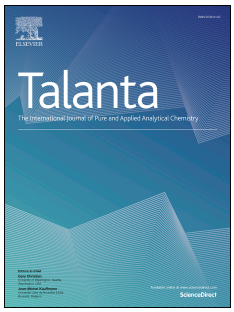
Journal Pre-proof



Advances in Analytical Techniques and Sample Preparation Methods for Anticancer Drug Monitoring: From Biological Fluids to Environmental Matrices

Elham Torabi, Maryam Asefi, Milad Moghadasi, Amirhassan Amiri, Masoud Mirzaei

PII: S0039-9140(26)00203-1

DOI: https://doi.org/10.1016/j.talanta.2026.129548

Reference: TAL 129548

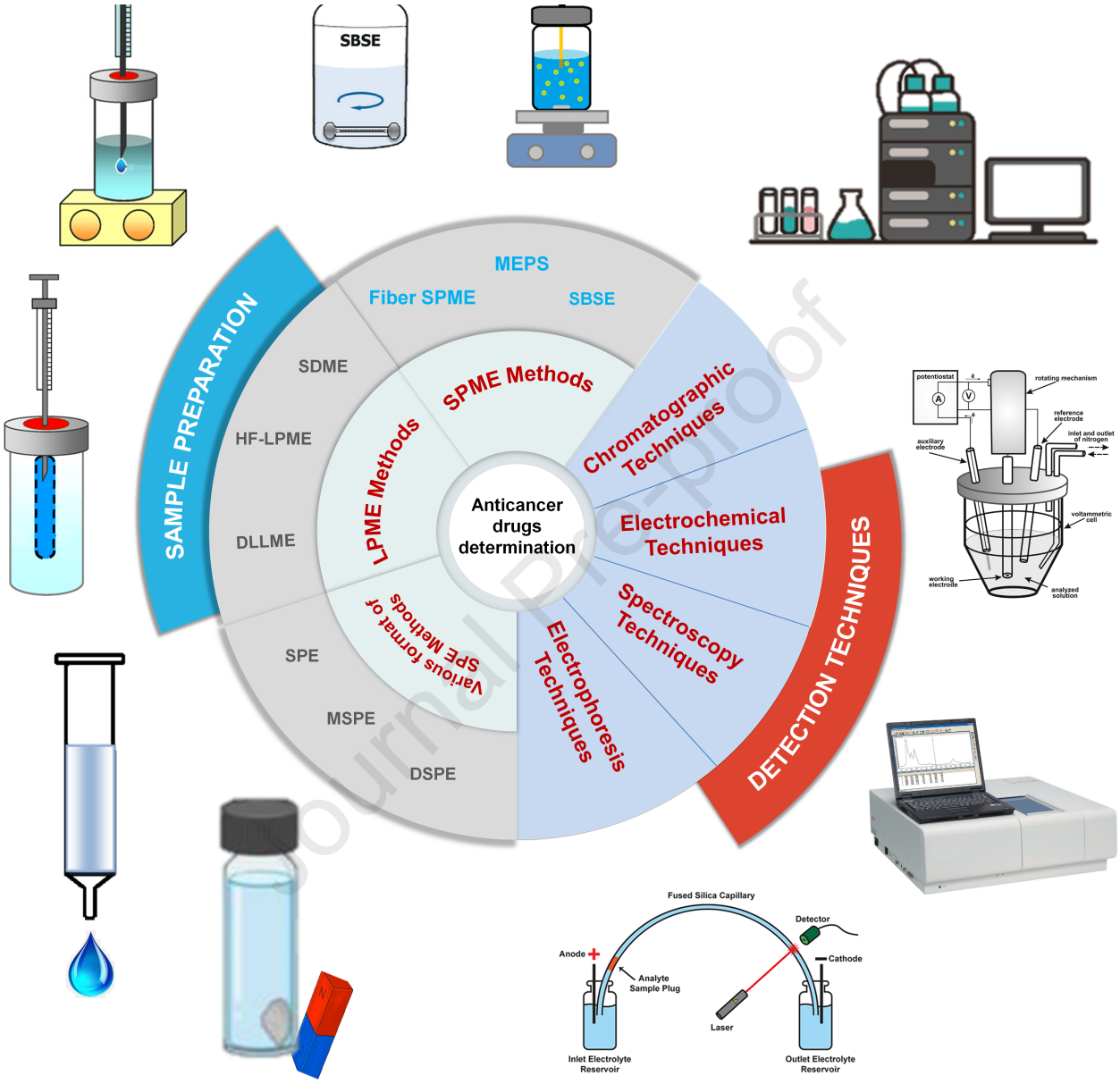
To appear in: *Talanta*

Received Date: 17 October 2025

Revised Date: 11 February 2026

Accepted Date: 15 February 2026

Please cite this article as: E. Torabi, M. Asefi, M. Moghadasi, A. Amiri, M. Mirzaei, Advances in Analytical Techniques and Sample Preparation Methods for Anticancer Drug Monitoring: From Biological Fluids to Environmental Matrices, *Talanta*, https://doi.org/10.1016/j.talanta.2026.129548.



to Environmental Matrices

Elham Torabi, Maryam Asefi, Milad Moghadasi, Amirhassan Amiri*, and Masoud Mirzaei**

Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad 9177948974, Iran.

**E-mail: ah.amiri@um.ac.ir*

***E-mail: mirzaeesh@um.ac.ir*

Monitoring their concentrations in biological fluids is essential for optimizing therapeutic efficacy, minimizing adverse effects, accurately adjusting dosage, and evaluating clinical outcomes. In parallel, the extensive use of chemotherapy agents has increased concern over the occurrence of anti-cancer drug residues in environmental matrices. Consequently, reliable and sensitive analytical approaches are required for the determination of these compounds in both biological and environmental samples. This review critically summarizes recent advances in the analysis of anti-cancer drugs, covering chromatographic, electrophoretic, electrochemical, and spectroscopic techniques. Particular emphasis is placed on the role of sample preparation, including conventional and modern extraction strategies, in improving analytical reliability and method performance. Comparative evaluation of analytical figures of merit, such as limits of detection and practical applicability, is presented to highlight current capabilities, methodological limitations, and emerging challenges. In addition, recent trends toward greener analytical strategies such as solvent minimization, micro- and miniaturized extraction techniques, and sustainable instrumental approaches are discussed in the context of therapeutic drug monitoring and environmental surveillance. Future perspectives integrating green chemistry principles, nanotechnology, and miniaturized analytical devices are also outlined.

Keywords: Anti-cancer drugs, Therapeutic drug monitoring (TDM), Chromatography, Electrophoresis, Electrochemical sensor, Sample preparation.

cancers, such as those that affect the blood or bone marrow, can also develop due to abnormal cell division. Surgery, chemotherapy, and/or radiotherapy are often the main therapies for this leading cause of death globally. Chemotherapy has utilized more than 100 different medications, frequently in conjunction with other medical procedures. Based on their mode of action, these medications can be divided into several groups, pl. Monoclonal antibodies, small molecule inhibitors, gene delivery tools, and histone deacetylase inhibitors are some examples of the molecular targeting agents' group. Carboplatin and oxaliplatin, which are metal-containing drug, constitute a third category of medications, distinguished by their ability to form either metal-DNA or metal-protein adducts [1].

Antibiotics, which can also be recognized as anti-cancer or antitumor agents in some contexts, are a class of medications that may interfere with DNA synthesis and replication either by intercalating into DNA or by donating electrons, thereby producing superoxide, a highly reactive oxygen species (ROS) capable of damaging DNA strand. This method may prevent cancer cells from multiplying and cause them to die [2].

Tumors caused by hormonal abnormalities can be treated with hormonal medicines, commonly referred to as hormone antagonists. Endogenous estrogens in women are steroid hormones, and studies have revealed that postmenopausal women who lack estrogen experience a variety of negative effects, including postmenopausal symptoms, coronary heart disease, a higher risk of osteoporosis, and Alzheimer's disease, among others [3].

Microtubule targeting agents are a type of anti-mitotic drug that can inhibit cell proliferation by disrupting microtubules, disrupting microtubules, which halts the cell cycle in the G2-M phase and the production of abnormal mitotic spindles. These agents are generally classified into two main categories based on their mechanism of action: stabilizing and destabilizing agents [4,5].

Since their initial clinical approval in the late 1990s, molecular targeting medicines have served as the cornerstone of precision medicine for the treatment of cancer. These agents use small molecule compounds or therapeutic monoclonal antibodies functioning as signal transduction inhibitors.

Platinum (Pt) treatments including cisplatin, carboplatin, and oxaliplatin are especially common metal-based medications used to treat cancer [7]. When there aren't enough ions of Pt to interact with the target DNA or when not enough Pt-DNA adducts are formed to kill cells, resistance to cisplatin might develop. Due to their lower toxicity, novel mechanisms, tumor selectivity, and non-cross-resistance potential, non-platinum and copper (Cu)/ruthenium (Ru) complexes may be superior to Pt complexes [8]. Depending on how hazardous they are to humans, this group of medications is categorized by the International Agency for Research on Cancer (IARC). They are classified as either human carcinogens (Group 1) or potentially human carcinogens (Groups 2A and 2B). However, many medications are still categorized as to their carcinogenicity in humans and are placed in Group 3 (mutagenic and teratogenic) due to a lack of toxicological knowledge (Fig. 1) [9].

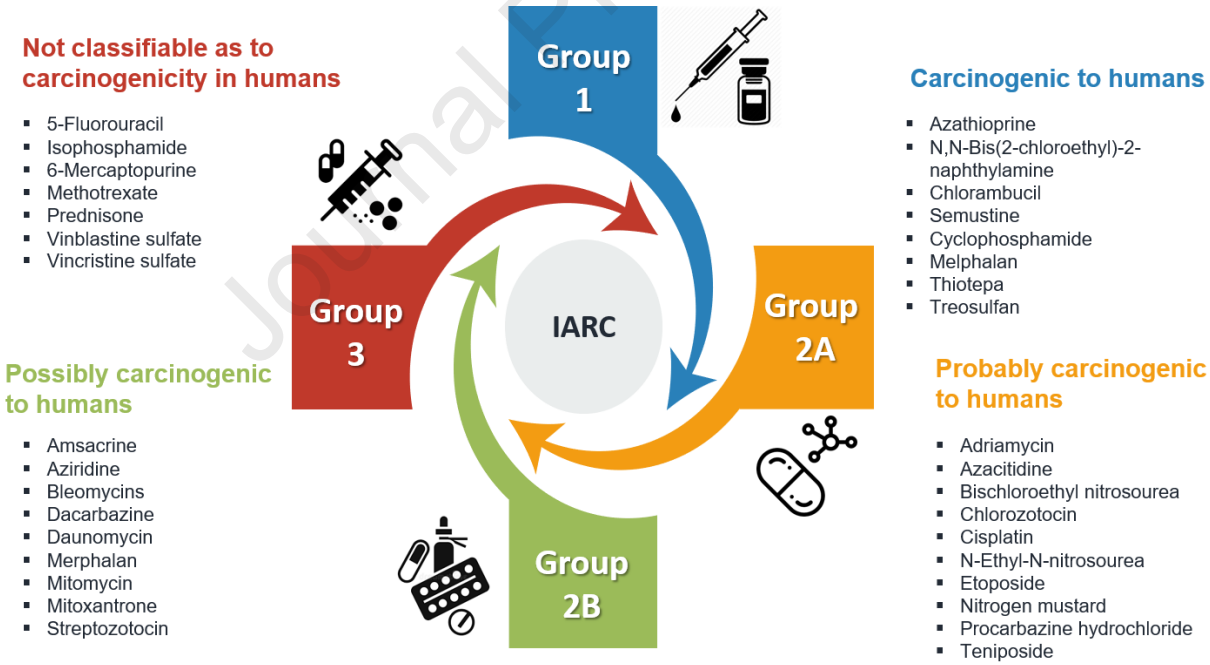


Fig. 1. Anti-cancer drugs are classified according to the IARC.

in bodily fluids is vital. However, due to the complex matrix of biological and environmental samples, which might result in substantial interference, detecting these medications has become extremely difficult [10]. Determination of the presence of anti-cancer medications requires the development of monitoring tools that are sensitive, picky, and reliable, such as analytical approaches [11]. The typical process of a toxicology lab for confirmation procedures involving analytical methods includes sample pre-treatment, for example, urine hydrolysis, hair decontamination and digestion, or tissue homogenization [12]; and at last extraction/cleanup of the analytes of interest [13].

Early analytical approaches for the determination of anti-cancer drugs primarily relied on liquid chromatography (LC) coupled with ultraviolet (UV) detection, which was mainly applied to stability studies and pharmaceutical formulation development at relatively high drug concentrations. Gas chromatography–mass spectrometry (GC–MS) was historically regarded as the reference technique in toxicology laboratories due to its high separation efficiency, reproducibility, and the availability of comprehensive MS spectral libraries that enable reliable compound identification. Over the past decade, significant advancements in GC and GC–MS instrumentation have substantially expanded their analytical capabilities. These developments include the introduction of high-resolution and tandem mass spectrometric detectors (GC–MS/MS), which improve selectivity and sensitivity through multiple reaction monitoring, as well as comprehensive two-dimensional gas chromatography (GC×GC) coupled with time-of-flight mass spectrometry, offering enhanced peak capacity and improved separation of complex mixtures [14]. Additionally, progress in injector design, column technology, and optimized derivatization strategies has enabled the effective analysis of thermally stable and derivatives polar anti-cancer drugs and their metabolites. Although recent advances in LC–MS have led to its increasing use for the analysis of polar and nonvolatile compounds by eliminating the derivatization steps typically required in GC–MS, both GC–MS and LC–MS remain the most widely employed analytical platforms in toxicological analysis because of their versatility and sensitivity [1]. In addition to these techniques, capillary electrophoresis (CE) and electrochemical methods have also been explored, with CE offering high sensitivity, low sample consumption, and compatibility with

biological matrices is often challenging because of low analyte concentrations and interference from endogenous components, highlighting the importance of efficient sample preparation [19]. Sample pretreatment techniques are therefore essential for the isolation, purification, and enrichment of target analytes prior to instrumental analysis [20−22]. Conventional approaches such as liquid–liquid extraction (LLE) and solid-phase extraction (SPE) typically involve multiple procedural steps and require large volumes of organic solvents, which may increase the risk of analytical errors [23−26]. This review provides a comprehensive overview of current analytical techniques and sample preparation strategies employed for the determination of anti-cancer drugs in real biological and environmental samples.

2. Analytical techniques for anti-cancer drugs analysis

Effective quantification of anticancer drugs requires analytical methods that are not only sensitive and selective but also clinically viable capable of detecting trace concentrations in limited, complex biological samples such as plasma, serum, or urine. Despite advancements, many published methods remain confined to idealized conditions, with limited validation in real patient matrices or under routine clinical settings. A wide range of techniques has been established to quantify these drugs in complex biological matrices such as blood, serum, and urine. To support pharmacokinetic studies and therapeutic drug monitoring, methods must be sensitive enough to detect trace drug levels in small sample volumes, with limits of detection (LODs) suitable for limited clinical specimens [18,19]. Current techniques are broadly categorized into chromatographic, electrophoretic, electroanalytical, and spectroscopic methods. The following sections provide a detailed discussion of each technique, highlighting their operational principles, recent advancements, and applications in anticancer drug analysis. Key attributes and comparative performance metrics are summarized in Tables 1–3 to facilitate method selection and evaluation.

2.1. Chromatographic techniques

Chromatographic methods represent a cornerstone in the modern investigation of therapeutically active compounds, playing an indispensable role in the synthesis, discovery, precise quantification, and application of agents used in cancer prevention, treatment, and diagnosis. Renowned for their

spectroscopy, mass spectrometry (MS), and fluorescence detection (FLD) enable the accurate identification and measurement of anticancer drugs along with their active and inactive metabolites across a wide range of biological and environmental matrices. The extensive body of contemporary literature attests to the versatility and reliability of these techniques, underscoring their critical importance in pharmacological research, therapeutic drug monitoring, and translational oncology. As an advanced form of liquid chromatography, high-performance liquid chromatography (HPLC) is extensively employed for the separation and quantification of specific analytes in complex biological matrices. Owing to its high accuracy, reproducibility, and exceptional selectivity, HPLC has become the method of choice for pharmaceutical analysis, including the determination of drug concentrations in biological fluids. Within anticancer drug development, reversed-Phase HPLC (RP-HPLC) represents the most widely adopted chromatographic mode, particularly for analyzing drug compounds and their metabolites in biological specimens. This preference stems from its compatibility with aqueous and organic mobile phases, robustness with a variety of detectors, and ability to handle a broad range of analyte polarities. The detailed analytical parameters and conditions applied in LC technique for anticancer drug analysis are summarized in Table 1.

2.1.1. HPLC-MS and HPLC-MS/MS

HPLC-MS and its tandem variant HPLC-MS/MS represent pivotal analytical platforms for the quantification and structural elucidation of pharmaceutical compounds. These techniques integrate the high-resolution separation capability of HPLC with the molecular specificity and high sensitivity of mass spectrometry, enabling precise qualitative and quantitative assessment of drugs and their metabolites. A notable application of HPLC-MS/MS is demonstrated in the determination of abiraterone and its metabolites specifically 3-keto-5-α-abiraterone and D(4)-abiraterone in human plasma. Using a triple-quadrupole linear ion trap (Q-Trap) mass analyzer operated in multiple reaction monitoring (MRM) mode, this method achieves high selectivity and sensitivity required for reliable pharmacokinetic and bioanalytical studies [27].

Recent methodological advances have enabled more rapid, economical, and high-throughput pharmacokinetic (PK) studies of anticancer agents. One such development is the integration

allows reliable quantification from low sample volumes. For instance, a TurboFlow™-coupled HPLC-MS/MS method was developed for the simultaneous determination of SN38 and irinotecan, streamlining PK research while maintaining robustness and cost-effectiveness [28]. In another study, an HPLC-MS/MS method utilizing a triple quadrupole (QqQ) mass spectrometer with positive ion mode electrospray ionization was established to quantify niraparib and its carboxylic acid metabolite in both plasma and urine matrices, demonstrating versatility across biological fluids [28]. Furthermore, a novel HPLC-MS/MS assay employing QqQ-MS with positive electrospray ionization was validated for the simultaneous quantification of uracil and its metabolites including α-fluoro-β-ureidopropionic acid, 5,6-dihydrouracil, α-fluoro-β-alanine, 5-fluoro-5,6-dihydrouracil, and 5-fluorouracil in plasma. This method marked the first reported simultaneous analysis of this full panel of analytes and offered substantial practical advantages, including reduced run time, lower labor requirements, and minimized consumption of reagents and sample volume [29].

The development of rapid, multi-analyte HPLC-MS/MS methods has greatly advanced the field of therapeutic drug monitoring (TDM) in oncology. One such method achieved a total run time of only 4.5 minutes, representing a significant reduction in analysis time for a multi-drug detection platform. This technique is applicable to both whole blood and plasma samples using consistent chromatographic conditions, sample preparation protocols, and analytical workflows, thereby simplifying clinical implementation [30]. In a broader application, an HPLC-MS/MS method was developed for the simultaneous quantification of 11 anticancer drugs: docetaxel, paclitaxel, pemetrexed, vinorelbine, vinblastine, carboplatin, etoposide, gemcitabine, cyclophosphamide, SN-38, ifosfamide, and irinotecan. Following rigorous validation, this multiplexed assay was successfully applied in clinical TDM for cancer patients, demonstrating its utility in personalized treatment strategies [30]. Further expanding the scope of multi-analyte monitoring, an HPLC-ESI-MS/MS method was established for the simultaneous determination of several tyrosine kinase inhibitors and their metabolites in human plasma, including sorafenib, sorafenib N-oxide, N-desethyl sunitinib, sunitinib, axitinib, and pazopanib—agents commonly used in renal cell carcinoma. The method exhibited excellent precision, with inter-day and intra-day coefficients of variation below 10.3% and relative errors within ±11.8%. Matrix effects for all analytes ranged

2.1.2. HPLC-UV/Vis

Following mass spectrometry, UV/Vis detection remains one of the most widely investigated and applied detection techniques in HPLC-based anticancer drug analysis. While generally offering lower sensitivity compared to MS detection with typical LODs in the μg mL^{-1} range versus the ng mL^{-1} range achievable with HPLC-MS—UV/Vis detectors are often favored for their simplicity, robustness, and cost-effectiveness, making them suitable for routine clinical and quality control applications [32]. Modern UV detectors are frequently equipped with diode array (DAD) or multi-wavelength monitoring capabilities, enabling simultaneous detection of multiple analytes at their respective absorption maxima. For example, a reversed-phase HPLC-UV method was developed for the simultaneous quantification of epirubicin, cyclophosphamide, and 5-fluorouracil, along with key metabolites, in human plasma. The method demonstrated recovery rates >93% for 5-fluorouracil and its metabolites, and >78% for cyclophosphamide and epirubicin. Precision was excellent, with relative standard deviation (RSD) below 2% in both plasma and aqueous matrix (pH 4.0), and accuracy exceeded 98% for all analytes. Stability studies revealed that 5-fluorouracil, 5,6-dihydro-5-fluorouracil, and epirubicin remained stable in aqueous solution at 28–30°C, whereas cyclophosphamide, fluorodeoxyuridine, and fluorouridine showed greater sensitivity to storage conditions. When drug-spiked plasma was stored at –80°C for 72 hours, only epirubicin and fluorouridine exhibited statistically significant changes in recovery ($p < 0.05$). The method was successfully validated using plasma samples from six patients, confirming its suitability for clinical monitoring [33]. Additionally, HPLC-UV assays have been routinely applied to quantify imatinib concentrations in human plasma and serum, supporting therapeutic drug monitoring in chronic myeloid leukemia patients [34−36]. Although lacking the specificity of MS, these methods offer a reliable and accessible alternative for laboratories with limited access to mass spectrometry instrumentation.

2.1.3. HPLC-PDA

HPLC coupled with photodiode array detection (HPLC-PDA, also referred to as HPLC-DAD) serves as a robust and accessible alternative to mass spectrometry for the quantitative analysis of

when combined with efficient sample preparation techniques. One notable application involved the determination of gefitinib in plasma and cerebrospinal fluid (CSF) of non-small-cell lung cancer patients with brain metastases. Using SPE for plasma and LLE for CSF, followed by HPLC-DAD analysis, the method demonstrated high sensitivity with a lower limit of quantification (LOQ) of 11 ng mL^{-1} in plasma and 0.11 ng mL^{-1} in CSF. Method optimization revealed that acidification with formic acid enhanced elution efficiency in CSF samples, whereas increased pH during loading improved purification but reduced elution recovery. The validated assay was deemed highly sensitive and suitable for therapeutic drug monitoring in neurologically involved cancer patients [37].

In another advanced application, a fabric-phase sorptive extraction (FPSE) technique combined with HPLC-DAD was developed for the simultaneous quantification of aromatase inhibitors exemestane, letrozole, and anastrozole in whole blood, plasma, and urine from patients undergoing standard therapy. Using propyl-*p*-hydroxybenzoate as an internal standard, this method offered a simple, efficient, green, and rugged analytical workflow [38]. Unlike many conventional methods that rely on protein precipitation (PP) or LLE and often report higher LOQs for anastrozole, the FPSE-HPLC-DAD approach achieved superior sensitivity. Furthermore, the entire analysis was completed within 20 minutes, offering a faster or comparable turnaround time relative to existing procedures.

