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Optimized QuEChERS Methodology for Reliable LC-MS/MS Quantification of Sertraline and Fluoxetine Hydrochloride in Biological Samples

Palak Sharma [1, a], Shweta Singh [1, a], Chintan Singh [1], Pratik Singh [1], Mahendra Pratap Singh [2], Prateek Pandya [1], Jyoti Singh [1,*]

[1]Amity Institute of Forensic Sciences, Amity University Noida Uttar Pradesh, J1 Block Amity University, Noida, 201303, Noida, India
[2]Department of Zoology Gorakhpur-273009, India, DDU Gorakhpur University Civil lines, India

ABSTRACT: In the present study, Liquid chromatography was Coupled with tandem mass spectrometry (LC-MS/MS) coupled with QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and Safe). The development of an analytical technique based on dispersive solid phase extraction (dSPE) has opted for the simultaneous detection of fluoxetine and sertraline hydrochloride at six distinct concentrations in the simulated gastric fluid. The antidepressants were identified and quantified using (ESI+) mode. With limits of detection (LOD) and quantification (LOQ) of 9.42 -10.40 ng/ml and 28.15 - 31.23 ng/ml, respectively, for each analyte, the process was validated. With an R2 > 0.998, the linear calibration curve between 5 to 200 ng/ml was obtained. Moreover, the method exhibited exceptional accuracy and robustness with a recovery range between 70-120% according to SWGTOX guidelines. In addition, this study provides a reliable and efficient approach to extracting and identifying antidepressants from gastric fluid.

1. INTRODUCTION

Antidepressant drugs are frequently prescribed to treat depressive illnesses, such as major depressive disorders (MDD) (Moorkoth et al., 2021). Based on its modes of action and chemical structure, it can be divided into various groups. (Taylor et al., 2005). Tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and typical antidepressants (Jia & Bartlett, 2020). SSRIs are one of the primary categories of antidepressant drugs, and non-tricyclic antidepressants are in fact one of the most commonly prescribed antidepressant drug groups (Chigome et al., 2017). They are considered as first-line treatment for moderate to severe depression (Stringaris, 2017). Selected serotonin reuptake in the brain is selectively inhibited by SSRI antidepressants (Fitzgerald & Bronstein, 2013). Serotonin is a neurotransmitter that plays a crucial role in mood regulation and emotional well-being (Young et al., 2011). By blocking serotonin reuptake, SSRIs increase their concentration in the synaptic gap between neurons, allowing for enhanced neurotransmission and improved mood (Giatti et al., 2022) . The selectivity of SSRIs refers to their specific action on serotonin reuptake without significantly affecting other neurotransmitters (Snamina et al., 2019), such as norepinephrine or dopamine, as seen in some other classes of antidepressants (Reddy, 2017). Sertraline Hydrochloride (SR) and Fluoxetine Hydrochloride (FX) primarily belong to the SSRIs family, as indicated in Table 1. the chemical structure SR is [(1S-cis)-4-(3,4-chlorophenyl)-1,2,3,4-tetrahydro-N-me- thyl-1-naphthalenamine], its metabolite desmethyl sertraline [(1S-cis)-4-(3,4-chlorophenyl)-1,2,3,4–tetrahydro-1-naphthalenamine]. The peak plasma concentration (Cmax) of sertraline is typically reached within 4.5 to 8.4 hours after oral administration (Serebruany et al., 2007). Individual variations can occur, and the absorption rate may be influenced by factors such as food intake and the specific formulation of the medication (Mcclintock et al., 2006) FX, which also belongs to the SSRIs family chemically known as N-Methyl-c-[4-(trifluoromethyl)phenoxy] benzenepropanamine hydrochloride. It is rapidly and completely absorbed orally, reaching a peak in 6–8 hours (Shamsipur et al., 2007). Blood is typically considered the primary specimen for postmortem toxicology analysis (Truta et al., 2016), and other biological exhibits such as gastric fluid, saliva, and urine can also be useful in certain situations. However, it is inaccurate to say that these specimens have a stronger association with biological effects or are more prevalent than whole blood in postmortem toxicology. A variety of criteria, such as the compounds of interest, the postmortem interval, and the

* Corresponding author.
E-mail address: jsingh4@amity.edu (Jyoti Singh)
[a] Equal contribution as a first author.

