using EME coupled with EA-LLME for analyte extraction. |
| GC- MS  | Amitriptyline       | Urine     | 27 - 5000000 ng L⁻¹ | 8 – 15 ng L⁻¹ | Temperature program: The column oven temperature was initially held at 100 °C for 1 min, programmed at a rate of 50 °C min⁻¹ to 190 °C, then programmed at a rate of 5 °C min⁻¹ to 225 °C (held for 3 min), followed by a rate of 20 °C min⁻¹ to 300 °C and held for 5 min. MS operational conditions were: electron ionization at 70 eV, ionic source temperature: 250 °C, transfer line temperature: 260 °C; mass range: m/z 30 – 400; acquisition rate: 20 Hz. Detector voltage: -1700 V. Using DSPE coupled with DES-based AA-LLME for analyte extraction. |
| GC-MS   | Methamphetamine     | Urine     | 5 – 1500 µg L⁻¹ | 1.5 µg L⁻¹ | Temperature program: The column temperature program was as follows: 2 min at 50 °C, raised up to 250 °C at a rate of 20 °C min⁻¹, and kept at 250 °C for 3 min. A split injection mode with split ratio of 1:5 was selected for the introduction of 1 µL of the extracts. The injector was kept at 260 °C. The electron impact ionization energy was 70 eV and the transfer line temperature was 180 °C. Chromatograms were recorded in full-scan mode (40–550 m/z). Using HLPME with DPA for analyte extraction. |
| CE-DAD  | Pregabalin          | Serum     | 1.5 – 100 µg mL⁻¹ | 0.8 µg mL⁻¹ | Each new capillary have been rinsed with NaOH (1.0 mol L⁻¹) for 30 min, deionized water for 20 min and background electrolyte (10 mmol L⁻¹ 5-ASA, 1 mmol L⁻¹ CTAB and 4 % (w/v) tri-sodium citrate) for 30 min, sequentially. Drug monitoring at 215 nm. |
The measured concentration in plasma taken from subjects treated with these drugs was
agent) followed by DLLME method by 1,2–dibromoethane as preconcentration solvent.
n-hexane as clean up and co–extraction solvent and sodium sulfate as phase separating
extraction by liquid–liquid–liquid extraction (LLLE) (acetonitrile as extraction solvent,
determination of amitriptyline, imipramine, and clomipramine in plasma samples after
plasma and urine samples, respectivly. Farajzadeh et al.
concentration in the ranges of 9.9 – 34.7 µg mL
valproate in plasma and urine samples by same method after extraction with an air
also determined sodium
reported a GC-FID method for determination of bisphosphonates in spiked urine
and serum samples after extraction by using zirconia nanoparticles (ZNPs) as a DMSPE. The
extracted analyte derivatized by o-phthalaldehyde in the presence of 2-mercaptoethanol
at basic medium to form fluorescent species. In other study, buprenorphine in urine
samples was determined by this method after extraction by magnetic MIP, magnetite cores
surrounded by polyamidoamine.125
Gas chromatography (GC)
GC is a technique of preference for separation of volatile compounds. FID and MS are the
commonly used detectors for this method. By using a GC – FID; Ahmadi et al.126
developed a method for simultaneous determination of imipramine and desipramine after
extraction from spiked plasma samples by using Fe3O8/SiO2/C/NH2 MNPs. Ghiasvand et al.127
determined nicotine in hair of smoker subjects after extraction by using sulphonated
graphene – polyaniline nanocomposite coated fiber as a headspace (HS)- SPME sorbent.
The reported concentration in two hair sample taken from smoker subjects is about
1.12 – 6.80 µg g−1. Feriduni et al.128 determined valproic acid and its main metabolite
(3-heptanone) in plasma samples after extraction by a DLLME method with chloroform
(as extractor) and acetonitrile (as dispersant). Abbaspour et al.129 also determined sodium
valproate in plasma and urine samples by same method after extraction with an air
assisted (AA)-LLME by using chloroform as extractor. They reported a sodium valproate
concentration in the ranges of 9.9 – 34.7 µg mL−1 and 0.5– 6.7 µg mL−1 for analyzed patient’s
plasma and urine samples, respectively. Farajzadeh et al.130 reported a GC-FID method for
determination of amitriptyline, imipramine, and clomipramine in plasma samples after
extraction by liquid–liquid–liquid extraction (LLLE) (acetonitrile as extraction solvent, n-hexane
as clean up and co–extraction solvent and sodium sulfate as phase separating agent) followed by DLLME method by 1,2–dibromoethane as preconcentration solvent.
The measured concentration in plasma taken from subjects treated with these drugs was
147 µg mL−1 for imipramine, 100 – 243 µg mL−1 for clomipramine and 95 – 191 µg mL−1
for amitriptyline. Mofazzeli et al.131 developed a GC-FID method for determination of
trace amounts of amitriptyline and doxepin in plasma samples. They used an AA-LLME
by using toluene as extraction solvent prior to measurement. Nojavan et al.132 validated a
method for simultaneous quantification of clomipramine and imipramine in spiked urine
samples. They used a tandem sample preparation method of EME combined with electro-assisted liquid-liquid micro-extraction (EA-LLME) for extraction and preconcentration
of analytes. Another sample preparation combinational method was performed by Mohebbi
et al.133 for determination of amitriptyline, nortriptyline and clomipramine. The extraction
procedure is schematically shown in Figure 7. As can be seen a DSPE method with C8
sorbent combined with DES (prepared from choline chloride and 4-chlorophenol)–
based AA-LLME was used for extraction of amitriptyline, nortriptyline and clomipramine prior to GC-MS determination. Other studies performed by using GC-MS
method including determination of methamphetamine in urine samples after extraction
by a homogeneous liquid–phase microextraction (HLPME) with the aim of dipropylamine
(DPA) as a solvent with switchable hydrophilicity134 and determination of ketoprofen,
naproxen, diclofenac and ibuprofen in plasma and urine samples after extraction by DLLME
method by a mixture of acetone (disperser solvent) and n-dodecane/TOPO (extraction solvent 95:5, v/v) associated with a back extraction.135
Capillary electrophoresis (CE)
CE is liquid separation technique that separates ions based on their electrophoretic
mobility with the use of an applied voltage. Main advantage of this method high separation
efficiency, high resolution, short analysis time, low consumption of sample and solvent,
and low sensitivity to sample matrix.136 Sargazi et al.137 developed a micellar electrokinetic
chromatographic method with indirect UV detection for pregabalin determination in
spiked serum samples. They used 5-aminosalicylic acid (5-ASA) as probe for indirect UV
detection. A decrease proportional with the concentration of pregabalin in the background
absorbance related to 5-ASA used to the quantification of pregabalin in serum samples.