2.1.4. HPLC-FLD

Fluorescence detection (FLD) coupled with HPLC (HPLC-FLD) is recognized as a highly sensitive quantitative technique, particularly suitable for the analysis of micro-samples and compounds with native or derivatized fluorescence [39−41]. Its ability to detect low concentrations with high specificity makes it valuable in therapeutic drug monitoring and metabolic studies. HPLC-FLD offers a highly sensitive and accessible analytical platform, particularly advantageous in settings where mass spectrometry is unavailable or cost-prohibitive. With sensitivity 10–1000 times greater than UV/PDA detection [42], HPLC-FLD enables reliable quantification of anticancer drugs and metabolites at trace levels, supporting both preclinical and clinical studies. For instance, an HPLC-FLD method was developed for the quantification of alpelisib in rat

98.1%, and recovery of 96.1–100% [43, 44]. Stability studies showed alpelisib remained stable for 24 hours in urine, plasma, and buffers with pH > 4.0, but degraded within 4 hours under acidic conditions. Pharmacokinetic evaluation in rats revealed dose-dependent changes in systemic exposure and gastrointestinal retention across doses from 0.5 to 10 mg kg^{-1}. Similarly, a simple RP-HPLC-FLD method was validated for ruxolitinib in plasma, demonstrating excellent precision, accuracy, and recovery with no matrix interference, supporting its use in therapeutic monitoring for myeloproliferative neoplasms [45].

In another application, HPLC-FLD provided a cost-effective alternative to LC-MS/MS for simultaneous quantification of tamoxifen and its metabolites (4-hydroxytamoxifen and endoxifen) in patient plasma, with a rapid run time of 16 minutes, precision of 0.23–6.00% RSD, and accuracy of 80–100%, all without the need for derivatization [46]. Furthermore, an HPLC-FLD assay was validated for irinotecan and its active metabolite SN-38 in dried blood spots (DBS), showing good precision (CV 2.15–10.07% for SN-38, 2.71–5.65% for irinotecan), accuracy (94.24–100.93%), and stability under storage conditions up to 42°C for two weeks, with strong correlation between DBS and plasma concentrations [47].

In summary, among contemporary techniques for the quantification of anticancer drugs, LC-MS and LC-MS/MS have emerged as the gold standard in bioanalysis, offering unparalleled sensitivity, specificity, and analytical throughput compared to conventional UV- or fluorescence-based chromatographic methods. These techniques not only simplify sample preparation by reducing pretreatment complexity and required sample volume, but also when integrated with SPE significantly mitigate matrix interference, a common limitation of precipitation-based approaches. While HPLC with fluorescence detection (HPLC-FLD) remains a valuable and economically viable alternative particularly noted for its wider linear range in certain applications and accessibility in resource-constrained laboratories—LC-MS/MS excels in multiplexed assays, delivering faster run times, higher resolution, and superior detectability for simultaneous multi-drug monitoring. The selection between these platforms should therefore be guided by specific analytical demands, including required sensitivity, sample throughput, operational cost, and available laboratory infrastructure.

Table 1. The summary of studies of chromatography methods on anti-cancer drugs.

Drug	Method	Sample preparation	Column	Mobile phase	Run time (min)	LOD (ng mL^{-1})
Abiraterone	HPLC-MS/MS	Mixing with 2 mL of water containing formic acid 0.25% (v/v) and 25 µL of internal standard	ACE C_{18} HL column (100×4.6 mm, 3 µm; Canadian Life Science, ON, Canada)	Water: Ammonium formate: Methanol	10	--
Niraparib	HPLC-MS/MS	Mixing with 300 µL ACN-MeOH (50:50, v/v)	SunFire C_{18} column (50 mm×2.1 mm, 5 µm)	Ammonium acetate in water: 0.1% formic acid in acetonitrile: Methanol (50:50, v/v)	7	--
Paclitaxel, Docetaxel, Vinblastine, Vinorelbine, Pemetrexed, Carboplatin, Etoposide, Cyclophosphamide, Ifosfamide, Gemcitabine, Irinotecan, SN-38	HPLC-MS/MS	Transferred to 1.5 mL Eppendorf tubes and stored at −80 °C until analysis	Atlantis T_3-C_{18} column (2.1 × 100 mm, 3.0 µm)	Acetonitrile and 10 mM ammonium acetate plus 0.1% formic acid in water	10	0.5–50.0
Sorafenib Sorafenib *N*-oxide Sunitinib *N*-desethyl Sunitinib Axitinib	HPLC-MS/MS	Deproteination with acetonitrile	Inertsil ODS-3 (100×2.1 mm, 2 µm; GL Sciences, Tokyo, Japan)	Acetonitrile: Ammonium formate	4.2, 3.7, 1.6, 2.4, 1.3, 2.2, 3.0	--

Pazopanib						
5-Fluorouracil, Epirubicin, Cyclophosphamide	HPLC-UV	Filtered through 0.22 μ spin filter	C_{18} column (4.6 mm I. D., 150 mm length, 5 μm; USA)	Water: methanol: Acetonitrile	10.51, 40.248, 60.31	2.0, 30.0 200.0
Gefitinib	HPLC-DAD	Plasma was basified with 0.1 mL of sodium hydroxide (2 M) and extracted with 2 mL of methyltert-butylether (MTBE) The cerebrospinal fluid transferred to a pre-conditioned SPE cartridge, washed with 3 mL of 20% methanol aqueous solution, and eluted with 6 mL of 5% formic acid in methanol solution	Zorbax Elipse XDB C_{18} (5 μm, 4.6×150 mm, Agilent, USA)	Triethylamine: Acetonitrile	10	--
Anastrozole, Letrozole, Exemestane	HPLC-DAD	Based on LLE	Luna C_{18} (250×4.6 μm, 5 μm; Phenomenex, Torrance, CA, USA)	Phosphate buffer (40 mM pH=3.5: acetonitrile	15	2-, 10, an 30
Alpelisib	HPLC-FLD	Vortex mixer for 5 min and centrifuged at 13000 rpm for 10 min at 4 °C	CAPCELL PAK C18 MGIII HPLC column (250×4.6 mm, 5 μm, 100 Å; Shiseido, Tokyo, Japan)	Potassium phosphate: Acetonitrile	12	0.3

Epirubicin	HPLC-FLD	SPE followed by PP with different deproteinizing agents	Synergi Hydro-RP 80A column (150×4.6 mm, 4 µm); Torrance, USA	Phosphate buffer at pH = 4.1 and acetonitrile (69:31, v/v)	8	0.25
Ruxolitinib	RP-HPLC-FL	Dissolving in dimethyl sulfoxide at 5 mg/mL, then diluting in 100% methanol	Waters Symmetry C_{18} (4.6×75 mm, 3.5 µm)	Water: Acetonitrile at pH = 4.8 and (67:33, v/v)	5	0.05
Tamoxifen, Endoxifen, 4-hydroxytamoxifen	HPLC-FLD	Based on LLE with hexane-isobutanol (68:32, v/v), and adding acetonitrile and K_3PO_4	C_{18} (Zorbax Eclipse plus 100×4.6mm i.d.; 5 µm Agilent, USA)	Acetonitrile-KH_2PO_4 (pH = 3.0; 38:62, v/v)	16	0.17, 0.35 and 0.32
Irinotecan SN-38	HPLC-FLD	DBS disk transferred to a polypropylene microtube and added with 350 µL of extraction solution	Eclipse Plus C_8 (150×4.6 mm, 5 µm)	Phosphate buffer (pH = 4.0 and acetonitrile 80:20, v/v)	17	--

novel trends are underway to find natural alternative chemotherapeutic agents, e.g., ferulic acid (FA), as natural substances featuring low toxicity. A tumor-targeting agent radiolabeled using $^{131}I^{-}$ on ferulic acid through the electrophilic substitution reactions *via* chloramin-T was investigated. Given the application of iodinated radiopharmaceuticals daily, the use of the short-lived ^{123}I, rapid, easy-to-perform, and simple radiochemical quality control process, it is advantageous to use miniaturized chromatography. Subsequently, the radiochemical purity (RCP) was appraised using a variety of analytical methods, such as thin-layer chromatography (TLC), paper chromatography (PC), paper electrophoresis (PE), HPLC, and instant TLC (ITLC), and was generalized to the application of mini-TLC, mini-column chromatography (silica, Sephadex-G25), and miniaturized PC (mini-PC). The ^{131}I-FA radiolabeling yield was equal to 96.23 ± 0.45%, and these systems indicated great effectiveness in the radiochemical purity estimation, which is comparable to the traditional techniques characterized by accurate, specific, linear, and precise specifications [48].

2.3. Spectroscopic techniques

Spectroscopic techniques provide rapid, sensitive, and often label-free alternatives to conventional chromatography for monitoring anticancer drugs in both clinical and environmental contexts. Within this domain, surface-enhanced Raman spectroscopy (SERS) has gained prominence as a transformative tool for therapeutic drug monitoring (TDM). Recognized for its non-destructive nature, exceptional signal enhancement (typically $>10^4$-fold), and compatibility with label-free, on-chip biosensing [49], SERS offers a sensitive, fast, and cost-effective platform for detecting trace analytes in biological fluids [50]. These characteristics position SERS as a practical and resource-efficient alternative to more complex chromatographic approaches. SERS has been successfully applied to the detection of several key anticancer agents. For instance, methotrexate, a pyrimidine-based antifolate, has been detected using copper-based SERS substrates (CRSC) [51]. Similarly, capecitabine, another pyrimidine derivative, spontaneously adsorbs onto chloride-capped silver nanoparticles (Ag NPs), enabling its sensitive identification [52]. The potent cytotoxic agent irinotecan, used in metastatic colorectal cancer, has been analyzed using both chloride-capped Ag NPs and citrate-capped gold (Au) NPs [53, 54]. Furthermore, the

0.93) with reference HPLC-MS/MS data while maintaining high analytical accuracy [55]. A significant advancement in SERS substrate design involves the use of hybrid nanomaterials to improve sensitivity and reduce matrix interference. Graphene oxide (GO)-supported Au NPs (Au@GO) have been employed as enhanced substrates for detecting cyclophosphamide and paclitaxel. Using crystal violet as an internal probe, the Au@GO hybrid demonstrated a SERS response twice as strong at 10^{-6} M compared to pure Au colloids at 10^{-4} M. Modification of these substrates with *L*-cysteine further reduced nonspecific protein adsorption, thereby improving selectivity in complex biological matrices (Fig. 2) [56]. This functionalized Au@GO platform enabled the detection of the non-aromatic drug cyclophosphamide at concentrations as low as 5 nM.

Compared to conventional chromatographic techniques, SERS offers distinct practical advantages, including reduced consumption of reagents and solvents, lower operational costs, faster analysis times, and less demand for highly specialized operator training. These features, combined with its high sensitivity and molecular specificity, position SERS as a promising tool for the decentralized and real-time monitoring of anticancer drugs in clinical and point-of-care settings.

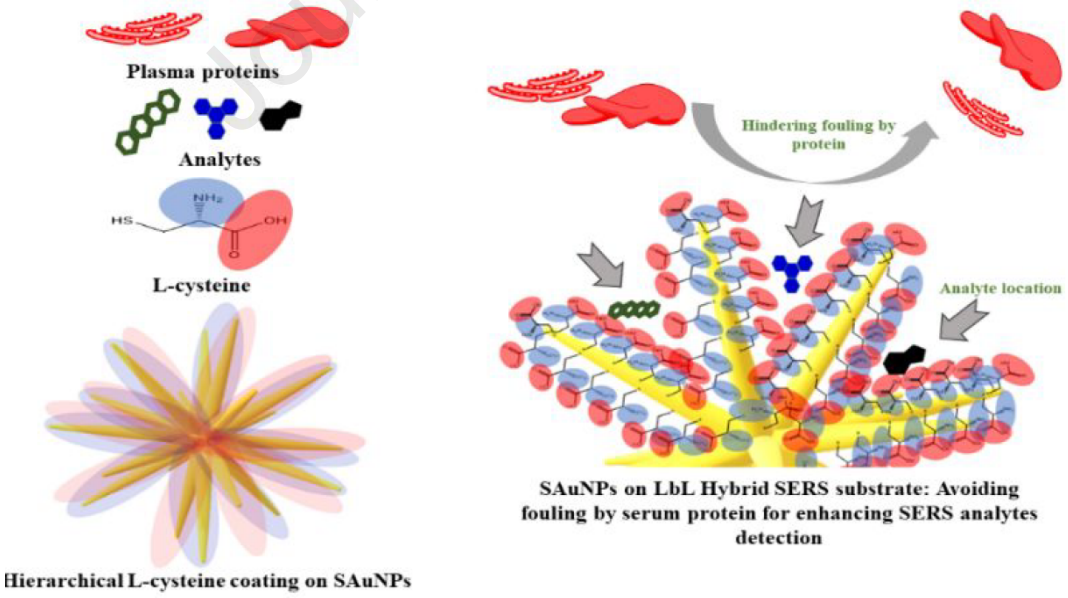


Fig. 2. Schematic representation of the modification of AuNP SERS-substrate with a zwitterionic *L*-cysteine SAM, serving as an anti-fouling brush. Reprinted from Ref. [56] with permission from ACS.

labor-intensive workflows. As a disruptive innovation, it enables miniaturization, automation, and integration of complex analytical processes into portable, efficient systems [57]. Concurrently, advancements in nanotechnology have facilitated the design of novel colloidal aggregates with tailored morphologies and long-term stability. These engineered NPs exhibit intrinsic SERS activity without the need for external aggregation, enhancing reproducibility and simplifying substrate preparation [58]. The convergence of these fields has led to the development of integrated SERS-microfluidic chips. One such platform was designed to generate controllable aqueous micro-droplets within an oil phase, enabling the detection of 6-thioguanine in human serum [59]. The droplet-based microfluidic approach creates isolated, stable micro-environments that confine both the drug molecules and SERS-active colloids, significantly improving signal homogeneity and analytical repeatability. This integrated system not only enhances detection reliability but also aligns with the broader trend toward point-of-care diagnostics and high-throughput screening in personalized oncology.

Similarly, fluorescence-based sensing provides highly sensitive, selective, and rapid optical detection of drugs through mechanisms such as photoinduced electron transfer (PET) and inner filter effects (IFE). Fluorescent probe-based sensors utilize the interaction between immobilized fluorescent markers and an evanescent field to generate a measurable optical signal, where fluorescence intensity correlates directly with target analyte concentration. Among fluorescent probes, metal nanoclusters (NCs) are particularly advantageous due to their high luminescence intensity, stability, and selectivity, making them ideal for the sensitive detection of anticancer drugs [60,61]. A fluorescent sensor was developed using carboxylated chitosan (CC) and dithiothreitol (DTT)-stabilized Au NCs (CC/DTT-AuNCs) for the determination of doxorubicin. The negatively charged CC/DTT-AuNCs interact electrostatically with positively charged doxorubicin, facilitating strong binding between the probe and the analyte. Upon photoexcitation, CC/DTT-AuNCs emit fluorescence, which is quenched *via* photoinduced electron transfer (PET) from the NCs to doxorubicin. This electron transfer results in the formation of two –OH groups on the doxorubicin molecule, accompanied by a significant decrease in its absorbance band between 400–600 nm following irradiation with 302 nm UV light for 30 minutes. The complete PET-mediated quenching mechanism between CC/DTT-AuNCs and doxorubicin is illustrated

doxorubicin in biological samples. The method provides a viable label-free, optical alternative to conventional electrochemical and chromatographic techniques, with potential for integration into miniaturized and point-of-care diagnostic systems.

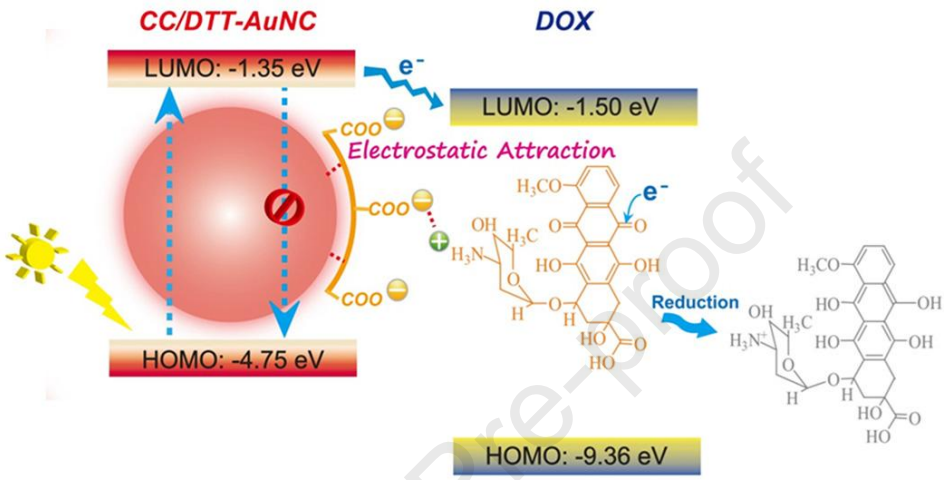


Fig. 3. Electron transfer from the excited state of a CC/DTT-AuNC to doxorubicin results in the suppression of the fluorescence of the CC/DTT-AuNC and the reduction of doxorubicin. Reprinted from Ref. [62] with permission from Elsevier.

Bimetallic NCs have garnered significant interest due to their enhanced physicochemical properties compared to single-metal counterparts, including superior fluorescence intensity, stability, and quantum yield, resulting from synergistic electronic and structural interactions [63]. A fluorescent probe composed of Au/Ag bimetallic NCs templated on *L*-tryptophan (*L*-Trp@AuAgNCs) was synthesized *via* a one-pot method. Compared to single-metal *L*-Trp@AuNCs, the bimetallic system exhibited a fivefold enhancement in fluorescence intensity, photostability, and quantum yield, making it a highly sensitive optical platform for drug detection. The fluorescence of *L*-Trp@AuAgNCs was quenched by the anticancer drugs methotrexate and doxorubicin through an inner filter effect (IFE), where absorption of excitation or emission light by the drug reduces the observed fluorescence. The sensor demonstrated linear responses over concentration ranges of 2.5–150 μM for both drugs, with impressive LOD of 2.5 nM for methotrexate and 3 nM for doxorubicin. Recovery studies in spiked

Bimetallic NCs-based fluorescent probes provide enhanced brightness, stability, and sensitivity compared to monometallic clusters, enabling low detection limits and a wide linear dynamic range. Their tunable surface chemistry allows for selective, multiplexed detection of anticancer drugs in biological fluids, supporting real-time, label-free analysis. By integrating nanomaterial engineering with fluorescence spectroscopy, these probes offer a rapid, sensitive platform for therapeutic drug monitoring suitable for point-of-care and personalized oncology applications.

2.4. Electrophoretic methods

Electrophoretic techniques, particularly capillary electrophoresis (CE) and its advanced modalities, have emerged as powerful tools in the bioanalysis of anticancer drugs. These methods exploit differences in electrophoretic mobility of charged species under an applied electric field, offering exceptional resolution for ionic and polar compounds, which are often challenging to separate using reversed-phase chromatographic approaches (Fig. 4). CE provides distinct advantages including high separation efficiency, minimal consumption of samples and solvents, rapid analysis times, and compatibility with various detection systems such as UV, fluorescence, and MS spectrometry.

To address the inherent sensitivity limitations due to small injection volumes, on-line preconcentration strategies like field-amplified sample stacking and transient isotachophoresis have been successfully integrated, enabling detection limits comparable to those of LC-MS in some applications. Furthermore, the development of tailored background electrolytes—incorporating ionic liquids, cyclodextrins, or polymeric additives has improved selectivity for structurally similar anticancer drugs and their metabolites. In clinical contexts, CE has been effectively applied to monitor a range of chemotherapeutic agents, including platin-based drugs, anthracyclines, and tyrosine kinase inhibitors, in biological matrices such as plasma, urine, and intracellular fluid. The technique's ability to directly inject minimally processed biological samples reduces pretreatment time and minimizes analyte loss. Recent innovations also include the coupling of CE with microfluidic and chip-based platforms, enhancing throughput and facilitating point-of-care therapeutic drug monitoring. Despite these advances, challenges remain in standardizing methods

in detection sensitivity, capillary coatings, and multidimensional CE systems is expected to further solidify the role of electrophoretic techniques in personalized oncology and precision medicine [18].

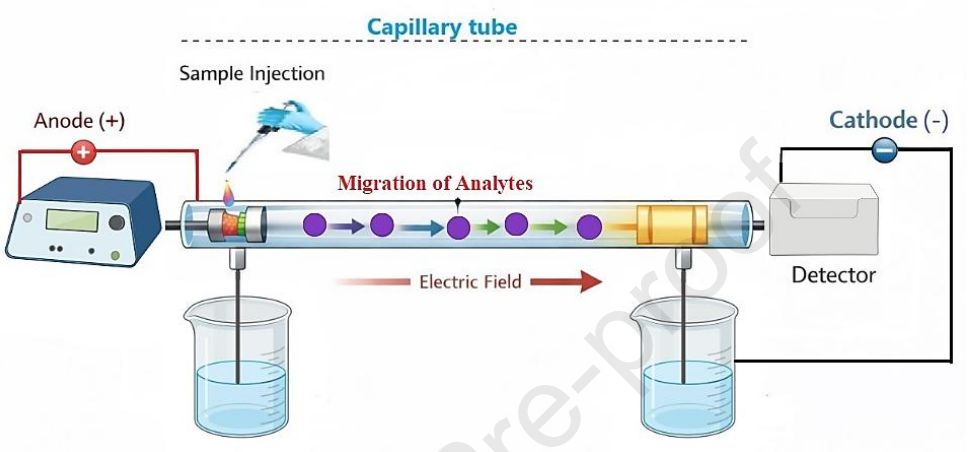


Fig. 4. Schematic representation of a capillary electrophoresis system.

In the context of developing green CE methods for pharmaceuticals, the work of El-Yazbi et al. [65] serves as a key example. They reported the first capillary zone electrophoretic (CZE) method for the direct determination of the anticancer drug tigecycline in infusion bags, achieving rapid separation (~5.9 min) using a phosphate buffer (pH 2.0) with minimal solvent consumption. Also, a CZE method was developed for the simultaneous separation of carboplatin and temozolomide. Using an acetate buffer (pH 3.6, 20 kV), the method achieved excellent separation with wide linear ranges (10–240 and 5–100 μg mL^{-1}) and low detection limits (2.5 and 1.3 μg mL^{-1}). This validated, green approach provides a rapid and sensitive alternative for quality control of this anticancer combination [66].