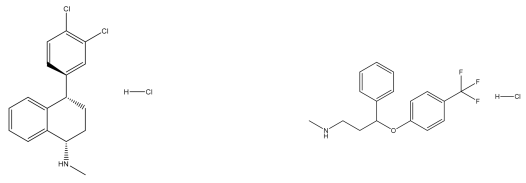
particulars of the case, influence the selection of specimen for toxicological examination. However, gastric fluid can be analyzed to determine the presence of substances that were recently ingested, such as drugs or poisons. Gastric fluid analysis is typically employed when there is a suspicion of acute poisoning or overdose (Gualdesi et al., 2013). As an outcome, several analytical methods for analyzing these medications from the matrices have been described. It has also been efficiently employed in forensic toxicology investigations with human biological materials. The analysis of drugs from matrices has been done previously employing a variety of hyphenated equipment, particularly liquid chromatography mass spectrometry (LC-MS) and gas chromatography (GC-MS). Still, LC-MS/MS is a powerful analytical technique that offers robustness and sensitivity, making it highly valuable in regular drug testing and screening (Choong et al., 2011). Various extraction techniques play a pivotal role in sample preparation for analytical research. Liquid-liquid, solid-phase, solid-liquid, and microextraction methods are commonly employed, each with its advantages and limitations (Fontanals et al., 2019; Giebułtowicz et al., 2020; Kepekci-Tekkeli et al., 2019; Runnqvist et al., 2010). These limitations may include factors like ensuring analytical accuracy, managing solvent usage, navigating complex solvation methods, and dealing with labor-intensive and exhaustive methodologies (Anderson et al., 2005).

To address these challenges in forensic toxicology, researchers have adapted the QuEChERS method, which was first created for the study of vegetable pesticides. The QuEChERS process involves two steps: cleaning and salting out. In this case, the use of QuEChERS is meant to increase the precision and dependability of analytical results in toxicological forensic investigations (Niell et al., 2014). Researchers can thus benefit from a method that balances effectiveness, cost, and ease of use in analyzing complex samples encountered in Forensic Toxicology research (Alves et al., 2017; Stefanović et al., 2017). The use of mass spectrometry (MS) in LC-MS/MS improves the system's ability to identify and measure analytes in biological matrices at the nanoscale. LC-MS/MS has emerged as a more sophisticated method in conventional drug testing solely due to its analytical resilience, sensitivity, and capacity to target possible analytes in biological matrices at the nanoscale level. It enables comprehensive and reproducible analysis, facilitating efficient drug and metabolite monitoring and detection spanning a range of applications, such as forensic toxicology, occupational drug testing, and clinical toxicology. Therefore, this research was conducted to identify drugs for depression (SR and FX) simultaneously from simulated gastric fluid extracted by QuEChERS and then detected by LC-MS/MS.

2. MATERIALS AND METHODS

2.1. Chemicals and Reagents

The substances used during the present study were all of the analytical grade. Reference materials of SR and FX were purchased from Sophisticated Industrial Materials Analytic



Name: SERTRALINE HYDROCHLORIDE
Chemical Name: 1S,4S)-4-(3,4-chlorophenyl)-N-methyl - 1,2,3,4-tetrahydronapthalen-1-amine hydrochloride

Name: FLUOXETINE HYDROCHLORIDE
Chemical Name: (3RS)-N-methyl-3-phenyl-3-[4-(trifluoromethyl) phenoxy]propane-1-amine hydrochloride

Figure 1. Chemical Structure of Sertraline and Fluoxetine Hydrochloride

(SIMA) Labs Pvt Ltd. MeOH, H_2O, CH_2O_2, HCOOH, an NH_4HCO_2 solution, $MgSO_4$, NaCl, $C_2H_3NaO_2$, and (PSA) were sourced from Sigma Aldrich, specifically for employing in HPLC (High-Performance Liquid Chromatography)Top of Form. The buffer solution used in the mobile phase was prepared with a concentration of 5 mM ammonium acetate and the buffer solution's pH. Mobile Phase Composition: The mobile phase used in the LC analysis consisted of methanol, 5 mM ammonium acetate buffer, and formic acid in a ratio of 35:65:0.1 (v/v/v). Using the QuEChERS_CEN salt pouch (5982-0650 - Agilent) from Agilent Technologies, To improve dispersive solid-phase extraction, this method involved adding 0.5 grams of sodium citrate dibasic and 1 gram of sodium citrate tribasic dihydrate in combination. The calibrated working stock solutions were made in methanol solution (1 mg/ml) and kept at -20°C. For these drugs, the working solutions were obtained by successively diluting the stock solution at six distinct concentrations ranging from 5-200 ng/ml.

2.2. Instrumentation and LC-MS/MS conditions

The Agilent 6470B instrument manufactured by Agilent Technologies, Inc., situated in Santa Clara, CA, USA, was used to carry out LC-MS/MS analysis. Precursor ion scans were performed in positive mode, comprising the mass-to-charge ratio (m/z) range of 100-500. 0.4 mL per minute was the flow rate which was developed. For the precursor ion scans, the collision energy was fixed around 0.3 and 2.0 V.