Table 3 Continued.

| GC-MS | Ketoprofen | Naproxen | Diclofenac | Ibuprofen | Plasma | Urine |
|-------|------------|----------|------------|-----------|--------|-------|
|       | 1 – 400 µg L−1 | 1 – 400 µg L−1 | 2 – 400 µg L−1 | 2.5–400 µg L−1 | -  |       |
|       | 2 – 400 µg L−1 | 2 – 400 µg L−1 | 5 – 400 µg L−1 | 2 – 400 µg L−1 | 1 – 400 µg L−1 |       |

Temperature program: The GC oven was initially held at 70 ºC for 2 min, then ramped to 280 ºC at 25
ºC min−1, and finally held for 15 min. Chromatograms were recorded in the range of m/z 160 – 380.
Using a DLLME associated with back extraction for analyte extraction.
Conclusions

The present review depicts the reported analytical methods which had developed and validated for the determination of pharmaceutical compounds in the biological fluids by Iranian analysts in year 2018. The literature are classified based on applied methodology and instrumentation and analytical properties of each report were tabulated. According to this review it has been concluded that most of the used methods for pharmaceutical analysis are of chromatographic methods coupled with various detectors and electrochemical methods, as these methods provides best reliability, and sensitivity in compared with optical methods. A brief study on the journals of investigated articles show that mean value for their impact factors is 3.2 ± 1.6 and Journal of Chromatography A (impact factor: 3.716), Analytica Chimica Acta (impact factor: 5.123) possess the first and second ranks with considering the number of articles published in 2018 and Journal of Molecular Liquids (impact factor: 4.513)/ Sensors and Actuators B (impact factor: 5.667)/ Journal of Electroanalytical Chemistry (impact factor: 3.235)/ Talanta (impact factor: 4.244)/ Journal of the Iranian Chemical Society (impact factor: 1.593) are in the third ranks.

Conflicts of Interests

There are no conflicts of interest to declare.

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