Micellar electrokinetic chromatography (MEKC) is a versatile CE mode that enhances the separation of both charged and neutral analytes through the incorporation of surfactant micelles into the background electrolyte. When surfactant concentration exceeds the critical micelle concentration (CMC), micelles form with a hydrophilic exterior and hydrophobic core. In a typical anionic surfactant system such as sodium dodecyl sulfate (SDS), micelles acquire a net negative charge and migrate toward the anode, while the electroosmotic flow (EOF) drives the bulk solution

micelles and slower migration. Without micelles, neutral compounds co-migrate with EOF and remain unresolved. MEKC has been effectively applied to the analysis of anticancer drugs and metabolites. For example, a stacking injection-MEKC-DAD (SIM-MEKC-DAD) method was developed for the simultaneous determination of 5-fluorouracil and 5-fluoro-2'-deoxyuridine in human plasma [67]. The method offered a 45-fold improvement in LOD compared to conventional HPLC-DAD, achieving detection limits between 5 and 250 ng mL^{-1}. This approach not only provides enhanced sensitivity but also benefits from operational simplicity, reduced organic solvent consumption, and shorter analysis times. Further extending the utility of electrophoretic techniques, hybrid methods such as field-amplified sample injection coupled with hollow fiber-liquid phase microextraction and CE-DAD (FASI-HF-LPME-CE-DAD) have been developed to improve preconcentration and matrix clean-up [68], offering a cost-effective alternative to more expensive LC-MS/MS platforms [69]. In another application, an MEKC-UV method was validated for the quantification of sodium 2-mercaptoethanesulfonate (MESNA) in human plasma using 2-chloro-1-methyl-lepidinium tetrafluoroborate as a derivatizing agent. The method achieved an LOQ of 0.5 μmol L^{-1}, with intra-day accuracy of 97.2–110.0% and inter-day accuracy of 94.0–101.2%, demonstrating its suitability for clinical monitoring [70]. MEKC thus represents a green, efficient, and sensitive analytical platform well-suited for the bioanalysis of polar and ionic anticancer drugs, particularly in laboratories seeking to balance performance with cost and operational simplicity.

Microemulsion electrokinetic chromatography (MEEKC) employs oil-in-water microemulsions as a pseudostationary phase to enhance the separation of both hydrophilic and hydrophobic analytes. However, when coupled with UV detection, MEEKC often suffers from limited sensitivity due to the short optical path length of the capillary and small injection volumes. To address this, online preconcentration strategies such as field-amplified sample injection (FASI) are frequently employed to improve detection limits. In one application, MEEKC-FASI was used for the analysis of fluorouracil in spiked urine and serum samples. The method utilized a microemulsion containing 10 mM SDS as the pseudo-stationary phase, with sample stacking performed at 10 kV for 6 seconds. This approach enhanced mass transfer and separation efficiency, achieving baseline separation and LOD of 0.68 μg mL^{-1} within a 12-minute run time using DAD detection at 200 nm.

separation platform for the analysis of various anticancer drugs when combined with UV-Vis detection [72].

On the other hand, non-aqueous capillary electrophoresis (NACE) employs organic solvents as the separation medium, offering distinct advantages for analyzing poorly water-soluble compounds and reducing undesired interactions with capillary walls. While traditional aqueous CE is valued for its simplicity, speed, and efficiency, it can be limited by matrix interference, poor reproducibility, and low UV sensitivity for weakly absorbing analytes. NACE circumvents many of these issues by enabling better solubility of hydrophobic drugs, enhancing selectivity, and improving compatibility with mass spectrometric detection due to easier solvent evaporation. The technique has been further advanced through integration with various detection systems (Table 2) and the development of automated multi-capillary devices and cost-effective commercial kits, which have collectively expanded its utility in clinical and research laboratories [18, 70, 73]. When applied to anticancer drug analysis, NACE facilitates the separation of hydrophobic chemotherapeutic agents and their metabolites with high resolution and reproducibility, making it a versatile complement to aqueous CE and chromatographic methods in modern bioanalytical workflows.

Table 2. Overview of Capillary Electrophoresis (CE) modes for the quantitative analysis of anticancer drugs.

Drug	Method	Sample preparation	Capillary Length (ID/Tot/Eff) (cm)	BGE	Time (min)	LOD (ng mL^{-1})
Tigecycline	CZE	1 mg/mL of Tygacil® vial (50 mg) in 50 mL 5% dextrose	50 µm i.d.	0.5 M NaOH with phosphate buffer pH 2.0	60	980
Carboplatin **Temozolamide**	CZE-HPLC-UV	0.1 M sodium hydroxide and deionized water for 5 min and 2 min	--	Acetate buffer pH 3.6	7–9	2500 1300
5-Fluorouridine **5-Fluoro-2'-deoxyuridine**	SIM-MEKC-DAD	LLE by 30 µl sodium acetate (1 M, pH 5.3), 0.3 ml sodium sulfate and 5.4 ml ethyl acetate	65.0×50.0 µm i.d.	45 mM phosphate and 50 mM SDS (pH 8, adjusted with 2 M of NaOH)	15	0.14 0.11
MENSA	MEKC-UV/Vis	Dissolvation in Tris (2-carboxyethyl) phosphine, Filtered through polyethersulfone membrane	41.5 cm (75 µm i.d.)	0.03 mol L^{-1} pH 7 phosphate buffer with the addition of 0.01 mol L^{-1} SDS, and 10% ACN	25	0.3 µmol L^{-1}
Fluorouracil	MEEKC-FASI-DAD	PP with MeOH (1:1) (v/v) and dilution with 10Mm sodium tetraborate (10 folds)	50 mm i.d. and 63/54.5	10mM SDS, 0.6% (v/v) 1-butanol, 0.5% (v/v) ethyl acetate and 98.9% (v/v) borate buffer (10 mM: pH 9)	12	680

platforms for the detection and quantification of anticancer drugs across a wide concentration range. Methods such as cyclic voltammetry (CV), linear sweep voltammetry (LSV), differential pulse voltammetry (DPV), and square-wave voltammetry (SWV) are commonly employed, with CV being particularly valuable for characterizing redox behavior and reaction mechanisms. These techniques leverage the electrochemical activity of drug molecules, offering high selectivity and sensitivity without the need for extensive sample preparation or expensive instrumentation. The performance of electrochemical sensors is heavily influenced by the choice of electrode material and modification strategies. Conventional electrodes made from carbon, Au, Pt, and glassy carbon provide a foundational platform, but recent advances have focused on enhancing sensitivity, catalytic activity, and biocompatibility through nanomaterial integration. Materials such as carbon nanotubes (CNTs), conductive polymers, metal NPs (e.g., Au, Ag, Pt), graphene, and quantum dots have been widely utilized to modify electrode surfaces. These nanomaterials improve electrical conductivity, increase active surface area, facilitate electron transfer kinetics, and in some cases, impart selective recognition through functionalization [74].

The combination of electrochemical methods with nanomaterial-based sensors enables the detection of anticancer drugs at clinically relevant levels in complex biological matrices such as blood, plasma, and urine. Moreover, the inherent portability and potential for miniaturization of electrochemical systems align well with the growing demand for point-of-care diagnostic devices and real-time therapeutic drug monitoring in oncology. Future developments in this field are likely to focus on multiplexed sensor arrays, wearable electrochemical platforms, and integration with wireless data transmission, further advancing personalized medicine through decentralized, accessible, and continuous drug monitoring.

2.5.1. Carbon-based electrodes

Carbon-based electrodes are widely employed in electrochemical sensing due to their favorable electrical conductivity, chemical stability, broad potential window, and cost-effectiveness. Commonly used configurations include glassy carbon electrodes (GCE), carbon paste electrodes (CPE), pencil graphite electrodes (PGE), carbon fiber electrodes, and carbon composite electrodes. Among these, GCE is often regarded as the most suitable platform for electrochemical drug

area, limited pore volume, and modest electrocatalytic activity—often necessitate surface modification to enhance analytical performance. To overcome these limitations, researchers have developed various nanomaterial-modified GCEs that significantly improve sensitivity, selectivity, and response time. For instance, a sea-urchin-like cobalt oxide (SC-Co_3O_4) modified GCE was developed for the determination of ruxolitinib using adsorptive stripping differential pulse voltammetry (AdSDPV). Compared to modifiers such as AuNPs, reduced graphene oxide (rGO), graphene quantum dots (GQD), and multi-walled carbon nanotubes (MWCNT), the SC-Co_3O_4/GCE sensor exhibited superior sensitivity, reproducibility, and rapid response. The method achieved LOD of 6.73 nM with a linear range of 0.08–20 μM, demonstrating high precision and accuracy suitable for therapeutic drug monitoring [75].

In another study, ZrO_2/rGO nanocomposite was synthesized *via* a one-pot hydrothermal method and deposited on GCE to fabricate a sensor for regorafenib. The ZrO_2 NPs (≈7 nm) were uniformly dispersed on rGO sheets, providing enhanced electrocatalytic activity. The ZrO_2/rGO/GCE sensor exhibited high selectivity even in the presence of common interferents such as ascorbic acid and uric acid, with a linear detection range of 11–343 nM and LOD/LOQ values of 17 nM and 59 nM, respectively (Fig. 5). Notably, these detection limits surpass those reported for HPLC (LOQ = 10 ng mL^{-1}), while the sensor also offers advantages in cost, simplicity, and analysis speed [76, 77].

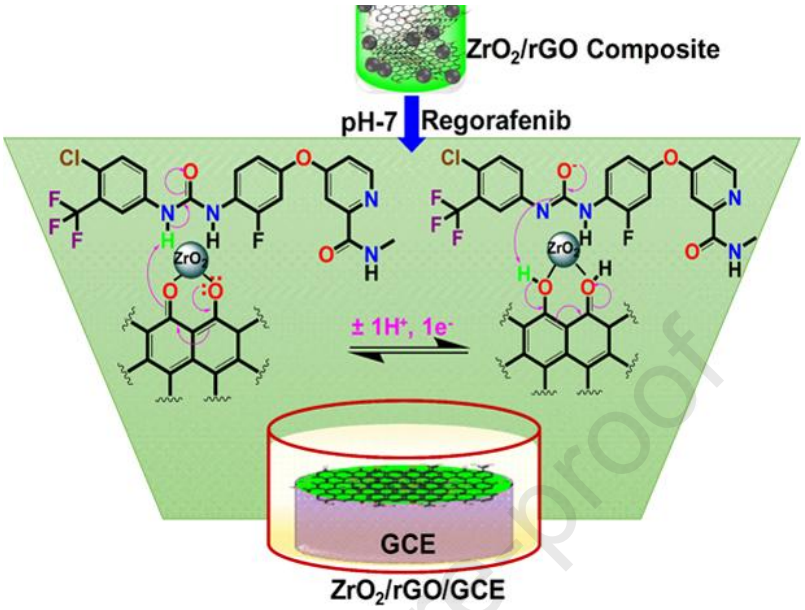


Fig. 5. The sensitive ZrO_2/rGO/GCE electrochemical sensor for the quantification of regorafenib. Reprinted from Ref. [77] with permission from ACS.

Electrochemical sensors are widely recognized for their reliability, sensitivity, and high stability, demonstrating robustness against variations in material composition, background noise, morphological changes, and environmental conditions. A notable advancement in this field is the development of a ratiometric electrochemical sensor based on a $Ti_3C_2T_x$-MXene nanocomposite-modified GCE, which incorporates MWCNTs to enhance electrical conductivity and methylene blue (MB) as an internal reference for signal normalization (Fig. 6). Using CV and AdSDPV, this sensor demonstrated excellent electrocatalytic activity toward mitoxantrone in complex biological matrices such as serum and urine. The linear detection range spanned from 3.0 nM to 11.0 μM, with an exceptionally low LOD of 79.15 pM. The sensor exhibited a rapid response time of under 120 seconds and maintained strong anti-interference performance against various coexisting compounds. Furthermore, the strong adsorption of MB onto the MXene surface ensured long-term stability, with no significant deterioration in sensitivity observed after one month of storage.

Despite these advantages, GCE-based sensors are often hindered by practical limitations such as complex handling, susceptibility to electrode fouling, and demanding cleaning protocols, making them less suitable for field applications. To overcome these challenges, a portable paper-based

the GCE-based system while offering additional benefits such as simple fabrication, excellent hydrophilicity, compact size, and disposability. Comparative studies between the GCE-modified and paper-based sensors confirmed that the paper platform performs comparably in detecting mitoxantrone in serum and urine samples, with the added advantages of ease of use, cost-effectiveness, and suitability for resource-limited or point-of-care settings. The straightforward development process, financial feasibility, and ability to analyze a wide range of biological samples make paper-based electrochemical sensors particularly valuable for emergency departments and regions with limited analytical resources [78].

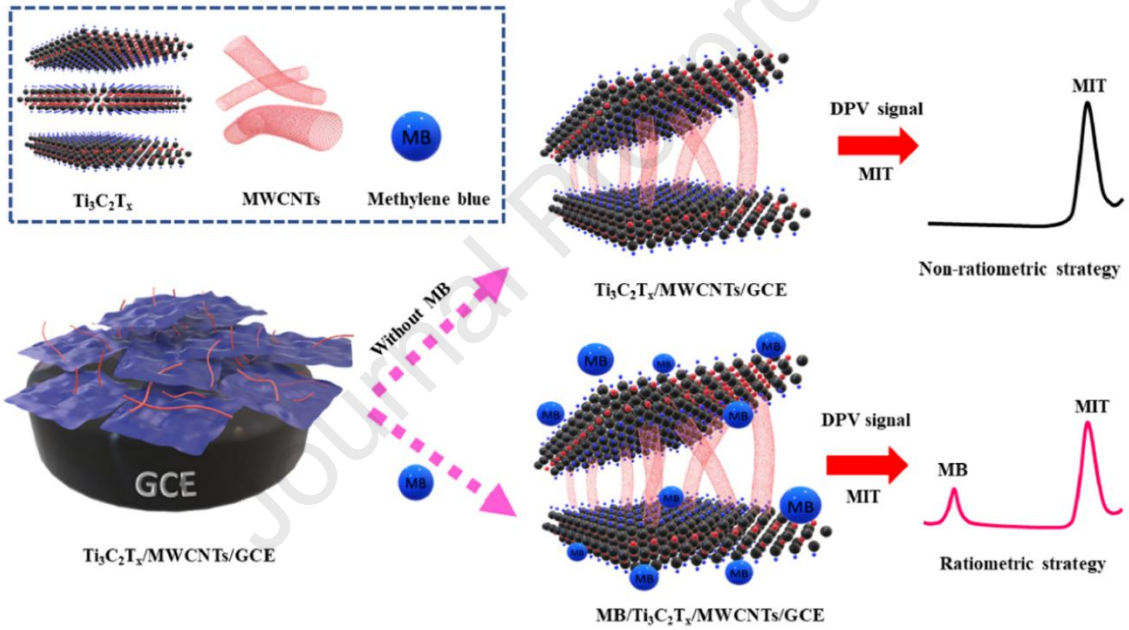


Fig. 6. MB/$Ti_3C_2T_x$/MWCNTs/GCE fabrication scheme for the quantification of mitoxantrone by ratiometric and non-ratiometric approaches. Reprinted from Ref. [78] with permission from Elsevier.

Beyond GCEs, pencil graphite electrodes (PGEs) and carbon paste electrodes (CPEs) offer practical, cost-effective alternatives with distinct advantages for electrochemical detection. PGEs are characterized by their wide availability, chemical inertness, mechanical hardness, low cost, and ease of surface modification. Similar to conventional metal electrodes, PGEs can be functionalized with nanomaterials, electroactive polymers, and other modifiers to enhance selectivity, sensitivity, and disposability. A promising modification approach involves the hybridization of conducting

stability of carbon substrates [79,80]. For instance, a PGE modified with polypyrrole (PPy) and rGO was developed for the detection of didanosine in pharmaceutical samples. Using differential pulse voltammetry (DPV), the oxidation currents of guanine and adenine decreased upon interaction with didanosine immobilized on ds-DNA/PGE/PPy/rGO. The sensor exhibited a dynamic range of 0.02–50.0 μM and a low LOD of 8.0 nM, outperforming UV/Vis (1.5 μM), CV (0.001 μM), and UPLC-MS/MS (0.04 μM) methods [81].

CPEs are widely used due to their broad potential window, simple preparation, affordability, and facile modification. However, unmodified CPEs often suffer from limited selectivity, sensitivity, and slow electron transfer kinetics. These limitations can be overcome through incorporation of nanomaterials, inorganic compounds, or polymeric layers. In one study, a ferrocene (FC) and MWCNT-modified CPE (FC/MWCNTs/CPE) was constructed for the analysis of flutamide in serum, plasma, and urine. Electrochemical impedance spectroscopy confirmed that this modified electrode exhibited the lowest charge transfer resistance (Rct) compared to MWCNTs/CPE and bare CPE, indicating enhanced conductivity. The FC/MWCNTs/CPE sensor offered a low LOD, wide linear dynamic range, high reproducibility, and excellent sensitivity, surpassing previously reported methods [82-84]. Importantly, the sensor required no pretreatment, simplifying the analytical workflow.

Further enhancements have been achieved through the integration of multi-component nanocomposites. For instance, a Fe_3O_4@MoS_2/rGO/ionic liquid-modified CPE (Fe_3O_4@MoS_2/rGO/IL/CPE) was developed for the simultaneous detection of dasatinib and doxorubicin using sensitive DPV. Under optimized conditions, the sensor demonstrated excellent sensitivity and selectivity across a concentration range of 0.02–390.0 μM, with an LOD of 6.0 nM for dasatinib. Two well-resolved oxidation peaks were observed with a peak separation of 0.38 V. Compared to previously reported electrodes, such as Fe_3O_4-SWCNT/IL paste electrodes, this sensor provided a ~8.6-fold improvement in sensitivity. Additionally, it significantly lowered the LOD relative to other modified electrodes, including AuNPs/rGO/ds-DNA/GCE (0.009 μM) and ZnO NPs/IL/CPE (0.5 μM), underscoring its enhanced performance for anticancer drug detection [85−88].

excellent conductivity, chemical stability, and catalytic properties. Gold electrodes, in particular, are commonly functionalized via thiol-based self-assembly to create stable interfaces for biosensing applications. This approach often involves the immobilization of antibodies or other biorecognition elements through the thiol (–SH) groups, enabling the development of highly specific immunosensors. A novel surface modification strategy employing diazonium salt chemistry was used to develop an electrochemical immunosensor for methotrexate detection. Instead of relying on traditional redox probes such as $Fe(CN)_6^{3-/4-}$, the sensor utilized electrochemical immittance spectroscopy (EIS) to directly monitor immunocomplex formation without the need for a redox mediator. Following optimization and stabilization, the sensor was successfully applied to the analysis of methotrexate in human blood serum, demonstrating its potential for clinical therapeutic drug monitoring [89]. The integration of bimetallic nanocomposites with graphene derivatives has been shown to significantly enhance electrocatalytic activity and electron transfer kinetics [90,91].

A notable example is the development of a highly sensitive sensor based on a Au/Pd@rGO@p(*L*-Cys) modified pencil graphite electrode (PGE) for the simultaneous determination of ifosfamide and etoposide. The sensor exhibited wide linear ranges of 0.10–90.0 μM for ifosfamide and 0.01–40.0 μM for etoposide, with impressively low detection limits of 9.210 nM and 0.718 nM, respectively. The sensing mechanism relies on the covalent immobilization of the target drugs via cysteine linkers on the Au surface. The –SH and amino ($–NH_2$) groups of cysteine facilitate hydrogen bonding with oxygen-containing functional groups on rGO, while also promoting dehydration through interaction with hydroxyl (–OH) groups. This design not only enhances binding affinity but also improves interfacial electron transfer. The Au/Pd@rGO@p(*L*-Cys) PGE sensor demonstrated excellent repeatability, reproducibility, and long-term stability, and was successfully applied to the detection of both drugs in complex biological matrices such as serum, urine, and pharmaceutical injection solutions [92].

electrochemical sensing, particularly for the detection of anticancer drugs. Researchers are increasingly focused on fabricating nanocomposite materials that exhibit enhanced properties such as superior electrocatalytic activity, excellent electrical conductivity, high surface area, and improved chemical, thermal, and mechanical stability. These attributes make nanocomposites ideal for constructing highly sensitive, selective, and durable electrochemical sensors [93,94]. Key nanomaterials used in electrode fabrication include metal and metal oxide NPs such as Au, Pd, Pt, ZnO, NiO, and CuO, which offer favorable electrochemical behavior and stability across a wide pH range [95,96]. In parallel, CNTs are widely employed due to their exceptional conductivity and nanoscale structure, which facilitate rapid electron transfer [97]. By integrating these materials into hybrid nanocomposites, synergistic effects can be achieved, resulting in sensors with significantly improved performance.

Nanomaterials have also gained considerable attention in the design of DNA-based electrochemical biosensors, which provide a rapid, cost-effective, and sensitive platform for applications ranging from gene sequencing and molecular diagnostics to drug monitoring and forensic analysis [98–101]. For example, a DNA biosensor for chlorambucil was constructed using a PGE modified with PPy, $NiCo_2O_4$, and Pt NPs. This sensor, depicted in Fig. 7, demonstrated a linear response over 0.018–200 μM and LOD of 4.0 nM. The sensing mechanism involves chlorambucil binding to the minor groove of DNA through π–σ interactions and hydrogen bonding, illustrating the ability of nanomaterial-enhanced platforms to probe specific molecular interactions [100]. In another study, a DNA biosensor was developed using a GCE modified with Pt–Pd–ZnO/SWCNTs nanocomposite for the detection of idarubicin. The sensor operates based on the intercalation of idarubicin into the guanine bases of immobilized double-stranded DNA (ds-DNA), enabling sensitive detection across a concentration range of 1.0 nM to 65 μM with recovery rates of 98.0–104.75% [102].

These examples underscore the potential of nanomaterial-modified electrodes to deliver high sensitivity, wide dynamic range, and reliable performance in complex biological matrices. Such advances pave the way for the next generation of electrochemical biosensors, supporting applications in therapeutic drug monitoring, personalized medicine, and point-of-care diagnostics.

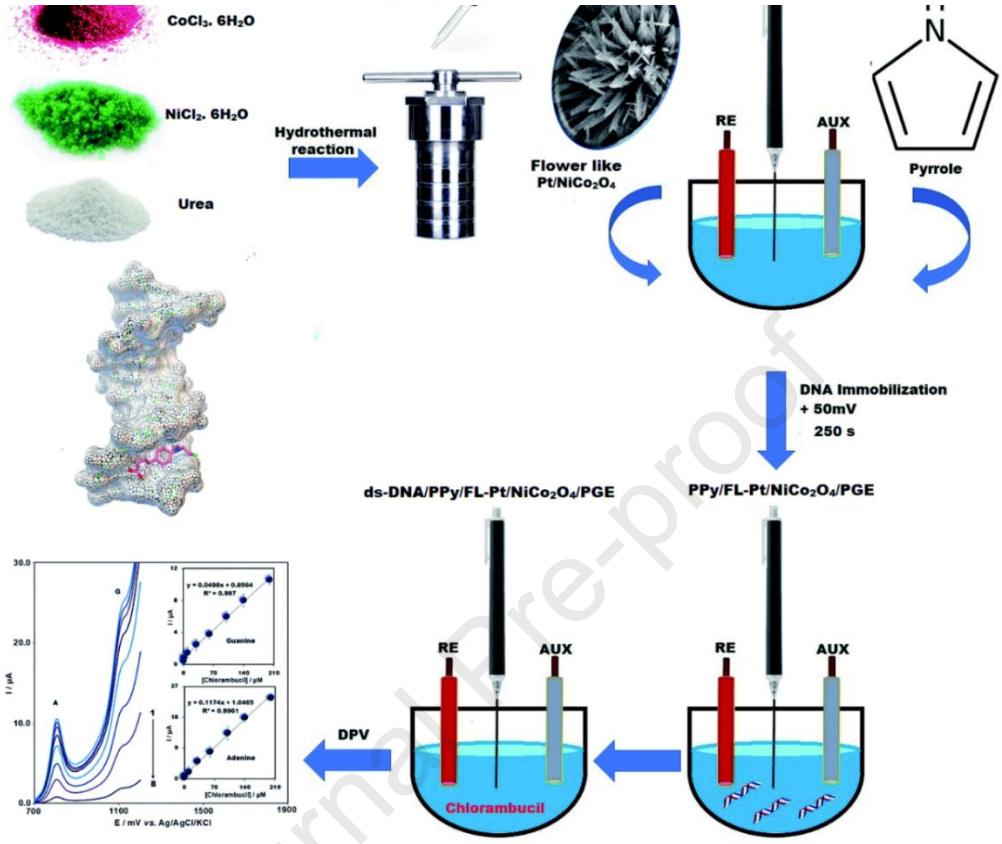


Fig. 7. The development of the DNA biosensor for chlorambucil determination. Reprinted from Ref. [100] with permission from RSC.