The sample solution was introduced into the system via injection, with a volume of 10 μL. The analytical column employed was a Poroshell 120 with an EC-C18 bonded phase (2.7 μm particle size, 3 mm x 150 mm dimensions), held at a constant temperature of 40°C throughout the analysis. When precursor ions undergo collision-induced dissociation (CID), leading to fragmentation and the formation of MS/MS spectra, the amount of energy delivered to these particles depends on the collision energy. The precursor ion isolation width was set to 4 atomic mass units (amu), which refers to the range of precursor ions selected for fragmentation in the MS/MS analysis. Flow rate refers to the rate at which the mobile phase (typically a solvent) is passed through the chromatography system, which carries the analytes to the mass spectrometer for analysis.

2.3. Preparation of gastric fluid

The artificial gastric fluid, specifically designed for scientific research work, was obtained by following the US Pharmacopeia's protocol, consisting of 0.03 M aqueous sodium chloride, 0.084 M aqueous hydrochloric acid, and 0.32 percent (w/v) pepsin. (Pietrzyńska & Voelkel, 2017).

2.4. QuEChERS Extraction

QuEChERS Extraction has been strengthened "via two-phase approach."

Step -1 Partitioning: A centrifuge tube was prepared with 5 ml of simulated gastric fluid (SGF), and drug concentrations spiked with five distinct concentrations (5-200 ng/ml). Then, 10 ml of methanol as a diluent was added to the SGF-containing tube. To ensure complete sample homogenization, the contents of the tube were extensively agitated for ten minutes using a vortex mixer.

For the subsequent purification in Step 2, The obtained mixture underwent a purification process involving the removal of moisture and water contents by employing QuEChERS salt, including magnesium sulfate, followed by PSA to simplify the compound. After that, the mixture was centrifuged in a centrifuge tube for 10 minutes at 6000 rpm and 2–8°C of specified temperature. After vortexing and centrifuging at 6000 rpm, the resultant supernatant was gently poured into a centrifuge tube containing 150 mg of MgSO4. A portion of 200 μL. After that, the mixture was centrifuged in a centrifuge tube for 10 minutes at 6000 rpm, and 2–8°C of specified temperature was withdrawn from the resulting extract and transferred to individual vials for purification. Following this, 10 μL of the prepared sample was directly introduced into the LC-MS/MS instrument for analysis, as shown in Table 2.

3. RESULTS AND DISCUSSION

3.1. QuEChERS Optimization

The QuEChERS extraction technique's efficiency and specificity can be influenced by many different variables; thus, fine-tuning these parameters is essential for achieving dependable and precise outcomes. (Alves et al., 2017). While establishing the QuEChERS technique, Several important variables may be evaluated and changed including the Removal Agent: The extraction solvent selection is influenced by the target analytes and sample matrix. Commonly used solvents include acetonitrile, methanol, and ethyl acetate. Enhancing extraction effectiveness and analyte recovery may be achieved by carefully choosing a solvent or solvent combination. The ratio of sample to solvent is crucial as it affects extraction efficiency. Adjusting the volume of the extraction solvent relative to the sample matrix can optimize the extraction of target analytes while minimizing the matrix effect (Rejczak & Tuzimski, 2015) (Perestrelo et al., 2019). Adjustment: In certain circumstances, modifying the sample's pH might improve the extraction's effectiveness. This is especially pertinent for fundamental or acidic analytes. The extraction conditions can be enhanced by introducing buffer solutions or pH modifiers. Type of Agitation: The type and intensity of agitation during the extraction step can impact the analyte recovery (Zheng et al., 2019). Different agitation methods like wrist-action shaking, vortex mixing, or mechanical shaking can be compared and optimized. Partition Salts: The type and quantity of partition salts, such as magnesium sulfate and sodium chloride, can affect the partitioning and extraction efficiency (Singh et al., 2023). Evaluating different salt combinations and their amounts can improve the extraction process. Cleanup Sorbents: After the partitioning step, cleanup sorbents are often used to remove interfering substances from the extract.

Choosing the appropriate sorbents and their quantities can enhance selectivity and reduce matrix effects. By conducting systematic studies and optimising these parameters, the QuEChERS method can be adapted to specific sample matrices and target analytes, improving the overall performance of the reliability process. The QuEChERS extraction technique was methodically refined to provide the lowest possible sample and solvent consumption. Methanol was used as the solvent at the determined ideal circumstances, and a salting-out effect was produced via the combination of sodium acetate and magnesium sulfate salts. Both vortexing and homogenizers were useful methods to accomplish agitation, and PSA in combination with magnesium sulfate was used to achieve sorbent cleaning Rodrigues et al. (2021). The entire methodology was rigorously validated to make sure it met strict standards for all analytical attributes, including proving specificity and accuracy in SR and FX analysis. During validation, the method displayed exceptional linearity, intermediate, and accuracy. Significantly, the method's recovery plummeted between 85 and 110 percent, demonstrating its dependability and effectiveness even more. The linearity plot showed that the regression's forecast suited the data exactly, with a range of 0 to 1.

