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Advances in Chlorpromazine Detection Technologies: A Review

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Abstract

Chlorpromazine (CPZ) is a representative phenothiazine antipsychotic that needs to be analytically assessed reliably in clinical therapeutic monitoring of drugs, residue analysis of animal-derived foods, forensic toxicology, and environmental fate and transformation research. Conventional techniques such as high-performance liquid chromatography, gas chromatography and enzyme-linked immunosorbent assay have traditionally been employed to analyze CPZ but remain limited in ultra-trace detection, scalability to complex matrices, swift on site screening, and multiplexed multi-analyte analysis. Over the past few years, chromatographic-mass spectrometry-based methodologies, spectroscopic and nano-optical assays, electrochemical sensors, new immunoassays and biosensors have grown at a fast pace offering new lines of analysis of the CPZ quantitation in plasma, oral fluid, tissue and animal samples, food, and environmental samples. The current review presents the advances in CPZ detection technologies in the last few years focusing on selected articles published between 2015 and 2025 on the chromatographic and chromatography-mass spectrometry methods, rapid testing approaches, and up-and-coming sensing technologies. Also considered are sample preparation, method optimization, technical comparison, applications, and future trends. On the whole, chromatography-mass spectrometry remains the most popular platform in confirmatory analysis and high-precision quantification, whereas fast optical, electrochemical, and immunochemical techniques are also promising in field screening, microsample analysis, and point-of-care testing.

Keywords

Chlorpromazine; chromatography-mass spectrometry; electrochemical sensing; immunoassay; rapid detection; simultaneous multi-analyte detection.

1. INTRODUCTION

One of the original typical phenothiazine antipsychotics that was introduced to clinical practice is chlorpromazine (CPZ), which continues to be a significant target in pharmaceutical, toxicological, food safety, and environmental analysis. Clinically, CPZ measurement is applied to therapeutic drug monitoring, pharmacokinetics assessment, and adverse reaction or medication adherence evaluation. In a non-clinical environment, CPZ and its analogues are of interest in animal-based foodstuffs, where illicit or improper usage can cause residue hazards, and in forensic toxics, where the need to screen multiple drugs and interpret post-mortem specimens is frequently necessary. Besides, more and more regard is being devoted to environmental behavior, degradation, and transformation products of CPZ that further increase the demands on analytical capabilities of detector technologies.

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Since such application scenarios can be very different in terms of analyte levels, matrix complexity, response time, and confirmatory needs, there are no universal methods that apply to all scenarios. The practical CPZ analysis should be sensitive, selective, tolerant to matrices, operationally simple, inexpensive, and potentially deployable on site. Traditional chromatographic solutions, particularly liquid chromatography and gas chromatography, have formed the fundamental basis of CPZ analysis. Combined with tandem or high resolution mass spectrometry they have enhanced trace analysis and structural verification in complex matrices significantly. At the same time, immunological, optical, and electrochemical methods have been rapidly evolving as alternative screening, microsample analysis, and portable test methods.

Recent advances in materials science, interface engineering, aptamer technology, molecular imprinting, and miniaturization have also contributed to the increased diversification of CPZ detection methods. In consequence, the analytical environment has shifted away of traditional laboratory testing towards a more holistic approach where confirmatory systems and rapid screening devices supplement one another. The review provides a summary of the typical developments in CPZ detection technologies, including chromatographic and chromatography-mass spectrometry methods, fast optical and electrochemical methods, immunoassay and biosensing methods, and the key trends that will define the future of analytical development.

2. CHROMATOGRAPHIC AND CHROMATOGRAPHY-MASS SPECTROMETRIC METHODS

The methods based on chromatography and chromatography-mass spectrometry are still considered the most prominent laboratory tools of CPZ analysis, as they are characterized by good selectivity, high sensitivity, and trustworthy confirmatory possibility. On average, techniques based on gas chromatography are more competitive with regards to alternative matrices, multi-drug screening and several forensic uses, whereas those based on liquid chromatography are more effective in therapeutic drug monitoring, monitoring of residues in food products produced by animals, and total parent drug-metabolite analysis. Sample preparation is a critical parameter along all the pathways because recovery, matrix effects, analyte stability and overall method robustness tend to be more dependent on pretreatment design than on the instrumentation parameters alone. [1-12]