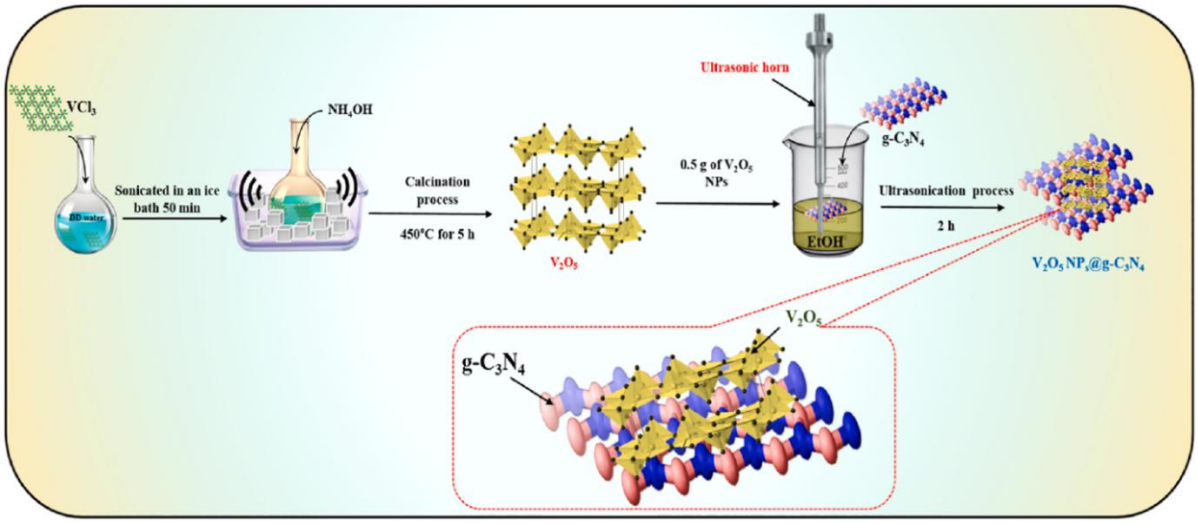
The emergence of GO nanoribbons (GONRs) has introduced a highly active nanomaterial with superior electrochemical properties compared to traditional graphene nanosheets and carbon nanotubes, primarily due to their abundant edge defect sites and enhanced chemical reactivity [102]. This has accelerated their application in the fabrication of sensitive electrochemical sensors.

A prominent example is the NiCo-BTC MOFs/N-GONRs/GCE sensor, which synergistically combines the high conductivity and electrocatalytic activity of nitrogen-doped GONRs (N-GONRs) with the large surface area of bimetallic metal–organic frameworks (NiCo-BTC MOFs). The sensor was constructed through a multi-step synthesis: first, MWCNTs were longitudinally unzipped to form GONRs; these were then hydrothermally reduced with urea to produce N-GONRs, which were subsequently drop-cast onto a GCE. Finally, NiCo-layered double

enhanced the sensor's electrochemical performance. Specifically, the anodic peak for doxorubicin shifted to a lower potential with increased current intensity compared to the NiCo-BTC MOFs/GCE, attributed to improved conductivity and electron transfer facilitated by N-GONRs. This enabled the sensor to detect doxorubicin at nanomolar concentrations in biological fluids such as serum and urine, demonstrating its suitability for therapeutic drug monitoring [103].

In a parallel development, a hierarchical g-C_3N_4@V_2O_5 nanocomposite was synthesized via a sonochemical method and deposited onto a screen-printed carbon electrode (SPCE) for methotrexate detection (Fig. 8). The modified V_2O_5@g-C_3N_4/SPCE sensor exhibited sharp voltammetric peaks, a broad linear range (0.025–273.15 μM), and high sensitivity (7.122 μA μM^{-1} cm^{-2}) when analyzed by differential pulse voltammetry (DPV). It also showed a stronger current response to methotrexate compared to bare SPCE, V_2O_5/SPCE, and g-C_3N_4/SPCE, confirming the synergistic effect of the hybrid structure. The sensor was successfully applied to the analysis of methotrexate in both pharmaceutical formulations and blood serum, highlighting its practical utility in clinical diagnostics [104].

Collectively, these studies underscore the potential of advanced nanomaterials such as GONRs, MOFs, and hybrid nanocomposites to enhance the sensitivity, selectivity, and speed of electrochemical sensors for anticancer drug detection, supporting the progression toward personalized and point-of-care medical solutions.



Electrochemical methods have established themselves as valuable tools for the quantification of anticancer drugs, with the majority of reported applications focusing on commercial pharmaceutical formulations, human urine, and serum samples (Table 3). These methods offer distinct advantages in terms of cost-effectiveness, rapid analysis, and suitability for point-of-care use. However, the field remains largely anchored in the analysis of relatively accessible matrices, with a pronounced gap in applications involving more complex, low-volume, or tissue-based samples. A critical limitation of many current studies is their reliance on spiked samples rather than real patient-derived matrices, which may not fully capture the complexity of clinical specimens, including variable protein content, metabolite interference, and heterogeneous drug-binding profiles. A significant and necessary evolution lies in the development of multiplexed detection platforms. Most existing sensors are designed for single-analyte detection, which does not reflect the combinatorial nature of modern cancer therapy, where patients often receive multi-drug regimens.

The concurrent electrochemical detection of several anticancer agents and their metabolites remains a substantial technical challenge but is essential for comprehensive TDM. Advances in microfabrication, array-based electrode design, and data deconvolution algorithms are critical to achieving this goal. The functionalization of carbon-based electrodes (e.g., GCE, PGE, CPE) with nanomaterials, conductive polymers, and molecularly imprinted polymers has undeniably driven improvements in sensitivity, often yielding significantly lowered LOD. However, a critical perspective must be maintained: improved LOD in buffer or spiked samples does not automatically translate to clinical utility. Key challenges persist, including: a) Fouling and stability: Electrode surfaces are susceptible to fouling by proteins and lipids in biological fluids, degrading performance over time. b) Reproducibility and standardization: The manual modification of electrodes often leads to batch-to-batch variability, hindering the transfer of methods from research labs to clinical settings. c) Selectivity in ultra-complex matrices: While functionalization improves selectivity, cross-reactivity with structurally similar endogenous compounds or co-administered drugs remains a potential source of error.

intra-individual biological variability. 2) Engineering robust, disposable, and user-friendly interfaces (e.g., fully integrated screen-printed strips) to move beyond laboratory-based three-electrode cells. 3) Embracing green electrochemistry by developing sustainable nanomaterials and minimizing toxic reagents in sensor fabrication and operation. 4) Integrating electrochemical sensors with microfluidics and wearable formats to enable continuous, non-invasive monitoring, which could revolutionize personalized dosing.

In conclusion, while electrochemical sensing holds immense promise for decentralizing anticancer drug monitoring, its journey from a promising analytical technique to a mainstream clinical tool requires a concerted shift in focus—from merely demonstrating low LODs in idealized conditions to solving the practical challenges of accuracy, reliability, and usability in the real-world clinical environment. The synergy of materials science, engineering, and clinical oncology will be paramount in realizing this potential.

Ruxolitinib	AdSDPV	GCE	*SC*-Co_3O_4	6.73 nM	Human serum	[75]
Regorafenib	DPV	GCE	ZrO_2/rGO	5.00 ng mL^{-1}	Human serum	[77]
Mitoxantrone	AdSDPV	GCE	MB/$Ti_3C_2T_x$/MWCNTs	7.915×10^{-5} μM	Serum and urine	[78]
Didanosine	DPV	PGE	PPy/rGO	8 nM	Pharmaceutical samples	[80]
Flutamide	CV and SWV	CPE	FC/MWCNTs	0.001 μM	Urine and blood serum	[82]
Dasatinib, Doxorubicin	LSV and DPV	CPE	Fe_3O_4@MoS_2/rGO	6.0 nM	Injection, dasatinib tablet, and river water specimens	[84]
Mitoxantrone	EIS-MVA	Au	Ab/NHS-EDC/CP/AuE	7.0×10^{-12} M	Serum	[89]
Ifosfamide, Etoposide	CV and DPV	PGE	Au/Pd@rGO@p(L-Cys)	9.210 and 0.718 M	Serum and urine	[92]
Chlorambucil	DPV	PGE	PPy/FL-Pt/$NiCo_2O_4$	4 nM	Serum, urine and drug	[100]
Idarubicin	DPV	GCE	Pt-Pd-ZnO/SWCNTs	0.8 nM	Serum	[101]
Doxorubicin	CV	GCE	NiCo-BTC MOFs/N-GONRs	6 nM	Serum and urine	[103]
Methotrexate	DPV	SPCE	V_2O_5@g-C_3N_4	13.26 nM	Human blood serum	[104]
Imatinib mesylate (IMAT)	DPV	GCE	TbFeO3/g-C3N4	0.6nM	plasma	[105]
Oxaliplatin (OXP)	DPV	GCE	g-C_3N_4–TiO_2	0.010 μM	serum and urine	[106]
Etoposide	CV	GCE	graphene nanoribbons (GNR)	0.1 μM	urine and serum	[107]
Sunitinib (STB)	DPV	GCE	2DMOF-CNTs	5 nM	urine and serum	[108]

3. Sample preparation methods

The direct analysis of biological matrices such as plasma, urine, and serum is generally impractical due to their complex composition. Endogenous constituents, including proteins, lipids, salts, and other co-extracted biomolecules, can severely compromise chromatographic performance by causing column fouling, peak distortion, and reduced separation efficiency. In addition, direct coupling of untreated biological samples with MS detection may result in ion suppression or enhancement effects, system contamination, and reduced long-term instrument stability, ultimately affecting analytical accuracy and sensitivity. Therefore, sample preparation is not merely a

minimize matrix effects, and achieve sufficient enrichment prior to instrumental analysis. While conventional extraction techniques such as PP, LLE, and SPE remain widely used due to their simplicity and robustness, they often suffer from drawbacks such as high solvent consumption, limited selectivity, and labor-intensive workflows. In contrast, modern sample preparation approaches aim to overcome these limitations by improving extraction efficiency, reducing matrix interferences, and enhancing method sustainability through miniaturization, automation, and the use of green solvents.

Emerging techniques including dispersive solid-phase extraction (dSPE), magnetic solid-phase extraction (MSPE), fabric-phase sorptive extraction (FPSE), and various liquid-phase and solid-phase microextraction methods offer improved selectivity, reduced solvent volumes, and shorter processing times. These advancements not only address the practical challenges of traditional methods but also align with the growing emphasis on environmentally responsible analytical practices.

3.1 Conventional sample preparation

Conventional sample preparation techniques, including LLE, and SPE, remain foundational in bioanalytical workflows for anticancer drug analysis. Their respective principles, applications, and limitations are systematically summarized in Table 4.

Protein precipitation (PP) is a widely employed technique in bioanalysis, valued for its simplicity, speed, and high analyte recovery. The procedure involves the addition of a protein-precipitating solvent typically methanol, acetonitrile, or mixtures thereof to a biological sample such as plasma or serum. Following homogenization and centrifugation, the precipitated proteins are pelleted, and the clear supernatant containing the target analytes is collected for direct analysis. Despite its practicality, PP yields less clean extracts compared to LLE and SPE, often resulting in significant matrix effects during mass spectrometric detection. Endogenous phospholipids, salts, and other non-proteinaceous components remain in the supernatant and can interfere with ionization efficiency, leading to ion suppression or enhancement. Studies have shown that LLE removes a broader range of interfering compounds and more effectively mitigates matrix effects than PP. Nevertheless, PP remains a suitable choice for specific applications, such as the extraction

low cost, high throughput potential, reduced solvent consumption relative to LLE, and lower environmental toxicity [109].

3.1.1. Liquid-liquid extraction (LLE)

LLE is a conventional separation technique based on the differential partitioning of analytes between two immiscible liquid phases—typically an aqueous matrix and an organic solvent. It is valued for its simplicity, low cost, and high extraction efficiency, particularly for lipophilic compounds, though automation remains challenging compared to solid-phase extraction (SPE). In a representative application, LLE using ethyl acetate and isopropanol (19:1) achieved recoveries of 59.3–90.2% for capecitabine and its metabolites [109]. To address environmental and operational limitations of traditional LLE, homogeneous LLE (hLLE), also known as salting-out assisted LLE, has been developed. This approach utilizes water-miscible organic solvents under high-salinity conditions to induce phase separation, reducing solvent consumption and extraction time. For instance, a method for determining doxorubicin in human urine employed acetonitrile as the extraction solvent under high salinity, followed by analysis with UHPLC–fluorimetric detection (λex/λem = 430/580 nm). The process was completed in under 15 minutes, with a limit of detection (LOD) of 10 ng mL^{-1}, recoveries of 94.7–106.3%, and relative standard deviation (RSD) below 5.1% [110].

3.1.2. Solid-phase extraction (SPE)

Solid-phase extraction (SPE) is a selective sample preparation technique that isolates analytes based on specific chemical and physical interactions between the target molecules and a solid sorbent. The process typically involves several steps: conditioning of the sorbent, sample loading, washing to remove interfering matrix components, and elution of the purified analytes. Compared to PP and LLE, SPE provides significantly cleaner extracts and better recovery for a wide range of analytes, but it is often more labor-intensive, time-consuming, and costly, which can limit its adoption in high-throughput or resource-constrained clinical settings such as routine TDM.

Conventional SPE often employs reversed-phase C18 cartridges, with elution using solvents like methanol or ethyl acetate—for example, in the extraction of ifosfamide [111–114]. Recent advances have introduced functionalized sorbents to improve selectivity. For

mechanism involves electrostatic attraction at pH 5, supplemented by π–π stacking and hydrogen bonding with organic ligands. These findings underscore the potential of N-heterocyclic poly(carboxylic acid) ligands in designing inorganic–organic hybrid sorbents with tailored affinity for anticancer drugs [115]. SPE can be performed in offline or online configurations. Online SPE coupled with LC enhances sensitivity, reproducibility, and overall analytical performance. In one study, online SPE-LC demonstrated moderate matrix effects (≤ 12%) for most analytes, except for capecitabine (–46.7%). Method accuracy ranged from 78–111% with precision better than 13%. The choice of SPE column proved critical: Hypersil GOLD AQ was optimal for cyclophosphamide/ifosfamide, while Hypersil GOLD Silica performed best for gemcitabine and methotrexate [116,117]. Miniaturized SPE formats, such as pipette-tip micro-SPE (PT-μSPE), have gained attention for their ability to reduce solvent consumption, minimize sample volume, and accelerate extraction. A notable example employed a CA/PAN/THY/Mg-MOF composite sorbent in PT-μSPE coupled with HPLC-UV for the simultaneous quantification of letrozole, gefitinib (0.1–1500.0 μg L^{-1}), and riluzole (0.25–1500.0 mg L^{-1}). The method achieved correlation coefficients up to 0.9996, low LOD (0.03–0.10 μg L^{-1}), LOQ (0.10–0.33 μg L^{-1}), and excellent precision (RSD ≤ 6.6% intra-day, ≤ 8.2% inter-day) [118-120]. These developments reflect a shift toward more selective, sustainable, and integrated SPE platforms that address the limitations of traditional methods while meeting the demands of modern anticancer drug analysis.

Table 4. Comparative overview of conventional sample preparation techniques for the quantitative analysis of anti

Drug	Sample preparation	Separation/Detection	LOD (ng mL^{-1})	LOQ (ng mL^{-1})	Recovery
Capecitabine	LLE	UHPLC-MS/MS	--	20	59.27–90.15%
Doxorubicin	LLE	UHPLC	10	100	94.7–106.3%
Doxorubicin	D-μSPE	HPLC-FLD	0.2	2	87.6%
Epirubicin	D-μSPE	HPLC-FLD	0.3	3	84.3%
5-Fuorouracil 2',2'-Difluorodeoxyuridine	On-line SPE	HILIC-MS/MS	1000–2000	--	111–115%
Cytarabine, Gemcitabine, Methotrexate, Ifosfamide, Cyclophosphamide, Capecitabine	On-line SPE	RPLC-MS/MS	500–5000	--	87–119%
Letrozole,	PT-μSPE	HPLC-UV	0.03	0.1	98.0
Gefitinib,			0.07	0.1	76.0
Riluzole			0.1	0.33	69.0

effectiveness, and alignment with green analytical chemistry principles. This section reviews the application of sorbent-based and liquid-based extraction approaches for the analysis and quantification of anticancer drugs. The discussion encompasses their operational principles, current applications, inherent limitations, and recent technological advancements aimed at improving selectivity, sensitivity, and throughput in both clinical and environmental monitoring.

3.2.1. Sorbent-based extraction methods

Sorbent-based extraction techniques represent a fundamental paradigm shift from conventional solid-phase extraction (SPE), centered on the principles of miniaturization, integration, and solvent minimization. These methods utilize sorbents—either in bulk form or as thin coatings immobilized on various supports to selectively isolate and preconcentrate target analytes from complex matrices. Their design directly addresses key limitations of traditional SPE, such as high solvent consumption, large sample requirements, and lengthy procedural times. The ultimate goal of this engineering effort has been to create techniques that are not merely smaller versions of SPE, but fundamentally new platforms that offer superior performance in terms of speed, sensitivity, greenness, and practicality for modern analytical challenges. Key techniques in this domain, such as dispersive solid-phase extraction (dSPE), solid-phase microextraction (SPME), magnetic solid-phase extraction (MSPE), fabric phase sorptive extraction (FPSE), stir bar sorptive extraction (SBSE), and microextraction by packed sorbent (MEPS), are characterized by their unique operational formats and applications in the analysis of complex matrices. A comparative summary of their fundamental characteristics, applications, advantages, and disadvantages is provided in Tables 5-6, with a generalized schematic of their workflows illustrated in Fig. 9.

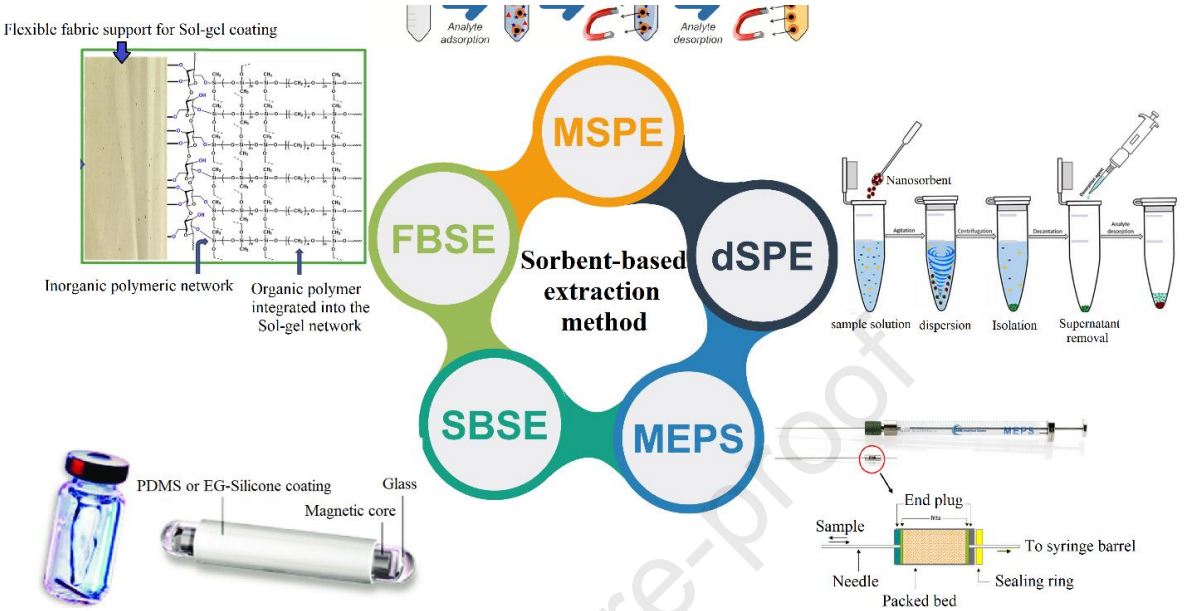


Fig. 9. Experimental setup for conventional SPME such as FPSE, MEPS, and SBSE, and SPE methods including dSPE and MSPE. Reprinted from Ref. [121-123] with permission.

3.2.1.1. dSPE

Conventional SPE, while foundational, is hampered by significant practical inefficiencies that can compromise analytical robustness. A primary limitation is the stringent requirement for exhaustive clean-up, necessitating multiple washing steps with various solvents to purge the sorbent of persistent matrix interferences. More critically, SPE cartridges are prone to irreversible pore clogging and bed channeling when handling complex biological matrices such as serum, plasma, or tissue lysates. This physical obstruction not only alters flow dynamics and sorbent capacity but also introduces variability in analyte retention, leading to diminished reproducibility and increased analytical uncertainty. In response to these shortcomings, dispersive solid-phase extraction (d-SPE) has emerged as a transformative adaptation. This methodology abandons the packed-bed format in favor of directly dispersing the sorbent material into the sample solution as a fine powder. This innovation achieves maximum interfacial contact, dramatically enhancing extraction kinetics and adsorption efficiency for trace-level analytes. Phase separation is subsequently achieved through rapid centrifugation or, in the advanced form of magnetic d-SPE (MSPE), via instantaneous isolation with an external magnet. By circumventing the issues of clogging and

matrix analyses [121].

The advancement of dispersive microextraction techniques is intrinsically linked to the strategic design of novel sorbent materials, each engineered to overcome specific limitations of conventional SPE and LLE. The integration of ionic liquids (ILs) represents a significant innovation in this domain. For instance, the development of magnetic mixed hemimicelles, comprising magnetic graphene oxide/polypyrrole (GO/PPy) coated with 1-hexadecyl-3-methylimidazolium bromide, targets the selective preconcentration of methotrexate [122]. This composite capitalizes on the combined advantages of its components: the GO/PPy substrate provides an extensive surface area and a π-conjugated system for hydrophobic and π-π interactions, while the IL imparts unique solvation properties and the potential for hydrogen bonding and electrostatic interactions. Analysis via HPLC-UV confirmed that this IL-functionalized sorbent offers superior sensitivity and extraction speed compared to traditional materials. Critically, it circumvents persistent issues associated with LLE, such as emulsion formation, high solvent consumption, and poor selectivity for polar analytes [123]. This approach exemplifies a deliberate shift from mere adsorption to tailored molecular recognition.