3.2. LC-MS/MS Implementation

They are optimising the chromatographic and spectrophotometric conditions of two compounds, i.e. SR and FX, using the LC-MS/MS System. Methanol was chosen over acetonitrile for better recovery. Concentration and pH of Buffer Solution: The addition of 5 mM ammonium acetate buffer improved peak shape and symmetry, while formic acid (0.1%) enhanced the signal response of the analytes. Diffusing clean standard solutions: Pure solutions of SR and FX were introduced directly into the LC-MS/MS system. This ensures that the analytes are in a known and controlled form for analysis. Precursor ion observation: The LC-MS/MS equipment detected the precursor ions of each compound. The precursor ion is the molecular ion of the compound before it undergoes fragmentation. Product ion identification: Two separate product ions (fragments) were identified for each compound. The fragmentation occurs by subjecting the precursor ions to collision-induced dissociation (CID) using varying collision energy voltages. These product ions are specific compound

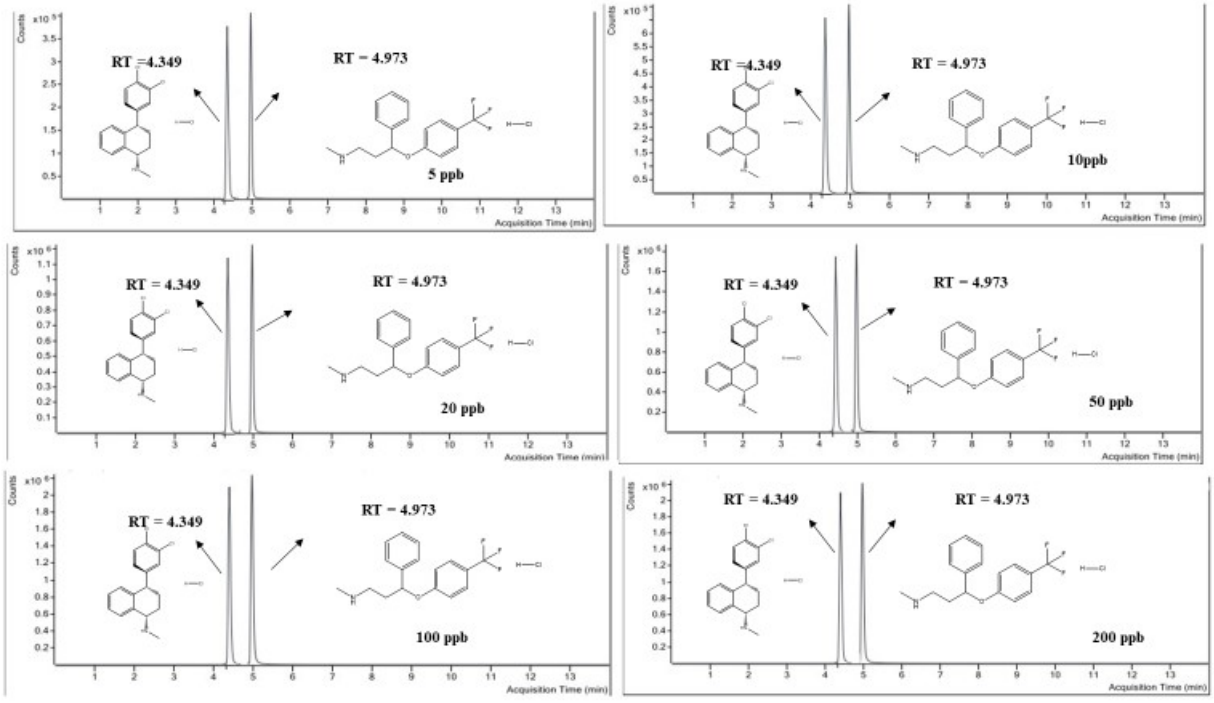


Figure 2. In gastric fluid, the LC-MS/MS chromatogram of SR and FX at six distinct concentrations (5-200 ng/ml).

fragments that can be identified and quantified. Quantifier and qualifier ions: From the identified product ions, one transition is selected as the quantifier ion, which is used to quantify the compound accurately. Another transition is chosen as the qualifier ion, which serves as a secondary identification and confirmation of the compound. Multiple reactions monitoring (MRM): MRM is a technique in LC-MS/MS where specific precursor-product ion pairs (transitions) are monitored during the analysis. These transitions are associated with the quantifier and qualifier ions selected in the previous step. The LC-MS/MS system automatically adjusts parameters such as collision energy voltages, dwell periods (time spent monitoring each transition), and other settings to optimise the analysis. By implementing MRM transitions and modifying the parameters automatically, the LC-MS/MS system ensures the accurate and efficient quantification of the compounds SR and FX, as shown in Figure 2. The product and precursor ion of SR and FX were 341.05, 346.05,345.11, and 348.11, respectively.