2.1. Gas Chromatography and Gas Chromatography-Mass Spectrometry

The main applications of GC and GC-MS have been in alternative biological matrices, plasma analysis and forensic toxicology. They are highly efficient in separation, with reasonably consistent fragmentation profiles, and large spectral libraries that make them especially useful in wide screening and retrospective studies. Nevertheless, CPZ is quite polar and not very thermally stable, therefore, GC processes tend to require a greater extraction efficiency, derivation-free compatibility, and injection conditions. [1-5]

The representative studies have found that GC-MS can be successfully applied to oral-fluid analysis, where non-invasive sampling demonstrates obvious practical benefits. Oral fluid and GC-MS had been combined which allowed incorporating CPZ into combined panel of psychoactive drugs screening thus enhancing possibilities of its use during roadside or field-oriented toxicology. The dried saliva spots added another layer to this idea by making the process of collecting, storing and transporting samples easier without compromising the compatibility to GC-MS/MS. It is indicative of a significant advantage of GC-based procedures: they can be combined with other sampling systems to detect multiple drugs. [1,3]

Also GC-MS was applied to plasma analysis of CPZ. Miniaturized pretreatment, microextraction in packed sorbent, coupled with GC-MS/MS, has shown that miniaturized pretreatment is capable of reducing solvent usage and sample size without compromising on

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quality performance of simultaneous analysis of antipsychotics. Single-target plasma measurement of CPZ has also been extended with dispersive liquid-liquid microextraction, suggesting that GC-MS remains a viable alternative to therapeutic drug monitoring when laboratory facilities or prior processes make this a viable choice. [2,4]

The technique of GC/MS continues to be very useful in forensic toxicology since it is able to screen a large number of compounds in post mortem blood and other complex matrices under a single analytical system. The capability to analyze many drugs and drugs of abuse in one run allows GC-based techniques to be particularly helpful in initial forensic identification and retrospective assessment. Nevertheless, they have been limited. In general, GC-based methods tend to perform more poorly in terms of metabolite coverage, ultra-trace quantitation, and/or compatibility with highly polar or thermally labile compounds, as compared to LC-MS/MS. Consequently, GC and GC-MS should be considered as effective screening instruments in certain situations instead of being considered as comprehensive substitutes of liquid-based mass spectrometric systems. [2-5]

2.2. Liquid Chromatography and Liquid Chromatography-Mass Spectrometry

LC and LC-MS/MS, as well as high-resolution LC-MS, have proven to be the most popular ways of measuring CPZ in complex matrices. The major advantage is the wide use of them; they do not require analyte volatility or good thermal stability and can be used with plasma, tissues, food and environmental samples. Moreover, tandem and high-resolution mass spectrometry offer strong selectivity with low detection limits and structural information that allows accurate quantification and confirmatory analysis. [6-10]

LC-MS/MS has proven to be highly effective in clinical analysis when it comes to both single-target and multi-analyte assays. UPLC-ESI-MS/MS has also been used effectively to quantify CPZ in plasma during pharmacokinetic investigations and has been found to be sensitive and quantitative. The fact that CPZ can be measured in multi-analyte plasma LC-MS/MS methods along with other antipsychotics highlights even more the appropriateness of this system to conduct routine monitoring, particularly when throughput, specificity, and simultaneous measurement are critical. These findings support the fact that LC-MS/MS is now the strongest choice in the therapeutic drug monitoring of CPZ in any standard clinical matrix. [6,7]

When it comes to food safety and residue analysis, LC-MS/MS has also been applied to tranquilizers in porcine and bovine kidney, indicating that LC-MS/MS can be applied to monitor animal tissue. Other more advanced investigations have widened the range starting with the parent compound itself to concomitantly analyze CPZ along with major metabolites. The combination of QuEChERS extraction, selective lipid cleanup and UHPLC-Q-Orbitrap MS has become even more important because it demonstrates the current trend of analytical focus shifting towards wider target selection, more complicated matrix and higher certainty confirmation. This combined approach to parent-metabolite is especially useful when used in regulatory or surveillance contexts because it enhances the reliability of the residue results and extends the ability to interpret the data. [8,9]

The use of LC-based mass spectrometry is also important in the field of environmental studies. CPZ can biotransform or abiotransform in water or similar systems, and LC-MSn or HRMS are able to deliver the structural details necessary to identify transformation products. It not only exceeds standard quantification but also allows LC-MS to be used as a main instrument in exploring degradation pathways, environmental fate, and the potential biological significance of transformation products. [9,10]

Though LC-MS/MS and HRMS are very good analytical tools, they have some limitations. The instrumentation and operation costs are higher and method development more challenging and matrix effects frequently need a thoughtful design of the pretreatment, the use of an internal

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standard, and validation. However, due to better compromise between selectivity, sensitivity, confirmation and matrix compatibility, these methods can be considered as the standard with respect to which new CPZ detection technologies are compared. [6-10]

2.3. Sample Preparation and Method Optimization

The preparation of samples and the optimization of methods are not to be considered as some peripheral measures, but as major parts of CPZ analysis. The fact that CPZ is usually measured in mixtures with proteins, lipids, salts, and endogenous small molecules means that pretreatment quality has a significant impact on recovery, matrix suppression or enhancement, stability, precision and repeatability. [2,4,6,9,11,12]

Initial plasma techniques were based largely on classical liquid-liquid extraction, which remains useful due to its simplicity and reasonable reproducibility. The subsequent advances focused on miniaturization and low solvent use such as MEPS and DLLME that minimized the amount of sample and solvent used but were still sufficiently analytically effective. Another valuable strategy was presented by magnetic solidphase extraction with the benefit of enhancing selectivity enrichment and ease of phase separation especially with biological fluid. [2,4,6,11]

Selective cleanup has been more important in fatty food matrices. The integration of QuEChERS and lipid-removal materials can be viewed as part of a larger trend in analytical design: contemporary pretreatment is not just about extracting an analyte, but about selectively eliminating interfering matrix elements based on matrix properties. This idea is very applicable to CPZ since analytical performance in foods and tissues largely relies upon the effectiveness of controlling lipids and coextractives. [9]

Stability of samples is yet another serious problem. Oral fluid research has indicated that stability testing ought to be regarded as an inherent component of the development of a method, not as a supplementary addition. It is particularly true in the case of alternative matrices and portable sampling formats when transportation, storage and delayed analysis can alter the accuracy. To a greater extent, CPZ analysis optimization has become a systematic approach comprising pretreatment, matrix control, stability evaluation, and formal validation. The framework connects traditional chromatography systems with more modern quick methods since the identical matrix-related problems also impact the transfer of optical, electrochemical and biosensing technologies to practical use. [12]

3. RAPID DETECTION AND EMERGING SENSING TECHNOLOGIES

Though chromatography-mass spectrometry is still considered the main confirmatory path, there has been growing interest in the use of rapid detection and new sensing technologies since they tend to save the analysis time, make the operation easier and be more field applicable. As applied to CPZ these technologies involve traditional and advanced optical techniques, electrochemical sensors, immunoassays, and aptamer-based biosensors. They are all aimed at providing a complementary tool of screening, point-of-care testing, or rapid decision-making and not necessarily a replacement of chromatographic confirmation.

3.1. Spectroscopic and Nano-Optical Rapid Detection

The traditional methods of spectroscopy, such as fluorescence, UV-Vis spectrophotometry and chemiluminescence, have been a part of CPZ analysis for many years. Their greatest benefits are inexpensive, ease of equipment and somewhat easy to operate. They continue to be effective with formulations and fairly simple samples. Nonetheless, they are susceptible to interference due to the fact that their signals are susceptible to oxidation, complexation or colour-forming reactions which limits their ability to be selective in complicated matrices. [13-19]

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Fluorescence-based techniques have been developed further using the combination of chromatographic separation and post-column oxidation and fluorescence detection to measure CPZ and related drugs in animal feed and tissues. UV-Vis methods have been enhanced due to better chromogenic systems and enrichment strategies, whereas chemiluminescence has demonstrated good sensitivity and fast response, particularly when used in conjunction with flow-injection models. Nevertheless, these conventional optical techniques are still more appropriate to standard analysis and initial screening rather than strict validation of difficult matrices. [13-19]

Improved optical techniques are a newer and more active area. The use of nanomaterials, MOFs, quantum dots, or aptamers has enhanced sensitivity of analysis and stability of signals. Ratiometric fluorescent sensor of CPZ in eggs and milk based on aptamers is an example of increasing importance of self-calibrating signal design in food analysis. Surface-enhanced Raman scattering is especially remarkable as it may provide very high sensitivity and fast readout. Metal nanoparticle-based SERS substrates, MXene-Au composite substrates or substrates containing MOFs have already been used with biological samples like urine or serum. In combination with aptamer recognition and three-dimensional tag architecture, SERS may also be used to detect CPZ together with other analytes within foods simultaneously. [20-25]