Parallel to IL-based systems, metal-organic frameworks (MOFs) have emerged as a cornerstone material for DμSPE, justified by their exceptional porosity, tunable pore chemistry, and structural robustness derived from strong metal-ligand coordination bonds [124–126]. A representative application is the extraction of antiandrogens—bicalutamide and flutamide using a ternary sorbent composite of CIM-80(AI) MOF, magnetic NiO NPs, and chitosan [127]. In this synergistic design, the CIM-80(AI) framework serves as the primary adsorption site, leveraging its porous structure for high-capacity uptake; the NiO NPs facilitate rapid magnetic separation; and chitosan acts as a biopolymeric binder that enhances mechanical stability and contributes to porosity. The reported method achieved commendable analytical figures of merit, including low LOD and high preconcentration factors, while aligning with green chemistry principles through minimal solvent use and a simplified operational workflow. However, the long-term stability of certain MOFs in aqueous or complex biological matrices remains a consideration for routine application.

trend is illustrated by the development of a mixed-mode DμSPE method for extracting lung surfactants from exhaled breath condensate. Guided by the principles of green analytical chemistry, an optimized sorbent blend of polystyrene (PS) and polymethylmethacrylate (PMMA) was implemented [129]. A notable strength of this work is the application of density functional theory (DFT) calculations to elucidate the extraction mechanism. The simulations quantified binding energies between the polymer blend and target surfactants, providing a molecular-level rationale for the observed high extraction efficiency, particularly for 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine. This integration of computational modeling with experimental design represents a sophisticated approach to sorbent selection, moving beyond trial-and-error towards predictive material science.

The evolution from IL-composites and MOFs to computationally designed polymer blends reflects a clear trajectory in sorbent development: a move towards multifunctionality, rational design, and environmental sustainability. Future progress will likely involve the increased use of hybrid materials that combine the strengths of different classes (e.g., IL-MOF composites), deeper integration of computational screening for sorbent design, and a stronger emphasis on materials that enable direct analysis or coupling with portable detection systems. The critical challenge remains balancing exceptional laboratory performance with the cost, reproducibility, and ruggedness required for widespread adoption in clinical and environmental monitoring.

3.2.1.2 MSPE

Magnetic Solid-Phase Extraction (MSPE) represents a significant advancement in solid-phase extraction technology, characterized by the integration of magnetic NPs (MNPs) as a core component with functional sorbent coatings. This hybrid design combines the high adsorption capacity of the sorbent material with the rapid, non-mechanical separability of superparamagnetic Fe_3O_4 particles using an external magnetic field [130]. Unlike conventional SPE, which requires packed cartridges, MSPE employs a dispersive format where the magnetic sorbent is directly introduced into the sample solution. This maximizes the interfacial contact area, facilitating faster mass transfer and achieving equilibrium more rapidly, while the magnetic separation step eliminates the need for centrifugation or filtration, making the process more efficient, economical,

layer, such as silica (Fe_3O_4@SiO_2) or a polymer (Fe_3O_4@polymer) [134]. The SiO_2 shell is particularly advantageous as its surface silanol (Si–OH) groups provide an anchoring point for further chemical modification, enabling the introduction of specific functional groups to tailor selectivity. For instance, a hyperbranched magnetic dendrimer sorbent (Fe_3O_4@SiO_2/DAG/MMA/ED/Gly-PEGylated) was developed for the extraction of letrozole from biological and pharmaceutical matrices [135]. This sorbent demonstrated a high adsorption capacity (20 mg g^{-1}, based on the Langmuir model) and, under optimized conditions, provided a linear range of 0.1–15 μg L^{-1} with a low LOD of 1.36 μg L^{-1}. Thermodynamic studies confirmed the adsorption was endothermic ($\Delta H° = 3.93$ kJ mol^{-1}), spontaneous ($\Delta G° < 0$), and driven by increased entropy ($\Delta S° = 0.045$ kJ mol^{-1} K^{-1}), indicating a favorable interaction between the drug and the sorbent surface. The material also exhibited excellent magnetic recoverability and reusability.

Surface modification is often essential to mitigate undesirable strong interactions, such as the irreversible adsorption of basic analytes onto residual silanols, which can impair recovery. A common strategy involves functionalizing silanized MNPs with acetic acid via amide coupling. This creates a more polar surface beneficial for extracting less nonpolar and polar analytes. Acetic acid-functionalized MNPs, modified with 3-aminopropyltriethoxysilane, were successfully applied to extract letrozole from human plasma prior to HPLC-FL analysis [136]. While MSPE methods for letrozole are not yet widespread, reported studies indicate promising performance with high extraction recoveries (93.5–104%) and competitive sensitivity (LODs ~23 ng mL^{-1} for HPLC-FL), though more sensitive detection via HPLC-MS/MS naturally yields lower LODs [137, 138].

Beyond silica-based coatings, carbonaceous materials are also widely employed. For example, magnetic carbon NPs (C/Fe_3O_4 NPs) were synthesized hydrothermally using glucose and used to extract cardiovascular drugs (amlodipine, carvedilol, losartan) from biological samples [139]. The MSPE method demonstrated broad linearity (1–7500 ng mL^{-1}), low LODs (0.09–0.69 ng mL^{-1}), high recoveries (62–97%), and good precision (RSD 1.6–5.8%), effectively handling protein-bound drugs without a prior deproteinization step.

with the sample to ensure intimate contact. After extraction, the sorbent is magnetically retrieved, and analytes are eluted with a suitable solvent for instrumental analysis. An innovative variant, effervescent-assisted dispersive magnetic micro-solid-phase extraction (EA-dM-μSPE), was developed for the quantification of tricyclic antidepressants (nortriptyline and amitriptyline) using a nitrogen-rich functionalized sorbent ($Fe_3O_4@SiO_2@N_3$) [140]. In this method, an effervescent reaction (between sodium carbonate and citric acid) generates CO_2 bubbles that promote the instantaneous and complete dispersion of the nanosorbent, reducing the adsorption time to just 1 minute and the total extraction time to under 6 minutes, showcasing the potential for ultra-rapid sample preparation.

3.2.1.3. SPME

Solid-phase microextraction (SPME) is a non-exhaustive, solvent-minimized sample preparation technique based on the equilibrium partitioning of analytes between a sample matrix and a sorbent-coated substrate. Its defining characteristic is the extremely small volume of the extraction phase relative to the sample, classifying it as a microextraction technique [141]. A key distinction from exhaustive methods like SPE is SPME's reliance on equilibrium extraction, which simplifies calibration but requires careful control of time, temperature, and matrix composition. The core SPME device typically features a fine fiber of fused silica or metal alloy coated with a thin layer of extracting phase, protected within a syringe-like needle when not in use. For analysis, the fiber is exposed to the sample (*via* direct immersion or headspace) and subsequently desorbed, most commonly by thermal means in a GC injector or by solvent in a dedicated interface for liquid chromatography (HPLC) [142].

SPME technology has evolved into several operational and format-based modes such as fiber SPME, thin-film SPME (TF-SPME), dispersive SPME (dSPME), pipette-tip SPME and in-tube SPME. For instance, ultrasonic-assisted dispersive SPME (UA-dSPME) using pH-sensitive molecularly imprinted chitosan NPs (MMIP@CS) was developed for the selective extraction of trace capecitabine from real samples. The MIP shell was synthesized using capecitabine as the template, 2-(diethylamino) ethyl methacrylate (DEAEMA) and 2-hydroxyethyl methacrylate (HEMA) as functional monomers and crosslinker, respectively, in a molar ratio of 1:4:20. Under

improving both selectivity and detection sensitivity [143]. Moreover, biocompatible SPME formats have been successfully integrated with direct mass spectrometry (MS) analysis, enabling rapid, in-situ detection without extensive sample preparation [144,145]. These advancements highlight the growing role of functionalized and biocompatible SPME platforms in sensitive, real-time bioanalytical applications.

The analytical workflow for SPME-based methods typically involves a three-step process: desorption of analytes from the SPME probe, chromatographic separation (often *via* LC), and final quantification. A notable innovation in this domain is the integration of SPME with fluorescence detection, enabling the development of portable and rapid monitoring systems A representative example is a fluorescence-based SPME platform designed for quantifying doxorubicin concentrations in complex biological matrices. In this system, extraction performance was evaluated using SPME fibers coated with C8-SCX (mixed-mode), C18 (reversed-phase), and HLB (hydrophilic-lipophilic balance) sorbents. Results demonstrated that the mixed-mode C8-SCX fiber exhibited the highest sensitivity, attributed to its combined hydrophobic and cation-exchange interactions, which are particularly effective for capturing doxorubicin's aromatic and $–NH_2$ functional groups. This trend highlights the significant challenge of matrix effects including fouling and competitive binding from endogenous biomolecules, which can compromise extraction efficiency and detection sensitivity in real-world samples. Thus, while SPME-fluorescence systems offer a promising route to portable, real-time therapeutic drug monitoring, and their practical application requires careful selection of fiber coatings and extensive validation in clinically relevant matrices to ensure accuracy and reproducibility in complex biological environments [146].

Thin-film SPME (TF-SPME) is a miniaturized SPME configuration that utilizes a planar sorbent film with a high surface-area-to-volume ratio. This design enhances both extraction kinetics and sorbent capacity, making it a sensitive and efficient platform for the extraction and purification of a wide range of analytes, including pharmaceuticals, food contaminants, pesticides, and environmental and biological markers [147–149]. An electrospun composite of polyfam and Co-MOF-74 was developed as a novel sorbent for TF-SPME of the tyrosine kinase inhibitors

intermolecular interactions including hydrogen bonding, hydrophobic effects, and π–π stacking enabled by the composite's high surface area, porosity, and abundant functional groups. However, several practical limitations hinder the implementation of this TF-SPME system. The absence of compatible interfaces prevents online coupling with analytical instruments, restricting automation and real-time analysis. Furthermore, the relatively large size of the TF-SPME device necessitates increased eluent volumes during desorption, leading to higher solvent consumption and prolonged extraction times. Additionally, the reliance on high-voltage electrospinning for sorbent fabrication introduces safety concerns and challenges for reproducible, scalable production [150].

3.2.1.4. FPSE

Fabric-phase sorptive extraction (FPSE) is a hybrid technique that merges the high capacity of SPE with the simplicity and solvent efficiency of SPME. It uses a fabric substrate (e.g., cellulose, polyester, or fiberglass) coated with a chemically bonded sol–gel sorbent, providing stability across wide pH ranges and enabling direct immersion into untreated samples such as whole blood, urine, milk, and environmental water. FPSE eliminates the need for conditioning, pretreatment, or extensive clean-up, streamlining workflow while maintaining high extraction efficiency through its porous, tunable sorbent layer. Its durability, reusability, and compatibility with both solvent and thermal desorption make FPSE a versatile, green, and practical alternative for pharmaceutical, clinical, and environmental analysis [151, 152].

FPSE has been effectively applied to the analysis of key therapeutic agents, including aromatase inhibitors such as letrozole, anastrozole, and exemestane, used in metastatic breast cancer treatment. An FPSE-HPLC method using a Luna C18 column with an acetonitrile-phosphate buffer mobile phase at 25°C enabled efficient quantification of these drugs in human whole blood, plasma, and urine samples [38]. The complete analytical run was achieved within 20 minutes, offering a faster or comparable alternative to existing methods, while maintaining ease of useeven for untrained personnel due to the straightforward coupling with HPLC-DAD detection [39].

Beyond clinical matrices, FPSE has also been adapted for environmental monitoring. A validated FPSE-UHPLC-MS/MS method was developed for the simultaneous extraction of five cytostatic drugs—etoposide, cyclophosphamide, vincristine, vinblastine, and tamoxifen from wastewater.

compounds. The practicality of the method was demonstrated by analyzing real wastewater samples collected from three treatment plants and a hospital area on Gran Canaria Island, Spain, confirming FPSE as a reliable sample preparation tool for trace-level environmental analysis of anticancer drug residues [153]. These applications underscore FPSE's versatility, speed, and sensitivity in both clinical therapeutic drug monitoring and environmental contaminant screening, supporting its growing role in modern analytical workflows.

3.2.1.5. SBSE

Stir bar sorptive extraction (SBSE) is a microextraction technique that employs a magnetic stir bar coated with a sorbent phase, providing a larger extraction volume compared to SPME fibers and thus higher sensitivity and capacity. Recent advancements have focused on developing new polar and functional coatings to expand SBSE's applicability to a wider range of analytes. A notable innovation involves the use of MOF-templated nanoporous carbons (NPCs) as SBSE coatings. In one study, ZIF-67 was directly carbonized under an inert atmosphere to produce Co-NPCs, which were then physically immobilized onto functionalized stir bars using silicone glue. This coating was applied to the extraction of 5-fluorouracil from aqueous, urine, and plasma samples. Under optimized conditions, the method demonstrated LODs of 0.36, 0.41, and 1.2 μg L^{-1} and LOQs of 1.2, 1.3, and 4.5 μg L^{-1} in water, urine, and plasma, respectively. The intra-day precision (RSD) at 10 μg L^{-1} was below 8.6% across all matrices, with a linear dynamic range of 1–200 μg L^{-1}. The Co-NPC coating exhibited strong adhesion, chemical stability, and mechanical robustness, retaining much of the porous structure of the parent MOF. Extraction was facilitated by π–π stacking interactions between the delocalized π-system of the carbonaceous coating and the aromatic ring of 5-fluorouracil, supplemented by hydrophobic interactions. This approach highlights the potential of MOF-derived carbon materials as high-performance, stable sorbents for SBSE, particularly for polar and biologically relevant analytes [154].

3.3.1. Liquid-Based Microextraction Methods

Liquid-based microextraction (LPME) techniques constitute a major branch of modern sample preparation, characterized by the use of microliter volumes of extraction solvent. This dramatic

factors. The primary techniques in this category include single-drop microextraction (SDME), hollow-fiber liquid-phase microextraction (HF-LPME), and dispersive liquid-liquid microextraction (DLLME), all of which have been extensively developed for the isolation and preconcentration of drugs from complex matrices [155]. A generalized schematic comparing their workflows is presented in Fig. 10.

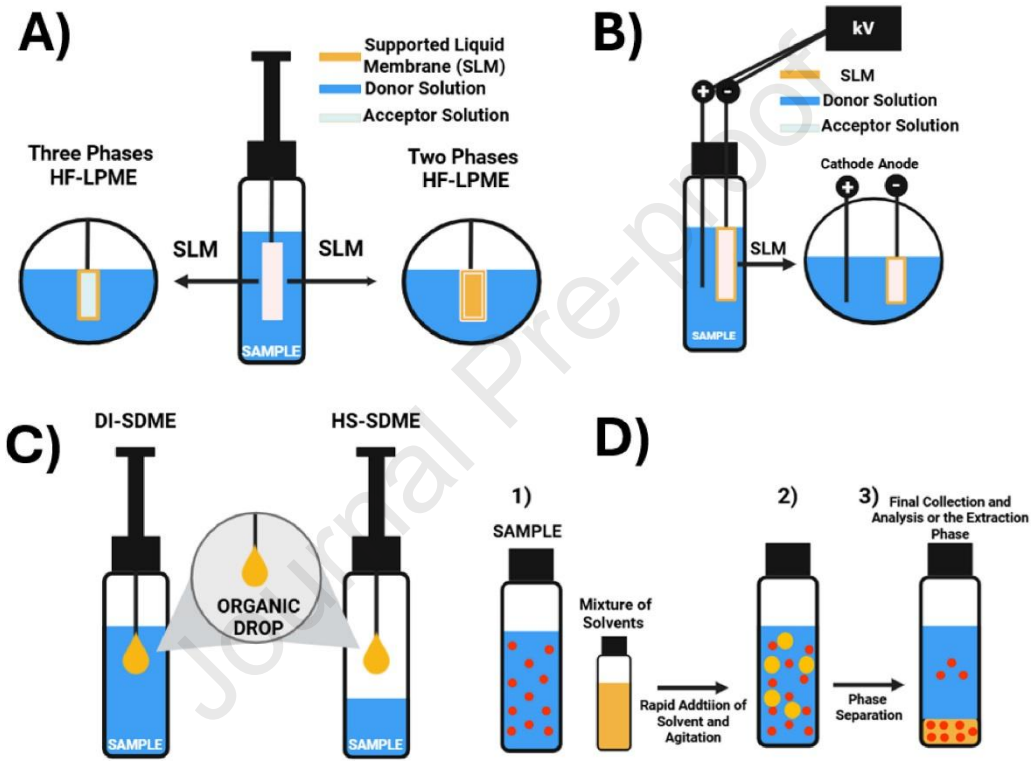


Fig. 10. The operational principles of common LPME configurations are schematically illustrated, including (A) HF-LPME, (B) electromembrane extraction (EME), (C) SDME, and (D) DLLME. Reprinted from Ref. [155] with permission from Elsevier.

Hollow-fiber liquid-phase microextraction (HF-LPME) exemplifies the drive toward miniaturization in solvent-based extraction, effectively reducing organic solvent consumption to the microliter or nanoliter scale per analysis [156]. The core principle of HF-LPME involves the use of a porous hollow fiber, typically made of polypropylene, whose pores are impregnated with a water-immiscible organic solvent to form a supported liquid membrane (SLM). This setup establishes a controlled microenvironment for the selective transport of analytes from an aqueous donor sample, across the organic SLM, and into a minute volume of acceptor solution held within

also acts as a physical filter, excluding macromolecules and particulates such as proteins and cellular debris from biological samples, thereby significantly reducing matrix effects and simplifying sample preparation. While HF-LPME offers clear advantages in solvent economy and clean-up, it is not without limitations. The extraction process is inherently equilibrium-based and diffusion-controlled, often resulting in lengthy extraction times (ranging from 15 minutes to several hours) to achieve sufficient analyte transfer, which can be a bottleneck for high-throughput analysis. The stability of the SLM can also be a concern; the organic solvent may slowly leach into the sample or acceptor phase, especially when dealing with highly complex matrices or during prolonged extraction, potentially affecting reproducibility. Furthermore, the manual handling of fragile hollow fibers including impregnation, loading of the acceptor, and introduction into vials can be tedious and requires skilled operation to ensure reproducibility between samples and operators [158]. Despite these challenges, HF-LPME remains a powerful technique for applications demanding ultra-clean extracts and high enrichment from small sample volumes, particularly in complex biological fluids. Its continued evolution, especially in hyphenation with EME (which uses an electrical potential to drive extraction and dramatically speed up kinetics), demonstrates its adaptability and enduring relevance in the landscape of modern microextraction.

A hyper-branched dendrimer-based sorbent was engineered for the pre-concentration of trace exemestane from aqueous samples. Silica NPs (SiO_2 NPs) were first functionalized with 3-aminopropyltriethoxysilane (APTES) to introduce amine groups, followed by iterative grafting of melamine and glutaraldehyde to construct hyper-branched dendrimeric structures (SiO_2@APTES@GAMEL). Following adsorption, the captured drug was efficiently released via ultrasonication. This eluate was then used as the donor phase in a subsequent HF-LPME step, achieving further analyte enrichment and significantly improving the detection limit of the overall method. Extraction was primarily driven by π-π interactions between the aromatic/double-bond systems of both the sorbent and exemestane, as well as hydrogen bonding between the carbonyl oxygen of exemestane and the amine groups of the dendrimeric sorbent [159].

Electromembrane extraction (EME) is an advanced microextraction technique that facilitates the controlled mass transfer of charged analytes across a supported liquid membrane (SLM) using an

solvent impregnated within the pores of a hollow fiber (the SLM), and concentrated into an aqueous acceptor solution on the opposite side. The direction and efficiency of this electromigrative transport are governed by electrophoretic mobility and are thus highly dependent on the magnitude and polarity of the applied voltage as well as the chemical composition of the SLM (e.g., type of organic solvent, potential ion-pairing agents). This coupling of electrophoretic principles with membrane-based separation results in exceptional selectivity for ionizable compounds, allowing for the clean extraction of target analytes even from complex biological matrices with minimal co-extraction of neutral or oppositely charged interferences [160]. Deep eutectic solvents (DESs) and ionic liquids (ILs) share significant similarities as designer solvents, offering tunable physicochemical properties, low volatility, and versatile solvation capabilities for green analytical applications. However, their fundamental chemical nature differs: ILs are composed entirely of ions, exhibiting low melting points due to weak electrostatic interactions between bulky, asymmetric cations and anions. In contrast, DESs are mixtures of a hydrogen bond acceptor (HBA, e.g., quaternary ammonium salt) and a hydrogen bond donor (HBD, e.g., carboxylic acid, polyol, or amide), which form a eutectic mixture with a depressed melting point through extensive hydrogen-bonding networks. A notable application leveraging the unique properties of DESs was reported by Heidari et al., who developed an ultrasound-assisted emulsification-microextraction (USAEME) method for extracting doxorubicin from urine using a DES as the extractant phase [161]. The USAEME-DES method, coupled with UV-Vis spectrophotometry in 96-well microplates, achieved performance metrics comparable to or better than established chromatographic methods, with a LOD of 0.098 μg mL^{-1} and a linear range of 0.3–15 μg mL^{-1} [134, 162, 163]. Moreover, the entire procedure including sonication, centrifugation, and spectrophotometric measurement was completed within 22 minutes, offering a significantly faster analysis time while enabling high-throughput simultaneous processing of multiple samples. This work underscores the potential of DES-based microextraction as a rapid, efficient, and environmentally benign alternative for the determination of anticancer drugs in biological matrices.

Solid/liquid phase microextraction (SLPME) is an emerging hybrid microextraction technique that integrates principles from both solid-phase and liquid-phase extraction within a single system

nanomaterials (e.g., NPs, mesoporous silica, carbon nanostructures) significantly enhances solute adsorption capacity and facilitates targeted solute transport due to their high surface-to-volume ratio and tunable surface chemistry. These nanomaterial-modified channels not only increase extraction efficiency but also improve selectivity and enrichment factors by providing specific interaction sites for target analytes.

An illustrative application of SLPME is the development of a hollow fiber-based SLPME (HF-SLPME) method coupled with capillary electrophoresis (CE) and in-column field-amplified sample injection (FASI) for the simultaneous extraction and determination of 5-fluorouracil and capecitabine (Fig. 11) [68]. In this system, the lumen of the hollow fiber was embedded with Ag NPs to enhance adsorption capacity and create additional pathways for solute transport effectively merging the mechanisms of LPME and SPME. Furthermore, mesoporous silica (MCM-41) was anchored to the Ag NPs to leverage its high surface area and selective interactions with organic functional groups. This engineered HF-SLPME setup enabled efficient extraction of both anticancer drugs from plasma samples with high recovery rates, demonstrating the potential of nanomaterials to advance the performance of conventional membrane-based microextraction techniques.