3.3. Sample Preparation Optimization

After dilution in two phases, gastric samples were examined. The final dilution of 0.1% formic acid produced a symmetrical graph. Measurements were conducted on the SR and FX precursor and product ions.

3.4. Method validation

An analysis was conducted at six distinct concentrations on the blank stomach fluid sample to assess the procedure. We did not see any interference peaks. Retention time for SR and FX were 4.349 and 4.973. The sample run time was 8 minutes.

3.5. Assessment of LOD and LOQ and Calibration method

By constructing a calibration curve combining the peak area-to-standard internal ratio of analytes at six distinct concentrations, the linearity of the method was shown to be accurate. The signal-to-noise ratios of 3:1 and 10:1, respectively, were evaluated to establish the (LOD) and (LOQ) limits, as indicated in Table 1. The calibration range was taken into account when a proposed linear curve was formed. Figure 3 illustrates that a reliable model adjustment fit is indicated by a linear coefficient R2 > 0.9999.

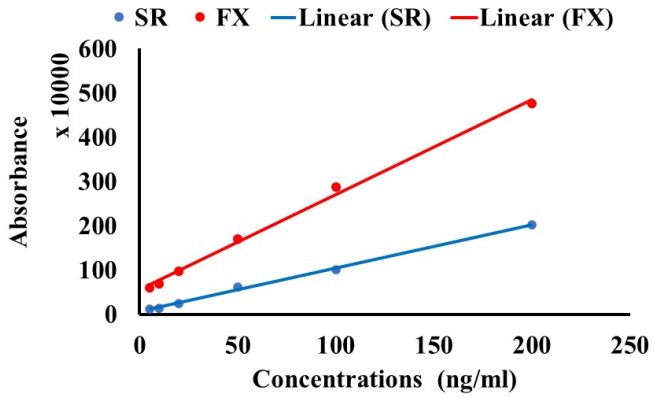


Figure 3. Calibration curve of SR and FX in simulated gastric fluid.

Table 1
Calibration models, Slope, Intercept, LOD, LOQ, and RSD% for the antidepressants by QuEChERS extraction and LC-MS/MS analysis.

Compound	R^2	Slope	Intercept	LOD(ng/ml)	LOQ(ng/ml)	RSD(%)
SR	0.998	0.0043	0.0017	10.40	31.23	1.123
FX	0.996	0.0025	0.0012	9.42	28.15	1.089

3.6. Precision and Recovery

ANOVA (Analysis of Variance) was used to study the precision. The analysis yielded a value called RSD (Relative Standard Unit). This study's precision and recovery values were compared to those observed previously (Zilfidou et al., 2019) . Additionally, all the working samples evaluated in the study met the acceptance criteria for precision limits, meaning the observed variations did not exceed 20%. The recovery values ranged between 70% and 120% of the permissible range. Additionally, for each analyte in the analysis, the extraction recovery was assessed. Extraction recovery measures how efficiently an analyte is extracted from a sample during extraction. This calculation helps assess the effectiveness of the extraction method used in the study. Two sets of sample sets were prepared to undergo analysis; one required extracting an extractable matrix (AE) and then spiking it. On the other hand, prior to extraction (BE), the other set was spiked in a blank working matrix. The study's recovery rates were determined using these sets. The recovery for the BE sample was determined utilizing the following formula:

$$Recovery\ (\%) = \frac{BE}{AE} \times 100$$

The percentage recovery of SR and FX was found in between the 85 -110% range in simulated gastric fluid. It was observed that even in less concentration, i.e. 5 ng/ml. QuEChERS proved significant in providing recovery of 85-90%, as shown in Figure 4 and Table 2 .

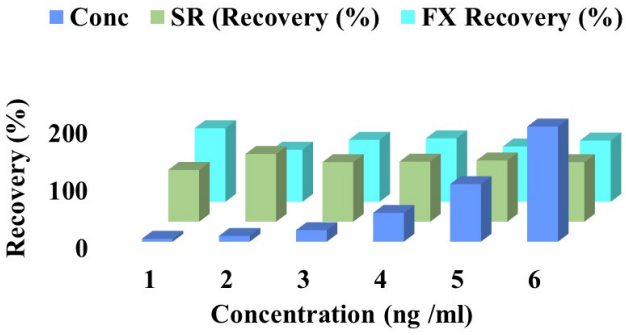


Figure 4. The recovery percentage of SR and FX at six distinct concentrations.

3.7. Matrix effect

Analytes were evaluated for matrix effects in two distinct concentration ranges: 200 ng/ml for higher quality control (HQC) and 5 ng/ml for lower quality control (LQC). The purpose of this analysis was to determine whether the sample matrix influenced the precision and accuracy of the analytical measurements. The findings revealed that the observed matrix effects for all analytes were within variances of less than 20% for both the LQC and HQC levels. This means the matrix effects did not exceed a 20% deviation from the expected values. This finding is considered acceptable according to the parameter set in the study and satisfies the recommended validation standards. Keeping matrix effects within a 20% variation is a common criterion used in analytical method validation to ensure accurate and reliable measurements. By demonstrating that the matrix effects for all analytes fell within this acceptable range, the study provides confidence in the validity and robustness of the analytical method employed. It suggests that the technique can provide accurate and precise measurements even in the presence of complex sample matrices.

Table 2
Data from LC-MS/MS analysis and QuEChERS extraction for SR and FX drugs, comprising LOD and LOQ.

SR and FX Spiked Concentrations in Gastric Fluid	Extracted Concentration of SR (ng/ml)	Extracted Concentration of FX (ng/ml)	Recovery (%) (SR)	Recovery (%) (FX)
5	5.5752	3.9082	90.23	85.56
10	8.4935	11.0505	117.73	90.49
20	19.3138	18.5707	103.55	107.69
50	55.3807	45.3356	104.45	110.28
100	93.9299	104.0241	106.46	96.131
200	193.2445	187.9377	103.49	106.42

4. CONCLUSION

Antidepressant drugs at six distinct concentrations can be extracted from gastric fluid using the LC-MS/MS technique. The method was validated according to SWGTOX guidelines, and the validation experiments demonstrated good precision and accuracy across these concentrations. Importantly, no observable interference was caused by endogenous compounds present in the gastric fluid samples. The extraction method employed in the analysis provided consistent and reproducible recoveries of the drugs, even in less concentration, i.e. 5 ng/ml, indicating its reliability. Simulated gastric fluid enables forensic scientists to create controlled experimental conditions closely mimicking the human stomach environment. This ensures reproducibility and consistency, which is challenging with variable biological samples. It eliminates the need for

actual human or animal gastric contents, addresses ethical and safety concerns, and reduces the risk of contamination. This tool is crucial for studying the dissolution, absorption, and degradation of drugs and poisons, enhancing our understanding of their interactions with gastric acids and enzymes vital for toxicology investigations. It also aids in developing and refining analytical techniques for detecting and quantifying substances in gastric contents, improving the precision and reliability of forensic analyses.

Furthermore, simulated gastric fluid provides a safe and consistent material for training forensic scientists and students, allowing them to practice analytical skills without ethical and practical challenges. Through extensive research and analysis of the method development and validation results, it has been concluded that the described method yields sensitive and highly reproducible results for analyzing these drugs. The simultaneous detection of multiple drugs is possible using this method. Additionally, the assay is characterized by its simplicity and rapidity, making it suitable for high throughput analysis. In forensic investigations, quickly processing a high volume of samples is paramount for timely and thorough analyses. With a processing time of just 8 minutes, this technology significantly boosts operational efficiency in forensic laboratories It expedites the investigative process by allowing forensic specialists to evaluate various samples within a suitable time limit. This fast processing speed expedites processes and quickens the pace of forensic testing and study. In summary, it enhances productivity and output, which facilitates easier and more efficient forensic investigations.

CONFLICTS OF INTEREST

The authors have no competing interests to declare relevant to this article's content.

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ORCID

Palak Sharma	0000-0001-5116-3959
Shweta Singh	0000-0001-8089-3467
Chintan Singh	0000-0002-1096-2196
Pratik Singh	0000-0003-3369-1349
Mahendra Pratap Singh	0000-0002-6237-7191
Prateek Pandya	0000-0001-7257-3754
Jyoti Singh	0000-0002-5518-5642

AUTHOR CONTRIBUTIONS

Palak Sharma: Research, Formal analysis, Data curation, Investigation, Writing-original draft, Writing-review & editing, and Visualization. Shweta Singh: Writing—review and editing, formal analysis, and visualization. Chintan Singh: Writing—review and editing, visual analysis, and formal analysis. Pratik Singh: Writing—review and editing, visual analysis, and formal analysis. Mahendra Pratap Singh: Formal analysis, conceptualization, methodology, supervision, writing, editing, and review. Prateek Pandya: writing—review and editing, conception, supervision, formal analysis, and methodology. Jyoti Singh: Formal analysis, conceptualization, methodology, supervision, writing, editing, and review.

REFERENCES

Alves, V., Conceição, C., Gonçalves, J., Teixeira, H.M., Câmara, J.S., 2017. Improved analytical approach based on QuECHERS/UHPLC-PDA for quantification of fluoxetine, clomipramine and their active metabolites in human urine samples. Journal of Analytical Toxicology. 41(1), 45–53. https://doi.org/10.1093/jat/bkw077

Anderson, C.R., Rupp, H.S., Wu, W.H., 2005. Complexities in tetracycline analysis - Chemistry, matrix extraction, cleanup, and liquid chromatography. Journal of Chromatography A. 1075(1-2), 23–32. https://doi.org/10.1016/j.chroma.2005.04.013

Chigome, A.K., Matsangaise, M.M., Chukwu, B.O., Matlala, M., Sibanda, M., Meyer, J.C., 2017. Review of selective serotonin reuptake inhibitors. SA Pharmaceutical Journal. 84(6), 52–59.

Choong, E., Rudaz, S., Kottelat, A., Haldemann, S., Guillarme, D., Veuthey, J.L., Eap, C.B., 2011. Quantification of 4 antidepressants and a metabolite by LC-MS for therapeutic drug monitoring. Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences. 879(19), 1544–1550. https://doi.org/10.1016/j.jchromb.2011.03.049

Fitzgerald, K.T., Bronstein, A.C., 2013. Selective Serotonin Reuptake Inhibitor Exposure. Topics in Companion Animal Medicine. 28(1), 13–17. https://doi.org/10.1053/J.TCAM.2013.03.003

Fontanals, N., Marcé, R.M., Borrull, F., 2019. Materials for solid-phase extraction of organic compounds. Separations. 6(4), 56. https://doi.org/10.3390/separations6040056

Giatti, S., Di, A., Diviccaro, S., Cioffi, L., Marmorini, I., Falvo, E., Caruso, D., Contini, A., Cosimo, R., 2022. Identification of a novel off-target of paroxetine : Possible role in sexual dysfunction induced by this SSRI antidepressant drug. Journal of Molecular Structure. 1268, 133690. https://doi.org/10.1016/j.molstruc.2022.133690

Giebułtowicz, E.G., Korytowska, N., Kłudka, G., Giebułtowicz, J., 2020. Determination of Antidepressants in Human Plasma by Modified Cloud-Point Extraction Coupled with Mass Spectrometry. Pharmaceuticals. 13(12), 458. https://doi.org/10.3390/ph13120458

Gualdesi, M.S., Esteve-Romero, J., Briñón, M.C., Raviolo, M.A., 2013. Development and validation of a stability indicating method for seven novel derivatives of lamivudine with anti-HIV and anti-HBV activity in simulated gastric and intestinal fluids. Journal of Pharmaceutical and Biomedical Analysis, 52–56. https://doi.org/10.1016/j.jpba.2013.01.027

Jia, E., Bartlett, M.G., 2020. Recent advances in liquid chromatographic methods for the determination of selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors. Biomedical Chromatography. 34(3), e4760. https://doi.org/10.1002/bmc.4760

Kepekci-Tekkeli, S.E., Durmus, Z., Kepekci-Tekkeli, S.E., Durmus, Z., 2019. Magnetic solid phase extraction applications combined with analytical methods for determination of drugs in different matrices review. Journal of the Chilean Chemical Society. 64(2), 4448–4458. https://doi.org/10.4067/S0717-97072019000204448

Mcclintock, S.M., Queenan, K., Faniran, O., Ranginwala, N., Husain, M.M., 2006. Sertraline in the treatment of depression

in the elderly. Aging Health. 2(2), 199–208. https://doi.org/10.2217/1745509X.2.2.199

Moorkoth, S., Prathyusha, N.S., Manandhar, S., Xue, Y., Sankhe, R., Pai, K.S.R., Kumar, N., 2021. Antidepressant-like effect of dehydrozingerone from *Zingiber officinale* by elevating monoamines in brain: in silico and in vivo studies. Pharmacological Reports. 73(5), 1273–1286. https://doi.org/10.1007/s43440-021-00252-0

Niell, S., Cesio, V., Hepperle, J., Doerk, D., Kirsch, L., Kolberg, D., Scherbaum, E., Anastassiades, M., Heinzen, H., 2014. QuEChERS-based method for the multiresidue analysis of pesticides in beeswax by LC-MS/MS and GC×GC-TOF. Journal of Agricultural and Food Chemistry. 62(17), 3675–3683. https://doi.org/10.1021/jf405771t

Perestrelo, R., Silva, P., Porto-Figueira, P., Pereira, J.A.M., Silva, C., Medina, S., Câmara, J.S., 2019. QuEChERS - Fundamentals, relevant improvements, applications and future trends. Analytica Chimica Acta. 1070, 1–28. https://doi.org/10.1016/J.ACA.2019.02.036

Pietrzyńska, M., Voelkel, A., 2017. Stability of simulated body fluids such as blood plasma, artificial urine and artificial saliva. Microchemical Journal. 134, 197–201. https://doi.org/10.1016/j.microc.2017.06.004

Reddy, P.H., 2017. A Critical Assessment of Research on Neurotransmitters in Alzheimer's Disease. Journal of Alzheimer's Disease. 57(4), 969–974. https://doi.org/10.3233/JAD-170256

Rejczak, T., Tuzimski, T., 2015. A review of recent developments and trends in the QuEChERS sample preparation approach. Open Chemistry. 13, 000010151520150109. https://doi.org/10.1515/chem-2015-0109

Rodrigues, T.B., Morais, D.R., Gianvecchio, V.A.P., Aquino, E.M., Cunha, R.L., Huestis, M.A., Costa, J.L., 2021. Development and Validation of a Method for Quantification of 28 Psychotropic Drugs in Postmortem Blood Samples by Modified Micro-QuEChERS and LC-MS-MS. Journal of Analytical Toxicology. 45(7), 644–656. https://doi.org/10.1093/jat/bkaa138

Runnqvist, H., Bak, S.A., Hansen, M., Styrishave, B., Halling-Sørensen, B., Björklund, E., 2010. Determination of pharmaceuticals in environmental and biological matrices using pressurised liquid extraction-Are we developing sound extraction methods? Journal of Chromatography A. 1217(16), 2447–2470. https://doi.org/10.1016/j.chroma.2010.02.046

Serebruany, V., Malinin, A., Dragan, V., Atar, D., Van Zyl, L., Dragan, A., 2007. Fluorimetric quantitation of citalopram and escitalopram in plasma: Developing an express method to monitor compliance in clinical trials. Clinical Chemistry and Laboratory Medicine. 45(4), 513–520. https://doi.org/10.1515/CCLM.2007.108

Shamsipur, M., Dastjerdi, L.S., Haghgoo, S., Armspach, D., Matt, D., Aboul-Enein, H.Y., 2007. Chiral selectors for enantioresolution and quantitation of the antidepressant drug fluoxetine in pharmaceutical formulations by 19F NMR spectroscopic method. Analytica Chimica Acta. 601(1), 130–138. https://doi.org/10.1016/j.aca.2007.08.017

Singh, C., Sharma, J., Nayak, B.P., Pandya, P., Khajuria, H., 2023. In-Vitro Modified QuEChERS Based Analytical Method for Simultaneous Detection of Antidepressant Drugs from Biological Matrices Using LC-MS/MS. Biointerface Research in Applied Chemistry. 13(5), 1–14. https://doi.org/10.33263/BRIAC135.448

Snamina, M., Wietecha-Posłuszny, R., Zawadzki, M., 2019. Postmortem analysis of human bone marrow aspirate - Quantitative determination of SSRI and SNRI drugs. Talanta. 204, 607–612. https://doi.org/10.1016/j.talanta.2019.06.054

Stefanović, S., Dordevic, V., Jelušić, V., 2017. Rapid and reliable QuEChERS-based LC-MS/MS method for determination of acrylamide in potato chips and roasted coffee. IOP Conference Series: Earth and Environmental Science. 85(1), 0–6. https://doi.org/10.1088/1755-1315/85/1/012010

Stringaris, A., 2017. Editorial: What is depression. Journal of Child Psychology and Psychiatry and Allied Disciplines. 58(12), 1287–1289. https://doi.org/10.1111/jcpp.12844

Taylor, C., Fricker, A.D., Devi, L.A., Gomes, I., 2005. Mechanisms of action of antidepressants: From neurotransmitter systems to signaling pathways. Cellular Signalling. 17(5), 549–557. https://doi.org/10.1016/j.cellsig.2004.12.007

Truta, L., Castro, A.L., Tarelho, S., Costa, P., Sales, M.G.F., Teixeira, H.M., 2016. Antidepressants detection and quantification in whole blood samples by GC-MS/MS, for forensic purposes. Journal of Pharmaceutical and Biomedical Analysis. 128, 496–503. https://doi.org/10.1016/j.jpba.2016.06.027

Young, S.Z., Taylor, M.M., Bordey, A., 2011. Neurotransmitters couple brain activity to subventricular zone neurogenesis. European Journal of Neuroscience. 33(6), 1123–1132. https://doi.org/10.1111/j.1460-9568.2011.07611.x

Zheng, W., Yoo, K.H., Choi, J.M., Park, D.H., Kim, S.K., Kang, Y.S., El-Aty, A., Hacımüftüoğlu, A.M., Jeong, A., Bekhit, J.H., Shim, A.E.D., Shin, J.H., C, H., 2019. A modified QuEChERS method coupled with liquid chromatography-tandem mass spectrometry for the simultaneous detection and quantification of scopolamine, L-hyoscyamine, and sparteine residues in animal-derived food products. Journal of Advanced Research. 15, 95–102. https://doi.org/10.1016/j.jare.2018.09.004

Zilfidou, E., Kabir, A., Furton, K.G., Samanidou, V., 2019. An improved fabric phase sorptive extraction method for the determination of five selected antidepressant drug residues in human blood serum prior to high performance liquid chromatography with diode array detection. Journal of Chromatography B. 1125, 121720. https://doi.org/10.1016/j.jchromb.2019.121720