Although there has been such a development, there are still significant challenges to the use of improved optical methods such as substrate reproducibility, quantitative consistency, and standardization of methods. These drawbacks are limiting their applicability mostly to sophisticated screening, proof-of-concept sensing, or supplementary analysis instead of replacing chromatographic confirmation on a regular basis. [20-25]

3.2. Electrochemical Sensing

Electrochemical sensing has been one of the most actively explored fields of CPZ analysis due to the combination of low cost, short response time, simplicity of instrumentation and good prospects of miniaturization. Although electrochemical techniques cannot offer similar structural assurance compared to mass spectrometry, they are very appealing to field screening, portable detectors, and small volumes of biological materials. [26-37]

Electrodes based on carbon-nanomaterials are one of the most popularly investigated systems. Their large surface area, high conductivity, and surface chemistry that can be tuned may help increase electron transfer, concentration of analytes, and prevent fouling. Improved electrochemical response of CPZ has been observed using reduced graphene oxide, polydopamine, carbon dots, carbon nanotubes and its derivatives. More sophisticated designs incorporate conductive carbon networks with MOFs, porous membranes or host-guest receptor motifs, which produce multifunctional interfaces with increased sensitivity, selectivity and applicability to real-world samples. Screen-printed disposable carbon electrodes show a particularly promising future as they are closely suited to point-of-care and field-based testing. [26-29]

The contributions of metal and metal-oxide nanomaterials are mostly through electrocatalysis. Mixed metal oxides, rare-earth-doped oxides, and porous nanocomposites have been shown to lower the oxidation overpotential, increase peak currents, and increase sensitivity. Designs of composites incorporating metal-oxide catalytic centers into carbon nanotubes, ionic liquids, or porous supports are particularly efficient since they combine both catalytic behaviour as well as enhanced conductivity and mass transport. Nevertheless, such systems may also be prone to aggregation, passivation and low selectivity in more complicated matrices. [30-33]

Molecular imprinting has also turned out to be a useful approach in solving selectivity issues. Electrochemical sensors based on molecular imprinting generate recognition zones that are

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size-, form- and functional-group-wise complementary to CPZ. Both sensitivity and selectivity may be improved when imprinted layers are mixed with carbon nanomaterials, metal nanoparticles, or MOFs. These sensors have reached extremely low detection limits and they have been used in tablets, serum and spiked urine. Nevertheless, there are still issues such as the inability to remove all templates completely, poor film reproducibility, nonspecific adsorption, and the recognition-layer thickness and charge-transfer trade-off. [34-37]

On the whole, sensing through electrochemistry is a very promising avenue of CPZ measurement, especially when mobility, rate of response and small volume of sample are critical factors. The impact of its future will be determined by enhanced reproducibility, more effective anti-interference behavior in actual matrices, as well as improved compatibility with disposable or portable systems. [26-37]

3.3. Immunoassays and Biosensing

Immunoassays and biosensing techniques are extremely useful in high-throughput screening and residual monitoring as they offer specific recognition and relatively easy to perform processes. This area has evolved in three primary directions in CPZ analysis: monoclonal-antibody-based ELISA, time-resolved fluorescence immunoassay, and aptamer-based biosensing. [20,24,38-42]

There are other immunological methods that are more developed than the ELISA method. The indirect competitive ELISA based on monoclonal antibodies has already been applied to detect CPZ residues in the liver of chickens and pigs, indicating that antibody-mediated recognition may be used to facilitate trace-level detection in animal tissues. Subsequent optimisation including hapten optimisation and heterologous coating increased sensitivity and specificity. Broad-spectrum ELISA techniques expanded this idea to phenothiazines as a family, which is all the more significant when screening foods because the practical demand is to conduct swift class-based residue inspection prior to confirmatory analysis. [38-40]

Time-resolved fluorescence immunoassay is a significant advancement towards the fast and lightweight quantification. TRFIA based on nanospheres to determine CPZ traces in pork showed low background and reasonable quantitative characteristics, short assay time, and satisfactory agreement with UPLC-MS/MS. It is thus among the clearest examples of how CPZ immunoassay is shifting its testing platform from laboratory-level to more practical field-level platforms. [41]

In addition to antibody-based systems, biosensing by aptamers is a promising technique. The chemical stability, batch consistency, and versatility of aptamers in terms of their integration with nanomaterials and multimodal signal designs are some of the advantages offered by aptamers. Fluorescent ratiometric aptasensors founded on MOFs have demonstrated sensitive CPZ detection in food-related matrices whereas aptamer-based 3D SERS systems have allowed simultaneous measurement of CPZ alongside other analytes. The implication of these studies is that future biosensing platforms might be able to integrate high selectivity with multiplexing functionality and portable readout formats. [20,24]

Currently though, there are still problems with the standardization, long-term reproducibility, and cross platform comparability of immunoassays and aptamer biosensors. This is why they should be considered not as independent substitutes, but as effective front-end screening methods and innovation-based additions to the chromatographic confirmation. [20,24,41,42]

4. TECHNICAL COMPARISON, APPLICATION SCENARIOS, AND DEVELOPMENT TRENDS

Comparatively, LC-MS/MS and HRMS remain the most effective methods in CPZ analysis due to their combination of sensitivity, selectivity, confirmation and good matrix compatibility.

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These are thus the best suited methods of monitoring therapeutic drugs, confirming residues and analysing parent-metabolites simultaneously. The GC-MS and GC-MS/MS systems are especially useful when other matrices are considered, multi-drug screening is performed, or when forensic procedures are required. Its advantages are effective wide screening and well-developed spectral support, however, it is typically less versatile than LC-MS with regard to matrix applicability and metabolite coverage. [6,7,9,20,24,28,41,43,44]

The rapid methods are in an entirely separate but more significant niche. Electrochemical sensors, immunoassays, and optical systems based on aptamers have obvious benefits in terms of speed, ease-of-use and field application. They are particularly appealing in the context of pre-screening food safety, mobile testing, or when a large number of samples need to be sorted rapidly. Nevertheless, they remain inferior to chromatographic mass spectrometry in terms of standardization, inter-laboratory comparison, and ultimate confirmatory capability. [20,24,28,41]

The choice of method must then be driven by its application. LC-MS/MS has been the preferred option in clinical therapeutic drug monitoring since it provides reliable low-level quantification in plasma and related matrices. GC-MS may also be applied as an additional pathway when appropriate laboratory settings are present. When monitoring animal-derived foods, a screening-and-confirmation approach is more reasonable: a large set of samples can be processed quickly with ELISA, TRFIA, or sensors based on an aptamer, but a regulatory confirmation of positive or suspicious ones can be done with LC-MS/MS or HRMS. GC-MS and LC-MS/MS continue to be indispensable in forensic toxicology and alternative-matrix monitoring since they allow extensive screening and complex-sample readout. LC-MSn and HRMS are more often selected in environmental research due to their better capability to detect transformation products and explore degradation pathways. [4,6,7,9,10,20,24,40,41]

In the future, CPZ detection is going to be based on three major directions. One is automation and intelligence, such as improved integration of samples handling, signal acquisition, and data processing. The other is miniaturization and portability, which is motivated by the requirements of point-of-care testing, field screening, and microsample analysis. The third is multiple technology integration and simultaneous multiple analyte detection. It involves class-specific immunological screening, multimodal aptamer-based sensors, parent-metabolite co-analysis and bigger analytical panels. These tendencies indicate that the analysis of CPZ in the future will become more dependent on coordinated analytical systems where fast screening and high-confidence confirmation are tightly associated. [3,9,20,24,28,40,41,43,44]

5. CONCLUSION

The CPZ detection technologies are now an advanced variety of analytical systems where confirmatory laboratory systems exist alongside fast and mobile screening systems. Chromatographic mass spectrometry continues to be the primary path towards precise quantification and dependable confirmation especially when dealing with complicated biological, food, forensic and environmental samples. Among them, LC-MS/MS and HRMS are currently the most effective in terms of overall analytical performance, whereas GC-based screening still has significant benefits to offer in the field of forensic screening as well as alternative-matrix screening. Simultaneously, sample preparation has become one of the main factors defining the quality of methods and their feasibility.

The fast optical procedures, electrochemical biosensors, immunoassays and aptamer-based biosensors have significantly increased the number of analytical possibilities in use to analyze CPZ. The most important advantage of these biosensors is the enhanced pace, portability, and applicability to field or high-throughput screening. Though such approaches are still under development in terms of standardization, reproducibility, and long-term compatibility with a

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matrix, they are gaining more and more importance as front-end tools that supplement mass-spectrometric confirmation.

Further advances in CPZ analysis are probably going to rely on improved interconnection between those two analytical realities. The next phase of development will be defined by the combination of automated and intelligent workflows, portable devices, microsample compatible pretreatment, multimodal sensing, and simultaneous multi-analyte detection. Further research in these fields will help achieve more accurate, fast and situation-specific measurements of chlorpromazine in clinical, food safety, forensic and environmental settings.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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