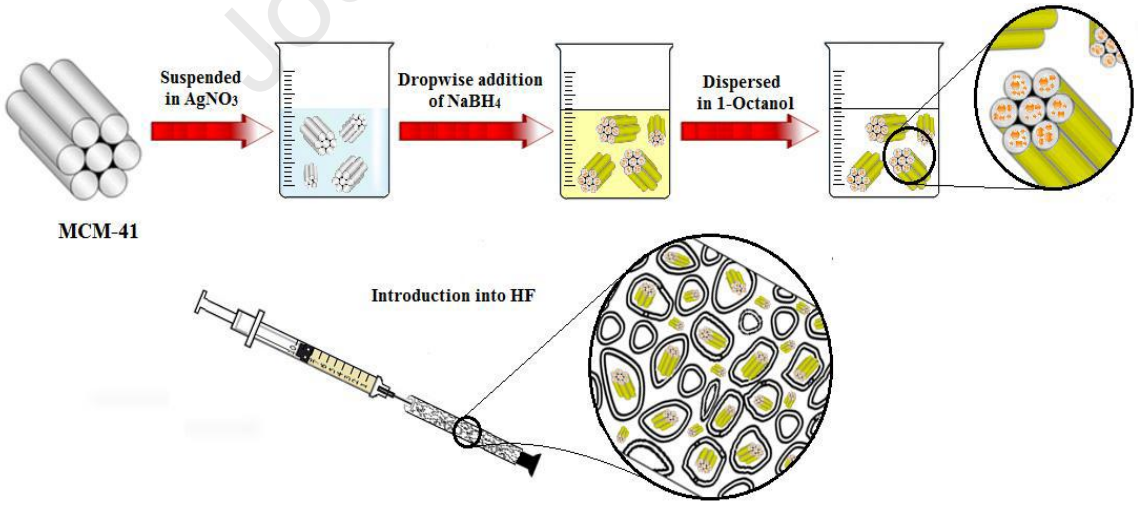


Fig. 11. Schematic depiction of the preparation process of the extraction device. Reprinted from Ref. [68] with permission from Elsevier.

solvent, 0.5–2 mL of dispersing solvent, and 5–10 mL of sample. Following extraction, phase separation is induced by centrifugation and/or temperature reduction, after which the separated extractant can typically be injected directly into analytical systems for analysis. The exceptional speed and efficiency of DLLME stem from the vast interfacial surface area created between the sample and the micro-droplets of extraction solvent, which significantly enhances mass transfer. Commonly employed extraction solvents include traditional organic solvents, ILs, and DESs the latter offering enhanced biodegradability, low toxicity, and tunable solvation properties for greener and more selective extraction [165].

The application of DLLME in the bioanalysis of anticancer drugs remains relatively limited, particularly when coupled with LC-MS, with most studies focusing on urine samples. For instance, one study employed HPLC-FLD combined with DLLME and SPE for the determination of epirubicin, daunorubicin, doxorubicin, and irinotecan in hospital wastewater. The validated method demonstrated excellent performance, with determination coefficients (R^2) exceeding 0.99, recoveries ranging from 74% to 105%, and intraday precision below 15%. The LOQ was reported as 1.0 μg L^{-1}, and the method showed negligible matrix effects [166]. In comparing the two methods, the results highlight several drawbacks of SPE, including: i) its multi-step nature, ii) the requirement for larger sample volumes (approximately 10-fold higher), iii) relatively more complex procedural stages, iv) dependence on vacuum-assisted and time-consuming sample loading, and v) additional costs incurred from disposable SPE cartridges. In contrast, DLLME enabled a significant reduction in chloroform ($CHCl_3$) consumption to only 500 μL, aligning well with the principles of green analytical chemistry [167].

An alternative and efficient strategy involves the sequential combination of dSPE and DLLME for the extraction of anticoagulant drugs (anagrelide, betrixaban, and apixaban) from urine prior to HPLC-DAD analysis [168, 169]. In this hybrid approach, the initial dSPE step employs a mixed sorbent (octadecylsilane, graphitized carbon black, and primary secondary amine) to adsorb the target analytes from the sample matrix. The analytes are then eluted and further concentrated *via* a DLLME step, which utilizes magnetic ILs (MILs) as the extraction solvent. This design achieves

extraction mechanism is multifaceted, involving π-π stacking between the aromatic rings of the analytes and graphitized carbon black, hydrogen and halogen bonding with the primary secondary amine, and hydrophobic interactions with octadecylsilane [170].

While DLLME is renowned for its operational simplicity, rapid extraction kinetics, and minimal equipment requirements, a significant historical drawback has been its reliance on dense, toxic halogenated solvents (e.g., CH_2Cl_2, $CHCl_3$, CCl_4). A key advancement in the field has been the adoption of low-density solvents (which form a separate top layer for easy retrieval) and solidifiable solvents (which can be solidified and physically removed), alongside the use of MILs as demonstrated above. These developments have effectively addressed the primary environmental and safety concerns associated with classical DLLME, transforming it into a greener and more practical sample preparation tool.

Table 5. Overview of modern extraction techniques for the quantitative analysis of anticancer drugs.

Drug	Method	Sorbent	Separation/Detection	LOD (ng mL^{-1})	LOQ (ng mL^{-1})	Recove
Methotrexate	D-μSPE	IL coated magnetic GO/PPy	HPLC-UV	7	10	84.0-
Bicalutamide **Flutamide**	D-μSPE	CIM-80 (Al)/mNiO/Chitosan	HPLC	0.35 0.27	1.2 0.89	90.2- 90.8-
Imatinib **Methotrexate** **Irinotecan**	D-μSPE	Fe_3O_4/CAU-1/PANI	HPLC-UV	0.09, 0.21 0.06, 0.15 0.12, 0.3	0.3, 0.7 0.2, 0.5 0.4, 1.1	90.0- 90.0- 88.0-
Tyrosine kinase inhibitors	UA-D-μSPE	Fe_3O_4/MPA	HPLC-UV	120–200	300–600	>
Letrozole	MSPE	Fe_3O_4@SiO_2/DAG/MMA/ED/Gly-PEGylated	HPLC-UV	1.36	4.54	75.6, 98
Paclitaxel **Gemcitabine**	MSPE	DABTC-Fe_3O_4	HPLC-DAD	1.38, 1.44	4.71, 4.78	96.8– 98.0–
Anastrozole **Letrozole**	MSPE	Fe_3O_4@TEPA	HPLC-DAD	1.14, 1.26	3.78, 3.86	98.4– 99.2–
Letrozole	MSPE	AA.FSLN.NPs	HPLC-FL	23.0	69.2	93.5
Losartan **Carvedilol** **Amlodipine besylate**	MSPE	C/Fe_3O_4	HPLC-UV	0.69 0.09 0.28	--	62.11- 91.67- 95.47-
Amitriptyline **Nortriptyline**	EA-dM-μSPE	Fe_3O_4@SiO_2@N_3	HPLC	0.05 0.03	0.10 0.07	97.3,
Doxorubicin	SPME	C_8-SCX	Fluorescence	100/3700	--	-
Capecitabine	UA-dSPME	pH-sensitive MMIP@CS NPs	HPLC-UV	5.67	1.87	93.41–
Sorafenib **Dasatinib** **Erlotinib hydrochloride**	TF-SPME	Polyfam/Co-MOF-74	HPLC-UV	0.03 0.15 0.2	--	78.5, 6(

5-Fluorouracil	SBSE	ZIF-67/Co-NPC	HPLC-UV	0.36/0.41/1.2	1.2/1.3/4.5	91-
Anastrozole **Letrozole** **Exemestane**	FPSE	Luna C_{18}	HPLC-DAD	20 10 30	50 250 100	-
Etoposide **Cyclophosphamide** **Vincristine** **Vinblastine** **Tamoxifen**	FPSE	Sol-gel UCON Sol-gel polycaprolactone triol	UHPLC-MS/MS	7400 3820 98000 39900 900	24700 12700 326800 132800 3100	64.4-
Capecitabine **5-Fluorouracil**	HF-SLPME	AgNPs@MCM41	FASI-CE	6.4 9.3	17 25	98– 102-
Doxorubicin **Daunorubicin** **Epirubicin** **Irinotecan**	SPE DLLME	Chromabond®C_{18} EC cartridge	HPLC-FLD	--	1.0	74.22- 74.61- 81.92– 82.53- 74.54- 74.28- 92.06- 87.98-
Exemestane	HF-LPME	SiO_2@APTES@GAMEL Dendr	HPLC-UV	0.1	--	92.68-
Exemestane **Letrozole** **Paclitaxel**	HF-LPME	Q3/2 Accurel polypropylene hollow fiber membrane	UV–Vis	0.6 0.3 0.4	--	90–1
Doxorubicin	USAEME	96-well microplates	UV–Vis	98	298	95.89–
Anagrelide **Betrixaban** **Apixaban**	dSPE + DLLME	Octadecylsilane Graphitized carbon black Primary secondary amine	HPLC–DAD	40, 50, 60	160, 190, 210	76-

Table 6. Comparative overview of sample preparation techniques for anti-cancer drug analysis.

Method	Advantages	
PP	Rapid, straightforward; minimal equipment needs; low cost	Poor cleanup e interfer
LLE	High extraction efficiency; broad applicability; well-validated	High organic solve
SPE	High sample clean-up efficiency, Good enrichment capability, Wide range of sorbents, Reproducible and automatable, Well-established and widely validated	Time-consuming cha
dSPE	Fast and simple procedure; reduced solvent use; suitable for complex matrices	Limited sorbent c Manua
MSPE	Rapid magnetic separation; reusable sorbents; minimizes centrifugation steps	Requires speciali limited c
SPME	Solvent-free or minimal solvent use, Fast and simple procedure, Minimal sample volume required, High enrichment factors	Limited sorbent c effects, Cost of
FPSE	Fast extraction, Green, Reusable, Easy handling	Limited coating va
SBSE	Green chemistry approach; minimal solvent use; high reusability	Long extraction tin C
EME	Exceptional selectivity; high enrichment; effective for ionizable compounds	Requires electri memb
SLPME	Enhanced selectivity, High enrichment factor, High surface-to-volume ratio	Complex fabrication Reproc
DLLME	Very fast; high enrichment and recovery; minimal solvent use	Requires centrifu interfere

persistent challenges underscore a methodology-accessibility divide. While LC-MS/MS remains the benchmark for sensitivity and selectivity, its dependency on high-cost infrastructure and specialized expertise restricts widespread adoption, particularly in resource-limited settings. Fluorescence-based HPLC offers a more accessible pathway for fluorescent analytes but lacks generalizability, whereas electrochemical sensors, despite their potential for point-of-care deployment, are hindered by stability issues and matrix susceptibility. Capillary electrophoresis (CE) provides exceptional separation efficiency with minimal solvent use, yet its sensitivity constraints necessitate sophisticated preconcentration strategies, complicating routine application. Meanwhile, GC is largely confined to volatile compounds, requiring extensive derivatization for most polar drugs, and HPLC-UV/PDA persists in pharmaceutical quality control despite inferior selectivity for complex biological matrices.

Sample preparation has progressively shifted toward miniaturized and selective microextraction techniques (e.g., SPME, MSPE, MEPS), which align with green chemistry principles by reducing solvent consumption and waste. Modern mixed-mode and functionalized sorbents improve selectivity and reduce matrix effects, yet batch-to-batch reproducibility of advanced nanomaterials and the long-term stability of sorptive coatings remain critical obstacles to standardization. The integration of these approaches with HPLC-MS/MS has enabled trace-level multicomponent analysis, yet complete automation and seamless coupling are still not routine.

Emerging technologies including nanostructured sorbents, microfluidic systems, surface-enhanced Raman spectroscopy (SERS), and lab-on-a-chip platforms hold transformative potential for decentralized and real-time monitoring. However, their translation into validated workflows is hampered by reproducibility challenges, scalability issues, and a lack of standardized protocols. Nanomaterial-based extraction phases, for instance, often suffer from inconsistent synthesis outcomes, while SERS quantification is plagued by substrate heterogeneity. Microfluidic devices struggle with real-world matrix complexity and reliable mass production.

Future advances must prioritize integration, sustainability, and robustness. Key directions include:

validation.

2. Design of Fully Automated and Miniaturized Analytical Systems that consolidate sample preparation, separation, and detection into closed, disposable, or regenerable cartridges suitable for point-of-care use.
3. Implementation of Green Chemistry Metrics (e.g., AGREE, GAPI, BAGI) as essential criteria in method development to quantify and minimize environmental impact.
4. Hybrid Sensor-Chromatographic Platforms that combine the selectivity of MS with the portability and cost-effectiveness of optical or electrochemical detectors, potentially leveraging paper-based microfluidics or chip-based interfaces.
5. Open-Source and Low-Cost Instrumentation to democratize access to high-quality analytical data, particularly in clinical settings with limited resources.

In conclusion, while analytical capabilities have reached unprecedented levels of sensitivity and multiplexing, the next frontier lies in bridging the gap between high-performance detection and practical, sustainable, and equitable implementation. Success will depend not only on technical innovation but also on systemic approaches to standardization, automation, and ecological design—ultimately enabling precise, personalized, and environmentally responsible management of anticancer therapies.

Acknowledgments

The authors express gratitude for the support of Ferdowsi University of Mashhad (FUM) and the Iran National Science Foundation (INSF).

methods for quantifying anti-cancer drugs in human samples: A systematic review, Anal. Biochem. 610 (2020) 113891. https://doi.org/10.1016/j.ab.2020.113891.

[2] V. Pak, The use of α-fetoprotein for the delivery of cytotoxic payloads to cancer cells, Ther. Deliv. 5 (2014) 885–892. https://doi.org/10.4155/tde.14.59.

[3] D. Lorente, J. Mateo, Z. Zafeiriou, A.D. Smith, S. Sandhu, R. Ferraldeschi, J.S. de Bono, Switching and withdrawing hormonal agents for castration-resistant prostate cancer, Nat. Rev. Urol. 12 (2015) 37–47. https://doi.org/10.1038/nrurol.2014.345.

[4] V. Čermák, V. Dostál, M. Jelínek, L. Libusová, J. Kovář, D. Rösel, J. Brábek, Microtubule-targeting agents and their impact on cancer treatment, Eur. J. Cell Biol. 99 (2020) 151075. https://doi.org/10.1016/j.ejcb.2020.151075.

[5] K. Haider, S. Rahaman, M.S. Yar, A. Kamal, Tubulin inhibitors as novel anti-cancer agents: an overview on patents (2013-2018), Expert Opin. Ther. Pat. 29 (2019) 623–641. https://doi.org/10.1080/13543776.2019.1648433.

[6] H.-Y. Min, H.-Y. Lee, Molecular targeted therapy for anti-cancer treatment, Exp. Mol. Med. 54 (2022) 1670–1694. https://doi.org/10.1038/s12276-022-00864-3.

[7] E. Boros, P.J. Dyson, G. Gasser, Classification of Metal-Based Drugs according to Their Mechanisms of Action, Chem. 6 (2020) 41–60. https://doi.org/10.1016/j.chempr.2019.10.013.

[8] R.L. Lucaciu, A.C. Hangan, B. Sevastre, L.S. Oprean, Metallo-Drugs in Cancer Therapy: Past, Present and Future, Molecules. 27 (2022) 6485. https://doi.org/10.3390/molecules27196485.

[9] R. Turci, C. Sottani, G. Spagnoli, C. Minoia, Biological and environmental monitoring of hospital personnel exposed to antineoplastic agents: a review of analytical methods, J. Chromatogr. B. 789 (2003) 169–209. https://doi.org/10.1016/S1570-0232(03)00100-4.

[10] N. Guichard, D. Guillarme, P. Bonnabry, S. Fleury-Souverain, Antineoplastic drugs and their analysis: a state of the art review, Analyst. 142 (2017) 2273–2321. https://doi.org/10.1039/C7AN00367F.

[11] Y. Pashaei, M. Mehrabi, M. Shekarchi, A review on various analytical methods for determination of anthracyclines and their metabolites as anti–cancer chemotherapy drugs in different matrices over the last four decades, TrAC Trends Anal. Chem. 130 (2020) 115991. https://doi.org/10.1016/j.trac.2020.115991.

[12] K. Maiphetlho, L. Chimuka, H. Tutu, H. Richards, Technical design and optimisation of

[13] A.B. Kanu, Recent developments in sample preparation techniques combined with high-performance liquid chromatography: A critical review, J. Chromatogr. A. 1654 (2021) 462444. https://doi.org/10.1016/j.chroma.2021.462444.

[14] P.Q. Tranchida, F. Franchina, P. Dugo, L. Mondello, Comprehensive two-dimensional gas chromatography–mass spectrometry: Recent evolution and current trends, Mass Spectrom. Rev. 35 (2016) 524–534. https://doi.org/10.1002/mas.21491

[15] M. Safaei, M.R. Shishehbore, A review on analytical methods with special reference to electroanalytical methods for the determination of some anti-cancer drugs in pharmaceutical and biological samples, Talanta. 229 (2021) 122247. https://doi.org/10.1016/j.talanta.2021.122247.

[16] M. Ghalkhani, S.I. Kaya, N.K. Bakirhan, Y. Ozkan, S.A. Ozkan, Application of Nanomaterials in Development of Electrochemical Sensors and Drug Delivery Systems for Anti-cancer Drugs and Cancer Biomarkers, Crit. Rev. Anal. Chem. 52 (2022) 481–503. https://doi.org/10.1080/10408347.2020.1808442.

[17] H. Helena, V. Ivona, Ř. Roman, F. František, Current applications of capillary electrophoresis-mass spectrometry for the analysis of biologically important analytes in urine (2017 to mid-2021): A review, J. Sep. Sci. 45 (2022) 305–324. https://doi.org/10.1002/jssc.202100621.

[18] M. Shah, N. Patel, N. Tripathi, V.K. Vyas, Capillary electrophoresis methods for impurity profiling of drugs: A review of the past decade, J. Pharm. Anal. 12 (2022) 15–28. https://doi.org/10.1016/j.jpha.2021.06.009.

[19] X. Chen, X. Wu, T. Luan, R. Jiang, G. Ouyang, Sample preparation and instrumental methods for illicit drugs in environmental and biological samples: A review, J. Chromatogr. A. 1640 (2021) 461961. https://doi.org/10.1016/j.chroma.2021.461961.

[20] F. Ghaemi, A. Amiri, Microcrystalline cellulose/metal−organic framework hybrid as a sorbent for dispersive micro-solid phase extraction of chlorophenols in water samples, J. Chromatogr. A. 1626 (2020) 461386. https://doi.org/10.1016/j.chroma.2020.461386.

[21] M. Akbari, M. Mirzaei, A. Amiri, Synergistic effect of lacunary polyoxotungstates and carbon nanotubes for extraction of organophosphorus pesticides, Microchem. J. 170 (2021) 106665. https://doi.org/10.1016/j.microc.2021.106665.

[22] A. Amiri, F. Ghaemi, Solid-phase extraction of non-steroidal anti-inflammatory drugs in human plasma and water samples using sol–gel-based metal-organic framework coating, J.

of microextraction sample preparation techniques in biological samples analysis, Biomed.

[24] E. Torabi, M. Moghadasi, M. Mirzaei, A. Amiri, Nanofiber-based sorbents: Current status and applications in extraction methods, J. Chromatogr. A. 1689 (2023) 463739. https://doi.org/10.1016/j.chroma.2022.463739.

[25] M. Bazargan, F. Ghaemi, A. Amiri, M. Mirzaei, Metal–organic framework-based sorbents in analytical sample preparation, Coord. Chem. Rev. 445 (2021) 214107. https://doi.org/10.1016/j.ccr.2021.214107.

[26] E. Torabi, M. Mirzaei, M. Bazargan, A. Amiri, A critical review of covalent organic frameworks-based sorbents in extraction methods, Anal. Chim. Acta. (2022) 340207. https://doi.org/10.1016/j.aca.2022.340207.

[27] P. Caron, V. Turcotte, E. Lévesque, C. Guillemette, An LC-MS/MS method for quantification of abiraterone, its active metabolites D(4)-abiraterone (D4A) and 5α-abiraterone, and their inactive glucuronide derivatives, J. Chromatogr. B. 1104 (2019) 249–255. https://doi.org/10.1016/j.jchromb.2018.12.003.

[28] L. van Andel, Z. Zhang, S. Lu, V. Kansra, S. Agarwal, L. Hughes, M.M. Tibben, A. Gebretensae, H. Rosing, J.H.M. Schellens, J.H. Beijnen, Liquid chromatography-tandem mass spectrometry assay for the quantification of niraparib and its metabolite M1 in human plasma and urine, J. Chromatogr. B. 1040 (2017) 14–21. https://doi.org/10.1016/j.jchromb.2016.11.020.

[29] O. Chavani, B.P. Jensen, R.M. Strother, C.M. Florkowski, P.M. George, Development, validation and application of a novel liquid chromatography tandem mass spectrometry assay measuring uracil, 5,6-dihydrouracil, 5-fluorouracil, 5,6-dihydro-5-fluorouracil, α-fluoro-β-ureidopropionic acid and α-fluoro-β-alanine in human plasma, J. Pharm. Biomed. Anal. 142 (2017) 125–135. https://doi.org/10.1016/j.jpba.2017.04.055.

[30] S. Gao, Z. Tao, J. Zhou, Z. Wang, Y. Yun, M. Li, F. Zhang, W. Chen, Y. Miao, One-Step Solid Extraction for Simultaneous Determination of Eleven Commonly Used Anti-cancer Drugs and One Active Metabolite in Human Plasma by HPLC-MS/MS, J. Anal. Methods Chem. 2018 (2018) 1–12. https://doi.org/10.1155/2018/7967694.

[31] S. Takasaki, M. Tanaka, M. Kikuchi, M. Maekawa, Y. Kawasaki, A. Ito, Y. Arai, H. Yamaguchi, N. Mano, Simultaneous analysis of oral anti-cancer drugs for renal cell carcinoma in human plasma using liquid chromatography/electrospray ionization tandem mass spectrometry, Biomed. Chromatogr. 32 (2018) e4184. https://doi.org/10.1002/bmc.4184.

Doxorubicin in pH-Sensitive Nanoparticles, Anal. Lett. 51 (2018) 1445–1463. https://doi.org/10.1080/00032719.2017.1380034.

[33] P. Gopinath, S. Veluswami, R. Thangarajan, G. Gopisetty, RP-HPLC-UV Method for Estimation of Fluorouracil–Epirubicin–Cyclophosphamide and Their Metabolite Mixtures in Human Plasma (Matrix), J. Chromatogr. Sci. 56 (2018) 488–497. https://doi.org/10.1093/chromsci/bmy020.

[34] M. Miura, N. Takahashi, K.-I. Sawada, Quantitative Determination of Imatinib in Human Plasma with High-Performance Liquid Chromatography and Ultraviolet Detection, J. Chromatogr. Sci. 49 (2011) 412–415. https://doi.org/10.1093/chromsci/49.5.412.

[35] K.L. Tan, R. Ankathil, S.H. Gan, Method development and validation for the simultaneous determination of imatinib mesylate and N-desmethyl imatinib using rapid resolution high performance liquid chromatography coupled with UV-detection, J. Chromatogr. B. 879 (2011) 3583–3591. https://doi.org/10.1016/j.jchromb.2011.09.048.

[36] M. Birch, P.E. Morgan, S. Handley, A. Ho, R. Ireland, R.J. Flanagan, Simple methodology for the therapeutic drug monitoring of the tyrosine kinase inhibitors dasatinib and imatinib, Biomed. Chromatogr. (2012) https://doi.org/10.1002/bmc.2796.

[37] L. Fang, Y. Song, X. Weng, F. Li, Y. Xu, N. Lin, Highly sensitive HPLC-DAD method for the assay of gefitinib in patient plasma and cerebrospinal fluid: application to a blood-brain barrier penetration study, Biomed. Chromatogr. 29 (2015) 1937–1940. https://doi.org/10.1002/bmc.3520.

[38] M. Locatelli, N. Tinari, A. Grassadonia, A. Tartaglia, D. Macerola, S. Piccolantonio, E. Sperandio, C. D'Ovidio, S. Carradori, H.I. Ulusoy, K.G. Furton, A. Kabir, FPSE-HPLC-DAD method for the quantification of anti-cancer drugs in human whole blood, plasma, and urine, J. Chromatogr. B. 1095 (2018) 204–213. https://doi.org/10.1016/j.jchromb.2018.07.042.

[39] M.B. Abubakar, S.H. Gan, A Review of Chromatographic Methods Used in the Determination of Anastrozole Levels, Indian J. Pharm. Sci. 78 (2016). https://doi.org/10.4172/pharmaceutical-sciences.1000101.

[40] Y. Nerthigan, A.K. Sharma, S. Pandey, H.-F. Wu, Cysteine capped copper/molybdenum bimetallic nanoclusters for fluorometric determination of methotrexate via the inner filter effect, Microchim. Acta. 186 (2019) 130. https://doi.org/10.1007/s00604-019-3230-2.

[41] L. Mitchell, C. Shen, H.C. Timmins, S.B. Park, E.J. New, A Versatile Fluorescent Sensor Array for Platinum Anti-cancer Drug Detection in Biological Fluids, ACS Sensors. 6 (2021)

combined with fluorescence detection for determination of ertugliflozin in rat plasma: Assessment of pharmacokinetic drug interaction potential of ertugliflozin with mefenamic acid and ketoconazole, J. Chromatogr. B. 1122–1123 (2019) 49–57. https://doi.org/10.1016/j.jchromb.2019.05.023.

[43] S.-W. Seo, J.-M. Kim, D.-G. Han, D. Geum, H. Yun, I.-S. Yoon, A sensitive HPLC-FLD method for the quantification of alpelisib, a novel phosphatidylinositol 3-kinase inhibitor, in rat plasma: Drug metabolism and pharmacokinetic evaluation in vitro and in vivo, J. Chromatogr. B. 1163 (2021) 122508. https://doi.org/10.1016/j.jchromb.2020.122508.

[44] N. Treder, O. Maliszewska, I. Olędzka, P. Kowalski, N. Miękus, T. Bączek, E. Bień, M.A. Krawczyk, E. Adamkiewicz-Drożynska, A. Plenis, Development and validation of a high-performance liquid chromatographic method with a fluorescence detector for the analysis of epirubicin in human urine and plasma, and its application in drug monitoring, J. Chromatogr. B. 1136 (2020) 121910. https://doi.org/10.1016/j.jchromb.2019.121910.

[45] B. Charlier, L. Marino, F. Dal Piaz, M. Pingeon, A. Coglianese, B. Izzo, B. Serio, C. Selleri, A. Filippelli, V. Izzo, Development and Validation of a Reverse-Phase High-Performance Liquid Chromatography with Fluorescence Detection (RP-HPLC-FL) Method to Quantify Ruxolitinib in Plasma Samples, Anal. Lett. 52 (2019) 1328–1339. https://doi.org/10.1080/00032719.2018.1537283.

[46] J.A. Rangel-Méndez, M. Graniel-Sabido, J. Sanchez-Cruz, R. Moo-Puc, Development of a high performance liquid chromatography method with fluorescence detection for the routine quantification of tamoxifen, endoxifen, and 4-hydroxytamoxifen in plasma from breast cancer patients, Biomed. Chromatogr. (2018) e4462. https://doi.org/10.1002/bmc.4462.

[47] R.Z. Hahn, P.C. Arnhold, N.B. Andriguetti, A. Schneider, H.M. Klück, S.L. dos Reis, M.F. Bastiani, I. Kael, A.C.C. da Silva, G. Schwartsmann, M. V. Antunes, R. Linden, Determination of irinotecan and its metabolite SN-38 in dried blood spots using high-performance liquid-chromatography with fluorescence detection, J. Pharm. Biomed. Anal. 150 (2018) 51–58. https://doi.org/10.1016/j.jpba.2017.11.079.

[48] G.A. Sedik, R.S.A. Rizq, I.T. Ibrahim, E.S. Elzanfaly, M.A. Motaleb, Miniaturized chromatographic systems for radiochemical purity evaluation of 131I-Ferulic acid as a new candidate in nuclear medicine applications, Appl. Radiat. Isot. 167 (2021) 109370. https://doi.org/10.1016/j.apradiso.2020.109370.

[49] P. Cui, S. Wang, Application of microfluidic chip technology in pharmaceutical analysis: A review, J. Pharm. Anal. 9 (2019) 238–247. https://doi.org/10.1016/j.jpha.2018.12.001.

[50] C. Li, Z. Ye, Y. Xu, S.E.J. Bell, An overview of therapeutic anti-cancer drug monitoring

[51] A. Subaihi, D.K. Trivedi, R.A. Hollywood, J. Bluett, T. Xu, H. Muhamadali, D.I. Ellis, R. Goodacre, Quantitative Online Liquid Chromatography–Surface-Enhanced Raman Scattering (LC-SERS) of Methotrexate and its Major Metabolites, Anal. Chem. 89 (2017) 6702–6709. https://doi.org/10.1021/acs.analchem.7b00916.

[52] Y. Xing, H. Fuss, J. Lademann, M.D. Huang, H. Becker-Ross, S. Florek, A. Patzelt, M.C. Meinke, S. Jung, N. Esser, A new concept of efficient therapeutic drug monitoring using the high-resolution continuum source absorption spectrometry and the surface enhanced Raman spectroscopy, Spectrochim. Acta Part B At. Spectrosc. 142 (2018) 91–96. https://doi.org/10.1016/j.sab.2018.02.007.

[53] A. Vicario, V. Sergo, G. Toffoli, A. Bonifacio, Surface-enhanced Raman spectroscopy of the anti-cancer drug irinotecan in presence of human serum albumin, Colloids Surfaces B Biointerfaces. 127 (2015) 41–46. https://doi.org/10.1016/j.colsurfb.2015.01.023.

[54] L. Litti, V. Amendola, G. Toffoli, M. Meneghetti, Detection of low-quantity anti-cancer drugs by surface-enhanced Raman scattering, Anal. Bioanal. Chem. 408 (2016) 2123–2131. https://doi.org/10.1007/s00216-016-9315-4.

[55] S. Fornasaro, A. Bonifacio, E. Marangon, M. Buzzo, G. Toffoli, T. Rindzevicius, M.S. Schmidt, V. Sergo, Label-Free Quantification of Anti-cancer Drug Imatinib in Human Plasma with Surface Enhanced Raman Spectroscopy, Anal. Chem. 90 (2018) 12670–12677. https://doi.org/10.1021/acs.analchem.8b02901.

[56] S.S. Panikar, G. Ramírez-García, S. Sidhik, T. Lopez-Luke, C. Rodriguez-Gonzalez, I.H. Ciapara, P.S. Castillo, T. Camacho-Villegas, E. De la Rosa, Ultrasensitive SERS Substrate for Label-Free Therapeutic-Drug Monitoring of Paclitaxel and Cyclophosphamide in Blood Serum, Anal. Chem. 91 (2019) 2100–2111. https://doi.org/10.1021/acs.analchem.8b04523.

[57] Y. Ai, F. Zhang, C. Wang, R. Xie, Q. Liang, Recent progress in lab-on-a-chip for pharmaceutical analysis and pharmacological/toxicological test, TrAC Trends Anal. Chem. 117 (2019) 215–230. https://doi.org/10.1016/j.trac.2019.06.026.

[58] L. Scarabelli, M. Coronado-Puchau, J.J. Giner-Casares, J. Langer, L.M. Liz-Marzán, Monodisperse Gold Nanotriangles: Size Control, Large-Scale Self-Assembly, and Performance in Surface-Enhanced Raman Scattering, ACS Nano. 8 (2014) 5833–5842. https://doi.org/10.1021/nn500727w.

[59] W.-S. Zhang, Y.-N. Wang, Y. Wang, Z.-R. Xu, Highly reproducible and fast detection of 6-thioguanine in human serum using a droplet-based microfluidic SERS system, Sensors Actuators B Chem. 283 (2019) 532–537. https://doi.org/10.1016/j.snb.2018.12.077.

fluorescence sensor for methotrexate detection based on the inner filter effect of N, S co-doped carbon quantum dots, Anal. Chim. Acta. 1047 (2019) 179–187. https://doi.org/10.1016/j.aca.2018.10.005.

[61] M. Shamsipur, F. Molaabasi, M. Shanehsaz, A.A. Moosavi-Movahedi, Novel blue-emitting gold nanoclusters confined in human hemoglobin, and their use as fluorescent probes for copper(II) and histidine, Microchim. Acta. 182 (2015) 1131–1141. https://doi.org/10.1007/s00604-014-1428-x.

[62] K.-Y. Huang, H.-X. He, S.-B. He, X.-P. Zhang, H.-P. Peng, Z. Lin, H.-H. Deng, X.-H. Xia, W. Chen, Gold nanocluster-based fluorescence turn-off probe for sensing of doxorubicin by photoinduced electron transfer, Sensors Actuators B Chem. 296 (2019) 126656. https://doi.org/10.1016/j.snb.2019.126656.

[63] S. Liu, S. Pang, A dual-model strategy for fluorometric determination of ascorbic acid and of ascorbic acid oxidase activity by using DNA-templated gold-silver nanoclusters, Microchim. Acta. 185 (2018) 426. https://doi.org/10.1007/s00604-018-2954-8.

[64] F. Meng, F. Gan, G. Ye, Bimetallic gold/silver nanoclusters as a fluorescent probe for detection of methotrexate and doxorubicin in serum, Microchim. Acta. 186 (2019) 371. https://doi.org/10.1007/s00604-019-3477-7.

[65] A.F. El-Yazbi, F.M. Aboukhalil, E.F. Khamis, R.M. Youssef, M.A. El-Sayed, In situ green analytical methods for the rapid and sensitive determination of a newly launched orphan anti-cancer drug; Tigecycline in infusion bags: comparative study, Beni-Suef Univ. J. Basic Appl. Sci. 11 (2022) 69. https://doi.org/10.1186/s43088-022-00250-y.

[66] N. A. Alarfaj, Evaluation of Chemotherapy Drugs Carboplatin and Temozolamide in Pharmaceutical Formulations and Biosamples via Capillary Zone Electrophoresis Approach, Int. J. Electrochem. Sci. (2018) 4512–4525. https://doi.org/10.20964/2018.05.55.

[67] N. Semail, S.S. Noordin, A.S.A. Keyon, M.N. Waras, B. Saad, S. Kamaruzaman, N.N. Mohamad Zain, J. Azizi, M.Y. Aziz, N. Yahaya, A simple and efficient sequential electrokinetic and hydrodynamic injections in micellar electrokinetic chromatography method for quantification of anti-cancer drug 5-fluorouracil and its metabolite in human plasma, Biomed. Chromatogr. 35 (2021). https://doi.org/10.1002/bmc.5050.

[68] M. Forough, K. Farhadi, R. Molaei, H. Khalili, R. Shakeri, A. Zamani, A.A. Matin, Capillary electrophoresis with online stacking in combination with AgNPs@MCM-41 reinforced hollow fiber solid-liquid phase microextraction for quantitative analysis of Capecitabine and its main metabolite 5-Fluorouracil in plasma samples isolated from can,

simultaneous determination of cyclophosphamide, docetaxel, doxorubicin and 5-fluorouracil in surface samples, J. Pharmacol. Toxicol. Methods. 82 (2016) 68–73. https://doi.org/10.1016/j.vascn.2016.08.004.

[70] N.-F. Semail, A.S. Abdul Keyon, B. Saad, S.S. Noordin, N.N.S. Nik Mohamed Kamal, N.N. Mohamad Zain, J. Azizi, S. Kamaruzaman, N. Yahaya, Analytical method development and validation of anti-cancer agent, 5-fluorouracil, and its metabolites in biological matrices: An updated review, J. Liq. Chromatogr. Relat. Technol. 43 (2020) 562–579. https://doi.org/10.1080/10826076.2020.1781654.

[71] Y. He, W. Zhang, J. Chen, F. Gu, J. Cheng, L. Zhang, G. Chen, Analysis of nucleosides and nucleobases by microemulsion electrokinetic capillary chromatography coupled with field-amplified sample injection, Anal. Methods. 7 (2015) 2603–2610. https://doi.org/10.1039/C4AY01796J.

[72] K. Giringer, H.U. Holtkamp, S. Movassaghi, W.D.J. Tremlett, N.Y.S. Lam, M. Kubanik, C.G. Hartinger, Analysis of ruthenium anti-cancer agents by MEEKC-UV and MEEKC-ICP-MS: Impact of structural motifs on lipophilicity and biological activity, Electrophoresis. 39 (2018) 1201–1207. https://doi.org/10.1002/elps.201700443.

[73] M. Wang, Q. Gong, W. Liu, S. Tan, J. Xiao, C. Chen, Applications of capillary electrophoresis in the fields of environmental, pharmaceutical, clinical, and food analysis (2019–2021), J. Sep. Sci. 45 (2022) 1918–1941. https://doi.org/10.1002/jssc.202100727.

[74] S. Sharma, N. Singh, V. Tomar, R. Chandra, A review on electrochemical detection of serotonin based on surface modified electrodes, Biosens. Bioelectron. 107 (2018) 76–93. https://doi.org/10.1016/j.bios.2018.02.013.

[75] S. Bilge, L. Karadurmus, E.B. Atici, A. Sınağ, S.A. Ozkan, A novel electrochemical sensor based on magnetic Co_3O_4 nanoparticles/carbon recycled from waste sponges for sensitive determination of anti-cancer drug ruxolitinib, Sensors Actuators B Chem. 367 (2022) 132127. https://doi.org/10.1016/j.snb.2022.132127.

[76] K. Fujita, M. Miura, H. Shibata, Quantitative determination of regorafenib and its two major metabolites in human plasma with high-performance liquid chromatography and ultraviolet detection, Biomed. Chromatogr. 30 (2016) 1611–1617. https://doi.org/10.1002/bmc.3730.

[77] M. Venu, S. Venkateswarlu, Y.V.M. Reddy, A. Seshadri Reddy, V.K. Gupta, M. Yoon, G. Madhavi, Highly Sensitive Electrochemical Sensor for Anti-cancer Drug by a Zirconia Nanoparticle-Decorated Reduced Graphene Oxide Nanocomposite, ACS Omega. 3 (2018) 14597–14605. https://doi.org/10.1021/acsomega.8b02129.

Chem. 378 (2023) 133103. https://doi.org/10.1016/j.snb.2022.133103.

[79] H. Karimi-Maleh, F. Tahernejad-Javazmi, N. Atar, M.L. Yola, V.K. Gupta, A.A. Ensafi, A Novel DNA Biosensor Based on a Pencil Graphite Electrode Modified with Polypyrrole/Functionalized Multiwalled Carbon Nanotubes for Determination of 6-Mercaptopurine Anti-cancer Drug, Ind. Eng. Chem. Res. 54 (2015) 3634–3639. https://doi.org/10.1021/ie504438z.

[80] A. Khodadadi, E. Faghih-Mirzaei, H. Karimi-Maleh, A. Abbaspourrad, S. Agarwal, V.K. Gupta, A new epirubicin biosensor based on amplifying DNA interactions with polypyrrole and nitrogen-doped reduced graphene: Experimental and docking theoretical investigations, Sensors Actuators B Chem. 284 (2019) 568–574. https://doi.org/10.1016/j.snb.2018.12.164.

[81] H. Karimi-Maleh, A. Bananezhad, M.R. Ganjali, P. Norouzi, A. Sadrnia, Surface amplification of pencil graphite electrode with polypyrrole and reduced graphene oxide for fabrication of a guanine/adenine DNA based electrochemical biosensors for determination of didanosine anti-cancer drug, Appl. Surf. Sci. 441 (2018) 55–60. https://doi.org/10.1016/j.apsusc.2018.01.237.

[82] P.K. Brahman, L. Suresh, K.R. Reddy, B. J. S., An electrochemical sensing platform for trace recognition and detection of an anti-prostate cancer drug flutamide in biological samples, RSC Adv. 7 (2017) 37898–37907. https://doi.org/10.1039/C7RA04243D.

[83] F. Ahmadi, J.B. Raoof, R. Ojani, M. Baghayeri, M.M. Lakouraj, H. Tashakkorian, Synthesis of Ag nanoparticles for the electrochemical detection of anti-cancer drug flutamide, Chinese J. Catal. 36 (2015) 439–445. https://doi.org/10.1016/S1872-2067(14)60209-6.

[84] Y.M. Temerk, H.S.M. Ibrahim, W. Schuhmann, Square Wave Cathodic Adsorptive Stripping Voltammetric Determination of the Anti-cancer Drugs Flutamide and Irinotecan in Biological Fluids Using Renewable Pencil Graphite Electrodes, Electroanalysis. 28 (2016) 372–379. https://doi.org/10.1002/elan.201500329.

[85] S. Tajik, A.A. Afshar, S. Shamsaddini, M.B. Askari, Z. Dourandish, F. Garkani Nejad, H. Beitollahi, A. Di Bartolomeo, Fe_3O_4@MoS_2 /rGO Nanocomposite/Ionic Liquid Modified Carbon Paste Electrode for Electrochemical Sensing of Dasatinib in the Presence of Doxorubicin, Ind. Eng. Chem. Res. (2022). https://doi.org/10.1021/acs.iecr.2c00370.

[86] A. Moghaddam, H.A. Zamani, H. Karimi-Maleh, A New Electrochemical Platform for Dasatinib Anti-cancer Drug Sensing Using Fe_3O_4-SWCNTs/Ionic Liquid Paste Sensor, Micromachines. 12 (2021) 437. https://doi.org/10.3390/mi12040437.

[88] S.A.R. Alavi-Tabari, M.A. Khalilzadeh, H. Karimi-Maleh, Simultaneous determination of doxorubicin and dasatinib as two breast anti-cancer drugs uses an amplified sensor with ionic liquid and ZnO nanoparticle, J. Electroanal. Chem. 811 (2018) 84–88. https://doi.org/10.1016/j.jelechem.2018.01.034.

[89] S. Phal, B. Shatri, A. Berisha, P. Geladi, B. Lindholm-Sethson, S. Tesfalidet, Covalently electrografted carboxyphenyl layers onto gold surface serving as a platform for the construction of an immunosensor for detection of methotrexate, J. Electroanal. Chem. 812 (2018) 235–243. https://doi.org/10.1016/j.jelechem.2017.12.072.

[90] R. Li, T. Yang, Z. Li, Z. Gu, G. Wang, J. Liu, Synthesis of palladium@gold nanoalloys/nitrogen and sulphur-functionalized multiple graphene aerogel for electrochemical detection of dopamine, Anal. Chim. Acta. 954 (2017) 43–51. https://doi.org/10.1016/j.aca.2016.12.031.

[91] W. Dong, Y. Ren, Z. Bai, J. Jiao, Y. Chen, B. Han, Q. Chen, Synthesis of tetrahexahedral Au-Pd core–shell nanocrystals and reduction of graphene oxide for the electrochemical detection of epinephrine, J. Colloid Interface Sci. 512 (2018) 812–818. https://doi.org/10.1016/j.jcis.2017.10.071.

[92] B. Hatamluyi, F. Lorestani, Z. Es'haghi, Au/Pd@rGO nanocomposite decorated with poly (L-Cysteine) as a probe for simultaneous sensitive electrochemical determination of anti-cancer drugs, Ifosfamide and Etoposide, Biosens. Bioelectron. 120 (2018) 22–29. https://doi.org/10.1016/j.bios.2018.08.008.

[93] A. Hojjati-Najafabadi, S. Salmanpour, F. Sen, P.N. Asrami, M. Mahdavian, M.A. Khalilzadeh, A Tramadol Drug Electrochemical Sensor Amplified by Biosynthesized Au Nanoparticle Using Mentha aquatic Extract and Ionic Liquid, Top. Catal. 65 (2022) 587–594. https://doi.org/10.1007/s11244-021-01498-x.

[94] M. Keyvanfard, H. Karimi-Maleh, F. Karimi, F. Opoku, E.M. Kiarii, P.P. Govender, M. Taghavi, L. Fu, A. Aygun, F. Sen, Electro-catalytic amplified sensor for determination of N-acetylcysteine in the presence of theophylline confirmed by experimental coupled theoretical investigation, Sci. Rep. 11 (2021) 1006. https://doi.org/10.1038/s41598-020-79872-0.

[95] M. Alizadeh, P.A. Azar, S.A. Mozaffari, H. Karimi-Maleh, A.-M. Tamaddon, Evaluation of Pt,Pd-Doped, NiO-Decorated, Single-Wall Carbon Nanotube-Ionic Liquid Carbon Paste Chemically Modified Electrode: An Ultrasensitive Anti-cancer Drug Sensor for the Determination of Daunorubicin in the Presence of Tamoxifen, Front. Chem. 8 (2020).

aflatoxin B1 immunosensor based on gold nanoparticle-decorated porous graphene nanoribbon and Ag nanocube-incorporated MoS_2 nanosheets, New J. Chem. 45 (2021) 11222–11233. https://doi.org/10.1039/D1NJ02293H.

[97] H. Huang, Y. Chen, Z. Chen, J. Chen, Y. Hu, J.-J. Zhu, Electrochemical sensor based on Ce-MOF/carbon nanotube composite for the simultaneous discrimination of hydroquinone and catechol, J. Hazard. Mater. 416 (2021) 125895. https://doi.org/10.1016/j.jhazmat.2021.125895.

[98] H. Karimi-Maleh, M. Alizadeh, Y. Orooji, F. Karimi, M. Baghayeri, J. Rouhi, S. Tajik, H. Beitollahi, S. Agarwal, V.K. Gupta, S. Rajendran, S. Rostamnia, L. Fu, F. Saberi-Movahed, S. Malekmohammadi, Guanine-Based DNA Biosensor Amplified with Pt/SWCNTs Nanocomposite as Analytical Tool for Nanomolar Determination of Daunorubicin as an Anti-cancer Drug: A Docking/Experimental Investigation, Ind. Eng. Chem. Res. 60 (2021) 816–823. https://doi.org/10.1021/acs.iecr.0c04698.

[99] M.M. Foroughi, S. Jahani, Z. Aramesh-Broujeni, M. Rostaminasab Dolatabad, A label-free electrochemical biosensor based on 3D cubic Eu^{3+}/Cu_2O nanostructures with clover-like faces for the determination of anti-cancer drug cytarabine, RSC Adv. 11 (2021) 17514–17525. https://doi.org/10.1039/D1RA01372F.

[100] H. Mahmoudi-Moghaddam, Z. Garkani-Nejad, A new electrochemical DNA biosensor for determination of anti-cancer drug chlorambucil based on a polypyrrole/flower-like platinum/$NiCo_2O_4$ /pencil graphite electrode, RSC Adv. 12 (2022) 5001–5011. https://doi.org/10.1039/D1RA08291D.

[101] H. Karimi-Maleh, A. Khataee, F. Karimi, M. Baghayeri, L. Fu, J. Rouhi, C. Karaman, O. Karaman, R. Boukherroub, A green and sensitive guanine-based DNA biosensor for idarubicin anti-cancer monitoring in biological samples: A simple and fast strategy for control of health quality in chemotherapy procedure confirmed by docking investigation, Chemosphere. 291 (2022) 132928. https://doi.org/10.1016/j.chemosphere.2021.132928.

[102] A.P. Johnson, C. Sabu, N.K. Swamy, A. Anto, H.V. Gangadharappa, K. Pramod, Graphene nanoribbon: An emerging and efficient flat molecular platform for advanced biosensing, Biosens. Bioelectron. 184 (2021) 113245. https://doi.org/10.1016/j.bios.2021.113245.

[103] N. Rezvani Jalal, T. Madrakian, A. Afkhami, M. Ahmadi, Ni/Co Bimetallic Metal–Organic Frameworks on Nitrogen-Doped Graphene Oxide Nanoribbons for Electrochemical Sensing of Doxorubicin, ACS Appl. Nano Mater. 5 (2022) 11045–11058. https://doi.org/10.1021/acsanm.2c02237.

[104] T.-W. Chen, U. Rajaji, S.-M. Chen, B.-S. Lou, N. Al-Zaqri, A. Alsalme, F.A. Alharthi, S.-

https://doi.org/10.1016/j.ultsonch.2019.104664.

[105] M. Baladi, H. Teymourinia, E.A. Dawi, M. Amiri, A. Ramazani, M. Salavati-Niasari, Electrochemical determination of imatinib mesylate using $TbFeO_3$/g-C_3N_4 nanocomposite modified glassy carbon electrode, Arab. J. Chem. 16 (2023) 104963. https://doi.org/10.1016/j.arabjc.2023.104963

[106] X. Ren, Q. Jiang, J. Dou, Electrochemical detection of oxaliplatin as an anti-cancer drug for treatment of breast cancer using TiO_2 nanoparticles incorporated graphitic carbon nitride, Alex. Eng. J. 82 (2023) 349–357. https://doi.org/10.1016/j.aej.2023.10.010.

[107] W. Zhang, R. Lu, X. Fan, Y. Weng, An electrochemical sensor based on graphene nanoribbon nano-catalyst for determination of etoposide as an approved drug in lung cancer, Alex. Eng. J. 82 (2023) 247–254. https://doi.org/10.1016/j.aej.2023.06.034.

[108] C. Zhang, L. Li, Study on electrochemical sensor for sunitinib cancer medicine based on metal-organic frameworks and carbon nanotubes nanocomposite, Alex. Eng. J. 8 (2024) 8–13. https://doi.org/10.1016/j.aej.2024.03.104.

[109] Z. Wang, X. Li, Y. Yang, F. Zhang, M. Li, W. Chen, S. Gao, W. Chen, A Sensitive and Efficient Method for Determination of Capecitabine and Its Five Metabolites in Human Plasma Based on One-Step Liquid-Liquid Extraction, J. Anal. Methods Chem. 2019 (2019) 1–10. https://doi.org/10.1155/2019/9371790.

[110] I.-C. Stratigou, A. Tsiasioti, P.D. Tzanavaras, C.K. Markopoulou, K. Fytianos, C.K. Zacharis, Homogeneous liquid liquid extraction using salt as mass separating agent for the ultra high pressure liquid chromatographic determination of doxorubicin in human urine, Microchem. J. 158 (2020) 105260. https://doi.org/10.1016/j.microc.2020.105260.

[111] B. Anılanmert, S. Sertler, F. Cavus, S. Cengiz, Validated method for occupational cyclophosphamide monitoring using LC-MS/MS and a Poroshell 120 column, Chem. Pap. 69 (2015). https://doi.org/10.1515/chempap-2015-0157.

[112] M. Asefi, A. Amiri, M. Gholizadeh, Effect of magnetized solvent on the porosity of magnetic graphene oxide@zirconium-based metal-organic framework sorbent for efficient extraction of remdesivir, J. Chromatogr. A 1748 (2025) 465839. https://doi.org/10.1016/j.chroma.2025.465839

[113] M. Moghadasi, M. Abbasi, M. Mousavi, M. Arab Apoorvari, A. Khoshghamat, A. Hosseini, S. Jalaeian, M. Sheida, M. Mobaraki, E. Torabi, Porous materials in analytical sample preparation: Current status and future perspectives, TrAC Trends Anal. Chem. 186 (2025) 118193. https://doi.org/10.1016/j.trac.2025.118193.

[115] Z. Khoshkhan, M. Mirzaei, A. Amiri, N. Lotfian, J. T. Mague, Anti-cancer Drug Extraction from Plasma Samples Using Three-Dimensional Polyoxometalate-Based Supramolecular Frameworks as Sorbents, Inorg. Chem. 63 (2024) https://doi.org/10.1021/acs.inorgchem.3c02130.

[116] A. Navarrete, M.P. Martínez-Alcázar, I. Durán, E. Calvo, B. Valenzuela, C. Barbas, A. García, Simultaneous online SPE–HPLC–MS/MS analysis of docetaxel, temsirolimus and sirolimus in whole blood and human plasma, J. Chromatogr. B. 921–922 (2013) 35–42. https://doi.org/10.1016/j.jchromb.2013.01.017.

[117] M.-A. Vaudreuil, S. Vo Duy, G. Munoz, A. Furtos, S. Sauvé, A framework for the analysis of polar anti-cancer drugs in wastewater: On-line extraction coupled to HILIC or reverse phase LC-MS/MS, Talanta. 220 (2020) 121407. https://doi.org/10.1016/j.talanta.2020.121407.

[118] S. Hejabri Kandeh, S. Amini, H. Ebrahimzadeh, Simultaneous trace-level monitoring of seven opioid analgesic drugs in biological samples by pipette-tip micro solid phase extraction based on PVA-PAA/CNT-CNC composite nanofibers followed by HPLC-UV analysis, Microchim. Acta. 188 (2021) 275. https://doi.org/10.1007/s00604-021-04931-w.

[119] S.H. Hashemi, M. Kaykhaii, A.J. Keikha, A. Parkaz, Application of Box–Behnken design in the optimization of a simple graphene oxide/zinc oxide nanocomposite-based pipette tip micro-solid phase extraction for the determination of Rhodamine B and Malachite green in seawater samples by spectrophotometry, Anal. Methods. 10 (2018) 5707–5714. https://doi.org/10.1039/C8AY02309C.

[120] P. Khodayari, N. Jalilian, H. Ebrahimzadeh, S. Amini, Electrospun cellulose acetate /polyacrylonitrile /thymol /Mg-metal organic framework nanofibers as efficient sorbent for pipette-tip micro-solid phase extraction of anti-cancer drugs, React. Funct. Polym. 173 (2022) 105217. https://doi.org/10.1016/j.reactfunctpolym.2022.105217.

[121] L. Adlnasab, M. Ezoddin, R.A. Shojaei, F. Aryanasab, Ultrasonic-assisted dispersive micro solid-phase extraction based on melamine-phytate supermolecular aggregate as a novel bio-inspired magnetic sorbent for preconcentration of anti-cancer drugs in biological samples prior to HPLC-UV analysis, J. Chromatogr. B. 1095 (2018) 226–234. https://doi.org/10.1016/j.jchromb.2018.08.001.

[122] S. Hamidi, A. Azami, E. Mehdizadeh Aghdam, A novel mixed hemimicelles dispersive micro-solid phase extraction using ionic liquid functionalized magnetic graphene oxide/polypyrrole for extraction and pre-concentration of methotrexate from urine samples

[123] D. Wu, T. Wang, T. Sun, N. Ouyang, J. Qian, A simple, rapid and reliable liquid chromatography-mass spectrometry method for determination of methotrexate in human plasma and its application to therapeutic drug monitoring, Biomed. Chromatogr. 29 (2015) 1197–1202. https://doi.org/10.1002/bmc.3408.

[124] A. Gutiérrez-Serpa, I. Pacheco-Fernández, J. Pasán, V. Pino, Metal–Organic Frameworks as Key Materials for Solid-Phase Microextraction Devices—A Review, Separations. 6 (2019) 47. https://doi.org/10.3390/separations6040047.

[125] S.S. Nadar, L. Vaidya, S. Maurya, V.K. Rathod, Polysaccharide based metal organic frameworks (polysaccharide–MOF): A review, Coord. Chem. Rev. 396 (2019) 1–21. https://doi.org/10.1016/j.ccr.2019.05.011.

[126] A. Saghafi, M. Ghorbani, M. Pakseresht, A. Shams, Synthesis and development of novel magnetic polymeric sorbent to simultaneous extraction of three anti-cancers using dispersive micro solid phase extraction procedure in biological and water samples, Microchem. J. 183 (2022) 108047. https://doi.org/10.1016/j.microc.2022.108047.

[127] P. Mohammadi, M. Ghorbani, M. Keshavarzi, A. Rastegar, M. Pakseresht, M. Mohammadi, Dispersive micro solid-phase extraction as a green procedure for extracting prostate anti-cancer drugs in real water and biological samples and optimization of sorbent composite with an optimal mixture design, Int. J. Environ. Anal. Chem. (2022) 1–20. https://doi.org/10.1080/03067319.2022.2045588.

[128] A. Jouyban, M. Nemati, M.A. Farazajdeh, A.A. Alizadeh Nabil, M.R. Afshar Mogaddam, A polymer-based dispersive solid phase extraction combined with deep eutectic solvent based-dispersive liquid–liquid microextraction for the determination of four hydroxylated polycyclic aromatic hydrocarbons from urine samples, J. Sep. Sci. 44 (2021) 4025–4036. https://doi.org/10.1002/jssc.202100269.

[129] M. Khoubnasabjafari, N. Altunay, M. Tuzen, S. Kaya, K.P. Katin, M.A. Farajzadeh, M. Hosseini, M.R. Afshar Mogaddam, A. Jouyban, Experimental and theoretical observations in a mixed mode dispersive solid phase extraction of exogenous surfactants from exhaled breath condensate prior to HPLC-MS/MS analysis, J. Mol. Struct. 1281 (2023) 135096. https://doi.org/10.1016/j.molstruc.2023.135096.

[130] I. Vasconcelos, C. Fernandes, Magnetic solid phase extraction for determination of drugs in biological matrices, TrAC Trends Anal. Chem. 89 (2017) 41–52. https://doi.org/10.1016/j.trac.2016.11.011.

[131] E. Akyol, H.İ. Ulusoy, E. Yilmaz, Ü. Polat, M. Soylak, Application of magnetic solid-phase extraction for sensitive determination of anti-cancer drugs in urine by means of diamino

[132] S. Ulusoy, M. Locatelli, A. Tartaglia, A. Kabir, H.I. Ulusoy, Sensitive determination of Anastrozole and Letrozole in urine samples by novel magnetic nanoparticles containing tetraethylenepentamine (TEPA) prior to analysis by high-performance liquid chromatography-diode array detection, Chem. Pap. 76 (2022) 3649–3659. https://doi.org/10.1007/s11696-022-02112-4.

[133] G. Li, M. Zhao, L. Zhao, Development and validation of an UPLC-MS/MS method for simultaneous determination of fifteen targeted anti-cancer drugs in human plasma and its application in therapeutic drug monitoring, J. Pharm. Biomed. Anal. 212 (2022) 114517. https://doi.org/10.1016/j.jpba.2021.114517.

[134] S. Alvani-Alamdari, S. Sajedi-Amin, R. Salehi, E. Rahimpour, A. Naseri, Development of a new magnetic nanogel based on a copolymer of polyacrylic acid-co-acrylamide-co-β-cyclodextrin for extraction/pre-concentration of doxorubicin from biological samples, J. Iran. Chem. Soc. 17 (2020) 3205–3216. https://doi.org/10.1007/s13738-020-02061-3.

[135] S.P. Hooshyar, H.A. Panahi, E. Moniri, M. Farsadrooh, Tailoring a new hyperbranched PEGylated dendrimer nano-polymer as a super-adsorbent for magnetic solid-phase extraction and determination of letrozole in biological and pharmaceutical samples, J. Mol. Liq. 338 (2021) 116772. https://doi.org/10.1016/j.molliq.2021.116772.

[136] M. Shaban, S. Ghaffary, J. Hanaee, A. Karbakhshzadeh, S. Soltani, Synthesis and characterization of new surface modified magnetic nanoparticles and application for the extraction of letrozole from human plasma and analysis with HPLC-fluorescence, J. Pharm. Biomed. Anal. 193 (2021) 113659. https://doi.org/10.1016/j.jpba.2020.113659.

[137] P.G. Vanol, P. Singhal, P.A. Shah, J. V. Shah, P.S. Shrivastav, M. Sanyal, SPE–UPLC–MS/MS assay for determination of letrozole in human plasma and its application to bioequivalence study in healthy postmenopausal Indian women, J. Pharm. Anal. 6 (2016) 276–281. https://doi.org/10.1016/j.jpha.2016.05.004.

[138] A.I. Platova, I.I. Miroshnichenko, S.N. Ptitsina, N.I. Yurchenko, Rapid and Sensitive LC-MS/MS Assay for Quantitation of Letrozole Using Solid-Phase Extraction from Human Blood Plasma and Its Application to Pharmacokinetic Studies, Pharm. Chem. J. 48 (2014) 292–297. https://doi.org/10.1007/s11094-014-1097-4.

[139] H. Heidari, B. Limouei-Khosrowshahi, Magnetic solid phase extraction with carbon-coated Fe_3O_4 nanoparticles coupled to HPLC-UV for the simultaneous determination of losartan, carvedilol, and amlodipine besylate in plasma samples, J. Chromatogr. B. 1114–1115 (2019) 24–30. https://doi.org/10.1016/j.jchromb.2019.03.025.

[140] B. Fahimirad, M. Rajabi, A. Elhampour, A rapid and simple extraction of anti-depressant

[141] Y. He, M. Concheiro-Guisan, Microextraction sample preparation techniques in forensic analytical toxicology, Biomed. Chromatogr. 33 (2019) e4444. https://doi.org/10.1002/bmc.4444.

[142] K. Schmidt, I. Podmore, Current Challenges in Volatile Organic Compounds Analysis as Potential Biomarkers of Cancer, J. Biomarkers. 2015 (2015) 1–16. https://doi.org/10.1155/2015/981458.

[143] S. Ansari, S. Masoum, Ultrasound-assisted dispersive solid-phase microextraction of capecitabine by multi-stimuli responsive molecularly imprinted polymer modified with chitosan nanoparticles followed by HPLC analysis, Microchim. Acta. 187 (2020) 366. https://doi.org/10.1007/s00604-020-04345-0.

[144] T. Vasiljevic, G.A. Gómez-Ríos, J. Pawliszyn, Single-Use Poly(etheretherketone) Solid-Phase Microextraction–Transmission Mode Devices for Rapid Screening and Quantitation of Drugs of Abuse in Oral Fluid and Urine via Direct Analysis in Real-Time Tandem Mass Spectrometry, Anal. Chem. 90 (2018) 952–960. https://doi.org/10.1021/acs.analchem.7b04005.

[145] C. Liu, G.A. Gómez-Ríos, B.B. Schneider, J.C.Y. Le Blanc, N. Reyes-Garcés, D.W. Arnold, T.R. Covey, J. Pawliszyn, Fast quantitation of opioid isomers in human plasma by differential mobility spectrometry/mass spectrometry via SPME/open-port probe sampling interface, Anal. Chim. Acta. 991 (2017) 89–94. https://doi.org/10.1016/j.aca.2017.08.023.

[146] V. Galievsky, J. Pawliszyn, Fluorometer for Screening of Doxorubicin in Perfusate Solution and Tissue with Solid-Phase Microextraction Chemical Biopsy Sampling, Anal. Chem. 92 (2020) 13025–13033. https://doi.org/10.1021/acs.analchem.0c01905.

[147] G.A. Gómez-Ríos, E. Gionfriddo, J. Poole, J. Pawliszyn, Ultrafast Screening and Quantitation of Pesticides in Food and Environmental Matrices by Solid-Phase Microextraction–Transmission Mode (SPME-TM) and Direct Analysis in Real Time (DART), Anal. Chem. 89 (2017) 7240–7248. https://doi.org/10.1021/acs.analchem.7b01553.

[148] H. Piri-Moghadam, E. Gionfriddo, A. Rodriguez-Lafuente, J.J. Grandy, H.L. Lord, T. Obal, J. Pawliszyn, Inter-laboratory validation of a thin film microextraction technique for determination of pesticides in surface water samples, Anal. Chim. Acta. 964 (2017) 74–84. https://doi.org/10.1016/j.aca.2017.02.014.

[149] A. Jerath, Q.J. Yang, K.S. Pang, N. Looby, N. Reyes-Garces, T. Vasiljevic, B. Bojko, J. Pawliszyn, D. Wijeysundera, W.S. Beattie, T.M. Yau, M. Wąsowicz, Tranexamic Acid

[150] F. Khodayari, N. Jalilian, H. Ebrahimzadeh, S. Amini, Trace-level monitoring of anti-cancer drug residues in wastewater and biological samples by thin-film solid-phase micro-extraction using electrospun polyfam/Co-MOF-74 composite nanofibers prior to liquid chromatography analysis, J. Chromatogr. A. 1655 (2021) 462484. https://doi.org/10.1016/j.chroma.2021.462484.

[151] A. Kabir, V. Samanidou, Fabric Phase Sorptive Extraction: A Paradigm Shift Approach in Analytical and Bioanalytical Sample Preparation, Molecules. 26 (2021) 865. https://doi.org/10.3390/molecules26040865.

[152] A. Kabir, K.G. Furton, Fabric phase sorptive extraction, in: Solid-Phase Extr., Elsevier, 2020: pp. 355–386. https://doi.org/10.1016/B978-0-12-816906-3.00013-3.

[153] S. Santana-Viera, R. Guedes-Alonso, Z. Sosa-Ferrera, J.J. Santana-Rodríguez, A. Kabir, K.G. Furton, Optimization and application of fabric phase sorptive extraction coupled to ultra-high performance liquid chromatography tandem mass spectrometry for the determination of cytostatic drug residues in environmental waters, J. Chromatogr. A. 1529 (2017) 39–49. https://doi.org/10.1016/j.chroma.2017.10.070.

[154] M. Ghani, S.M. Ghoreishi, M. Shahin, M. Azamati, Zeolitic imidazole framework templated synthesis of nanoporous carbon as a coating for stir bar sorptive extraction of fluorouracil and phenobarbital in human body fluids, Microchem. J. 146 (2019) 798–806. https://doi.org/10.1016/j.microc.2019.02.007.

[155] R.O. Martins, C. Will, M.F. Magalhães, F.M. Lanças, Advances in miniaturized liquid sample preparation techniques for environmental analysis: A special look towards green solvents and automation, J. Chromatogr. 8 (2025) 100240. https://doi.org/10.1016/j.jcoa.2025.100240

[156] M. Alexovič, Y. Dotsikas, P. Bober, J. Sabo, Achievements in robotic automation of solvent extraction and related approaches for bioanalysis of pharmaceuticals, J. Chromatogr. B. 1092 (2018) 402–421. https://doi.org/10.1016/j.jchromb.2018.06.037.

[157] F. Hansen, E.L. Øiestad, S. Pedersen-Bjergaard, Bioanalysis of pharmaceuticals using liquid-phase microextraction combined with liquid chromatography–mass spectrometry, J. Pharm. Biomed. Anal. 189 (2020) 113446. https://doi.org/10.1016/j.jpba.2020.113446.

[158] A. Nazaripour, Y. Yamini, H. Bagheri, Extraction and determination of trace amounts of three anti-cancer pharmaceuticals in urine by three-phase hollow fiber liquid-phase microextraction based on two immiscible organic solvents followed by high-performance liquid chromatography, J. Sep. Sci. 41 (2018) 3113–3120. https://doi.org/10.1002/jssc.201800183.

https://doi.org/10.1016/j.molliq.2022.121142.

[160] C. Huang, Z. Chen, A. Gjelstad, S. Pedersen-Bjergaard, X. Shen, Electromembrane extraction, TrAC Trends Anal. Chem. 95 (2017) 47–56. https://doi.org/10.1016/j.trac.2017.07.027.

[161] H. Heidari, R. Ahmadi, A deep eutectic solvent-based microextraction procedure for simple and fast extraction of doxorubicin as an anti-cancer drug from urine samples followed by 96-well microplates-based spectrophotometric detection, J. Iran. Chem. Soc. (2022). https://doi.org/10.1007/s13738-022-02709-2.

[162] T. Sikora, K. Morawska, W. Lisowski, P. Rytel, A. Dylong, Application of Optical Methods for Determination of Concentration of Doxorubicin in Blood and Plasma, Pharmaceuticals. 15 (2022) 112. https://doi.org/10.3390/ph15020112.

[163] A. Roszkowska, M. Tascon, B. Bojko, K. Goryński, P.R. dos Santos, M. Cypel, J. Pawliszyn, Equilibrium ex vivo calibration of homogenized tissue for in vivo SPME quantitation of doxorubicin in lung tissue, Talanta. 183 (2018) 304–310. https://doi.org/10.1016/j.talanta.2018.02.049.

[164] Y. Yang, J. Chen, Y.-P. Shi, Recent developments in modifying polypropylene hollow fibers for sample preparation, TrAC Trends Anal. Chem. 64 (2015) 109–117. https://doi.org/10.1016/j.trac.2014.08.016.

[165] M. De Boeck, S. Missotten, W. Dehaen, J. Tytgat, E. Cuypers, Development and validation of a fast ionic liquid-based dispersive liquid–liquid microextraction procedure combined with LC–MS/MS analysis for the quantification of benzodiazepines and benzodiazepine-like hypnotics in whole blood, Forensic Sci. Int. 274 (2017) 44–54. https://doi.org/10.1016/j.forsciint.2016.12.026.

[166] D.M. Souza, J.F. Reichert, A.F. Martins, A simultaneous determination of anti-cancer drugs in hospital effluent by DLLME HPLC-FLD, together with a risk assessment, Chemosphere. 201 (2018) 178–188. https://doi.org/10.1016/j.chemosphere.2018.02.164.

[167] S. Armenta, F.A. Esteve-Turrillas, S. Garrigues, M. de la Guardia, Green Analytical Chemistry, in: 2017: pp. 1–25. https://doi.org/10.1016/bs.coac.2017.01.003.

[168] E.F. Fiorentini, M.B. Botella, R.G. Wuilloud, A simple preconcentration method for highly sensitive determination of Pb in bee products by magnetic ionic liquid dispersive liquid-liquid microextraction and electrothermal atomic absorption spectrometry, J. Food Compos. Anal. 95 (2021) 103661. https://doi.org/10.1016/j.jfca.2020.103661.

[170] A. Mohebbi, A. Jouyban, M.A. Farajzadeh, M. Nemati, S. Raha, Y. Vaez Gharamaleki, M. Tuzen, M.R. Afshar Mogaddam, Combination of mixed mode dispersive solid phase extraction with magnetic ionic liquids based dispersive liquid–liquid microextraction for the extraction of anticoagulant drugs from urine samples, Microchem. J. 183 (2022) 108065. https://doi.org/10.1016/j.microc.2022.108065.

3. Future trends in green and miniaturized methods explored.

that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: