Development of a Sensitive Spectrophotometric Method for Determination of the Charge-Transfer Complex of Aripiprazole in Pharmaceutical Formulations: Spectrometric Characteristics and Analytical Applications

Demet Dincel[†]*, Fatemeh Bahadori[‡], Evrim Tekkeli[§], Armağan Önal[#]

[†] Bezmialem Vakif University, Faculty of Pharmacy, Department of Analytical Chemistry, 34093, Istanbul, Turkey; *e-mail: ddincel@bezmialem.edu.tr
[‡] Istanbul University-Cerrahpasa, Faculty of Pharmacy, Department of Analytical Chemistry, 34500, Istanbul, Turkey;
[§] Istanbul Health and Technology University, Faculty of Pharmacy, Department of Analytical Chemistry, 34275, Istanbul, Turkey;
[#] Istanbul University, Faculty of Pharmacy, Department of Analytical Chemistry, 34116, Istanbul, Turkey

Received: October 20, 2024; Accepted: November 11, 2024
DOI: 10.17721/moca.2024.219-225

This study presents a simple, rapid, and accurate spectrophotometric method for the determination of Aripiprazole (ARP) in tablets. The determination procedure is based on the reaction of ARP with 7,7,8,8-tet racyanoquinodimethane (TCNQ), producing a colored product that was quantitated spectrophotometrically at 392 nm. Various variables affecting the reaction were optimized. The method exhibited a good linearity range with a correlation coefficient of 0.9994, observed as 0.25–3 μg/mL. The developed method was validated according to the International Council for Harmonisation (ICH) guidelines, assessing specificity, linearity, accuracy, precision, robustness, limit of detection (LOD), and limit of quantitation (LOQ). The formation of the CT-complex and the interaction sites were confirmed by elemental analysis, DSC, IR, and 1H NMR spectroscopy. The method was successfully applied to the determination of ARP in pharmaceutical preparation.

Keywords: schizophrenia, antipsychotics, aripiprazole, spectrophotometric method, pharmaceutical preparations

Introduction

Schizophrenia is a significant psychiatric disorder with a chronic course, characterized by psychosocial symptoms such as hallucinations, delusions, negativism, and cognitive dysfunction. Typically, schizophrenia manifests in late adolescence or early adulthood. It is a complex disorder influenced by genetic predisposition, neurotransmitter system dysfunctions, and neurodegenerative processes. Neurodevelopmental deviations are observed, making schizophrenia one of the most severe psychiatric disorders. Approximately 1% of the population is affected by this important brain disorder associated with neurodevelopmental issues [1]. Neurodevelopmental problems in schizophrenia affect various brain functions such as “perception, cognitive functions, thoughts, and emotions”, leading to a complex clinical picture. Genetic, environmental, and social factors also contribute to the neurodevelopmental issues in schizophrenia, making the definitive treatment of the disease challenging [2,3].

Currently, existing antipsychotic drugs primarily target dopaminergic overactivity but remain insufficient in addressing the negative symptoms and cognitive dysfunctions that are key contributors to the disease’s progression. These dysfunctions can act as limiting factors for treatment. Therefore, it is imperative to improve our understanding and develop more effective treatments for schizophrenia, a condition that still presents significant clinical challenges.

Aripiprazole (ARP) (Figure S1) is a second-generation atypical antipsychotic that has been approved for treating schizophrenia and is also effective in managing bipolar disorder. It is the first member of a new atypical antipsychotic group known as dopamine system stabilizers. Unlike other antipsychotic drugs, which are full dopamine agonists, aripiprazole is a partial dopamine agonist, making its mechanism of action different. Atypical antipsychotics are part of standard care for schizophrenia and similar disorders, often considered a first-line treatment option in managing psychosis, except for clozapine. Aripiprazole was approved by the FDA for the treatment of schizophrenia on November 15, 2002 [4].

Analyzing aripiprazole in tablets for quality control in the industrial field is crucial for better understanding and effective treatment of schizophrenia, a disease that remains clinically complex. Studies on the nature

and severity of schizophrenia often focus on the therapeutic monitoring of aripiprazole. While research on therapeutic monitoring is important, analyzing aripiprazole in tablet formulations is essential for maintaining quality standards and preventing potential issues in treatments. Developing this new method will enable the determination of aripiprazole in pharmaceutical formulations, facilitating quality control in preparations containing aripiprazole. Existing literature shows that the determination of ARP often relies on expensive systems like LC-MS/MS [5] or SPE-UPLC-MS/MS [6] for analysis from urine [7], human plasma [8], and rat plasma [9], which are not available in every laboratory. There are also HPLC methods [10, 11] for ARP determination, but they require several sample preparation steps, such as liquid-liquid extraction [10], and some need specialized equipment like column switching [12]. Therefore, it is important to develop a low-cost method and increase the variety of analysis methods.

Charge-transfer (CT) reactions are commonly used in spectrophotometric methods to determine drugs that react with specific electron acceptors (π-acceptors), like 7,7,8,8-tetracyanoquinodimet hane (TCNQ) [13, 14]. Methods relying on these interactions are usually straightforward and suitable for drug substances. This study intended to develop a fast, simple, sensitive, and precise spectrometric determination method for pharmaceutical preparations using the charge transfer complexes formed with 7,7,8,8-tetracyanoquinodimethane (TCNQ), known as π-acceptors of ARP. The structure of the final products in the solid state was determined using DSC, ^{1}H-NMR, and FTIR spectra.

Experimental part

Instrumentation

Spectrophotometric measurements were performed using a Hitachi spectrometer Model U-2900 equipped with a Xenon lamp and 1 cm quartz cells. ^{1}H-NMR spectra of the compounds were recorded in $CDCl_3$ using a Bruker Avance NEO 500 NMR spectrometer. FT-IR was employed to examine the molecular state of ARP and its related CT complexes. Spectra of ARP and ARP-TCNQ were measured using an Alpha Platinum ATR (Bruker, USA) over 25 scans. Experiments were performed at room temperature, covering a range of 400 to 4000 cm^{-1}. The incorporation of CT component (TCNQ) was studied using Differential Scanning Calorimetry (DSC). Ideally, this study should be conducted in an aqueous system in micellar form. However, due to the high mass ratio of water and other ingredients in the system, the amount of other components was relatively low, making it difficult to observe significant and distinct peaks. To overcome this challenge, ARP and its CT complex were lyophilized to eliminate the effect of water. Measurements were taken using a Perkin Elmer Jade type differential scanning calorimeter under dynamic nitrogen (20 mL/min) at a heating rate of 5°C/min. Each sample underwent two rounds of heating. In the first step, the temperature was raised from 0°C to 300°C (0°C to 180°C is shown in the results to facilitate interpretation). The second step involved cooling at the same rate, followed by a third step, which was the second round of heating from 0°C to 300°C.

Chemical and solutions

ARP was generously provided by Ali Raif Pharmaceuticals (Istanbul, Turkey), and its pharmaceutical preparation (Aripa) containing 5 mg of ARP per film tablet was taken from a local pharmacy. All chemicals and reagents were used as analytical grades. TCNQ was supplied from Fluka-Neu-Ulm, Germany.

Synthesis of the solid charge-transfer (CT) complex

The reaction products were prepared by adding 450 mg (1 mmol) of ARP and 205 mg (1 mmol) of TCNQ in 10 mL of acetonitrile. The mixture was stirred for about 20 minutes and then filtered to remove any unreacted species and avoid contamination. The solutions were left to stand for nearly 2 hours at room temperature in the dark to acquire the solid reaction products. Afterward, the solid products were filtered and washed multiple times with acetonitrile to eliminate any remaining reagents and drug substance.

Optimization of the Method

Choice of Solvent. During the choice of the most proper solvent for the reaction and measurement, various solvents including acetonitrile, dimethyl sulfoxide (DMSO) and methanol were tested.

Reaction Time and Temperature. To understand at which temperature and for how long the formation of the charge transfer complex occurs quantitatively, reactions were performed at room temperature, 60°C, 70°C and 80°C, with waiting times of 10, 20, 30, and 45 minutes.

Stoichiometry of the Reaction. The molar ratio of the reagent in the reaction mixture was analyzed using Job's method for this approach [15].

Development of Calibration Curves. A calibration curve for the method was constructed by analyzing a stock solution of ARP (1 mg/mL) at different dilutions. Sample preparation followed the same procedure as previously described. The calibration curve was established using linear least squares regression, plotting absorbance against concentration. The resulting equation for this method is $A = aC + b$, where C represents the concentration in μg/mL and A denotes the absorbance.

Assay Method for Tablets. Ten tablets were used and each tablet was individually weighed, and the mean weight per tablet was calculated. The tablets were then finely powdered using a mortar. An amount of the powder that corresponded to the weight of five tablets was precisely measured and transferred into a 100 mL volumetric flask. About 50 mL of acetonitrile was

added, and the mixture was subjected to mechanical stirring for 20 minutes, followed by sonication for an additional 20 minutes. The volume was then adjusted to 100 mL with acetonitrile, and the resulting solution was filtered. Portions of the filtered solution were diluted with acetonitrile and subsequently processed as outlined for the calibration curve preparation. The nominal concentrations of the tablets were determined using either the calibration graph or the respective regression equation.

Method Validation. The developed analytical method was validated following the the ICH guideline Q2 (R1) [15]. The particularity of the method was assessed using a mixture of common tablet excipients such as hydroxypropyl cellulose, lactose monohydrate, starch, magnesium stearate, iron oxide, etc. Calibration curve was constructed according to Beer's Law using absorbance values (6 replicates per level) measured at 5 concentration levels.

The interday and intraday precision were assessed by analyzing standards on the same day and on five different days (n=6 for each day).

The limits of quantitation (LOQ) and limits of detection (LOD) were calculated using the following formulas:

LOQ = 10(SDa) / b

LOD = 3(SDa) / b

Where SDa represents the standard deviation of the intercept, and b denotes the slope. The accuracy of the proposed method was detected using the standard addition method. Three various concentrations of standard aripiprazole solutions were added to different amounts of sample solutions, and the resulting mixtures were analyzed.

The percentage recovery of the standard included to the test samples was calculated using the following equation:

Recovery % = [(*Ct*−*Cu*)/*Ca*)]×100

where: *Ct* represents the total concentration of the analyte, *Cu* is the concentration of the analyte present in the formulation, and *Ca* refers the concentration of the analyte added to the formulation.

The proposed method was assessed by analyzing aripiprazole in a pharmaceutical dosage form to assess the method's applicability.

Results and Discussion

Optimization of the Method

Choice of Solvent. Experiments have shown that acetonitrile is the most suitable solvent for dilution. It provides excellent solvation for the TCNQ reagent and produces the highest absorbance value.

While the formation of the TCNQ·− radical was observed in both methanol and DMSO, the color intensity in these solvents was less pronounced compared to acetonitrile (Figure 1).

Reaction Time and Temperature. To discover the optimal reaction temperature, reactions were conducted at room temperature, 60°C-80°C, and the absorbance values were recorded. As shown in Figure 2, the CT complex undergoes degradation at elevated temperatures, with room temperature being the optimum condition for the reaction. Following experiments conducted at room temperature with various waiting times, it was observed that the highest efficiency was achieved after a 2-hour period.

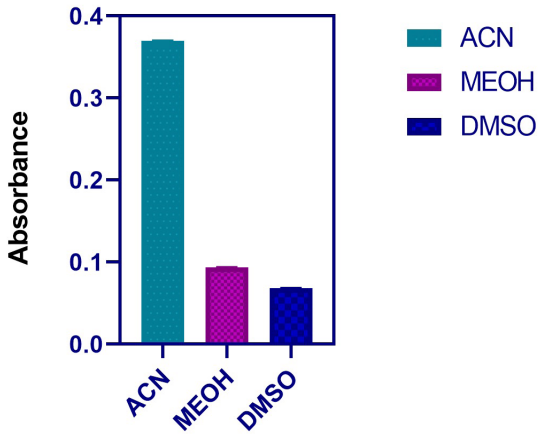

Figure 1. Choice of solvent for CT complex.

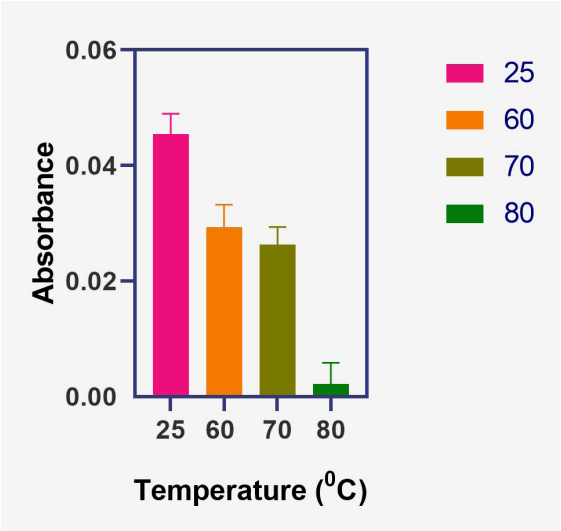

Figure 2. Effect of Temperature for CT complex.

Stoichiometry of the reaction. The molar ratio of the reagent in the reaction mixture was selected for this method using Job's method [17]. The absorbance of the reaction products was quantified and plotted in relation to the mole ratios. The reaction stoichiometry for this proposed method was determined to be approximately a 1:2 ratio (ARP/reagent) (Figure 3).

Method Validation

In the method validation studies, no interactions were observed between the additives and excipients such as lactose monohydrate, hydroxypropyl cellulose, magnesium stearate, and starch, iron oxide. A linear relationship between the absorbance and the

concentration was found in the range of 0.25-3 μg/mL. The regression equation parameters of the developed method are shown in Table 1. The LOD (limit of detection) value of the method was calculated to be 0.065 μg/mL, and the LOQ (limit of quantification) value was calculated to be 0.216 μg/mL.

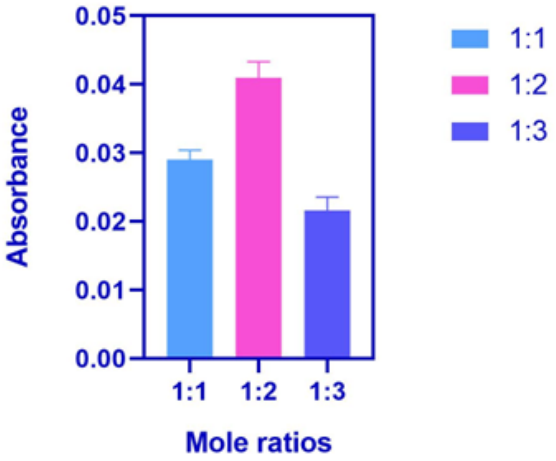

Figure 3. Stoichiometry of the Reaction for CT complex.

In the precision study, the relative standard deviation (RSD) values ranged from 0.18% to 0.32% for intra-day precision and from 0.26% to 0.34% for inter-day precision. These results, shown in Table 2, demonstrate excellent repeatability and reproducibility.

Accuracy assessments were performed through the standard addition method, with the results displayed in Table 3. The mean recovery percentages varied between 102.28% and 106.43%, suggesting that the proposed method demonstrates high accuracy. In robustness studies of the proposed methods, minor adjustments to procedure variables, including reaction time (5±0.5 minutes) and reagent amount (1.0 ± 0.05 mg), were tested. It was provided that these changes did not affect the methods.

The developed method was used to quantify the pharmaceutical preparation of aripiprazole, with the results presented in Table 4. This method yielded results that were both accurate and precise, showing impressive recovery percentages along with low relative standard deviation (RSD) values.

Table 1. Validation parameter results for proposed method.

Parameter	Method
Linearity range (μg/mL)	0.25-3
Regression equation	A = 0.3055C - 0.003
Slope ± SD	0.3055
Intercept ± SD	0.003
Correlation coefficient, r	0.9994
LOD	0.065
LOQ	0.216

Table 2. Precision study results obtained with the proposed method.

Quantity taken (μg/mL)	Intraday RSD[a] (%)	Interday RSD[a] (%)
0.5	0.26	0.34
1	0.18	0.26
2.5	0.32	0.28

[a] Six independent analyses

Characterization of the Reaction Product

^{1}H-NMR and IR spectrum of ARP-TCNQ

The ^{1}H-NMR spectrum of ARP showed the characteristic peaks of dichlorophenylpiperazinyl unit and the dihydrocarbostyril group which is presented

Table 3. The results of the recovery study obtained using the standard addition method.

Amount taken (μg/mL)	Amount added (μg/mL)	Total amount found[a] (μg/mL) (Mean ± SD[b])	Recovery (%)	RSD (%)
1	0.5	1.51±0.0016	102.28	0.11
	1	2.06±0.0018	106.43	0.09
	2	3.11±0.0016	105.76	0.05

[a] Six independent analyses; [b] Standard deviation

Table 4. Analysis of ARP in tablets containing 5 mg of the drug.

(Mean ± SD)*	Recovery (%)	RSD (%)
5.046 ± 0.0094	100.92	0.18

*Aripa tablet®, containing 5 mg of ARP per tablet

in Table S1 and Figure S2a. As it could be seen in Table 3 and Figure S2a the N-H proton is presented in 9.19 ppm which is followed by the aromatic protons of the ARP structure. Aromatic protons are followed by the etheric CH_2 group. Piperazine and quinolinone CH_2 groups are presented at 3.07- 2.61 ppm. Finally, butoxy carbons are existed at 2.48 to 1.70 ppm. These data are in well agreement with the previously reported data [18].

The ^{1}H-NMR spectra of ARP-TCNQ which are shown in Table S2 is almost identical. Additional aromatic proton peaks of TCNQ are presented in the related region of the ARP-TCNQ ^{1}H-NMR spectrum. Also, a new quartet peak around 5.30 ppm is presented in the ARP-TCNQ spectrum. Furthermore, the singlet peak of N-H in 9.19 ppm is shifted to downfield (9.66 ppm), appears as a weakened and broadened peak but the intensity is increased from one to two. Also, the chemical shifts of the aromatic peaks of ARP are significantly altered in the ^{1}H-NMR spectra of ARP-TCNQ. Although the presence of aromatic peaks of TCNQ in the spectrum of ARP-TCNQ shows the complexation of these reagents with ARP without losing its structure, the quartet peak at 5.30 ppm shows a reduction in the structure of pi-acceptors resulting in the appearance of the new alkene protons. This could point out to formation of a new chemical bound between ARP and π-acceptors. Furthermore, butoxy protons show a significant down-field shifting resulting in the overlapping of cyclic -CH_2 groups with methylene protons of the carbon chain. It could be concluded that the complexation of pi-acceptors via making chemicals bound together with the interaction of π-acceptors with the aromatic rings of dichlorophenylpiperazinyl unit cause a significant de-shielding in the protons of the butoxy chain.

The FT-IR spectrum of ARP is shown in Figure S3a. Previously ten different conformational polymorphs of ARP have been characterized and demonstrated by Braun et.al. [19]. The FT-IR spectrum of ARP used in our study is in well accordance with polymorph 3 of the previous study. A very weak N-H stretching peak is observed at 3187 cm^{-1} along with aromatic C-H stretchings at 3187 cm^{-1}. Aliphatic C-H_2 stretchings are observed at 2810-2944 cm^{-1} and C=O stretching at 1647 cm^{-1} is the strongest peak of the FT-IR spectra of ARP. C-Cl peak is identified at 795 cm^{-1} [20].

The most significant difference between the FT-IR spectrum of ARP and that of CT complex (Figures S3a and S3b) is the disappearance of the peaks related to N-H and C=O groups. Also, aromatic CH and aliphatic CH_2 stretching (2600-2850 cm^{-1}) are significantly intensified in the FT-IR spectra of CT complexes. Another intensified peak is the one related to the C-N stretching at 1286 cm^{-1}. Also, the C≡N vibration at 2221 cm^{-1} is observed in the ARP-TCNQ spectrum (Figure S3b).

All evidence gathered from FT-IR studies confirms the results of ^{1}H-NMR spectra in which, it was shown that the complexation of π acceptors with ARP happens on the C=O neighboring N-H group and dichlorophenylpiperazinyl unit. Previously it has been shown that the intensity of IR peaks is proportional to the changes in dipole moment that a bond undergoes during a vibration [21]. The decrease in the band intensity of C=O and N-H groups clearly reveals the occupation of these groups by the functional groups of another component in the system. Similarly, the increase in the intensity of C-N at 1237 cm^{-1} indicates an increase in its dipole moment. Also, the intensified aromatic CH and aliphatic CH_2 peaks reveals the incorporation of these groups with one more molecule of π acceptors on the dichlorophenylpiperazinyl unit.

The DSC thermograms were recorded by heating each sample from 0 to 300 °C, cooling them back, and re-heating them to the same temperature. The thermogram of first heating of ARP (Figure S4) is in well accordance with previous studies [19, 20] by observation of a melting endotherm in the range of 123–141 °C with a maximum at 128 °C. In the 2nd round heating of ARP this endothermic peak is disappeared, indicating the complete deterioration of the structure (Figure S5). Although the ^{1}H-NMR and FT-IR spectra of ARP-TCNQ were identical, there was a significant difference between their DSC thermograms. This is where the melting endotherm of ARP-TCNQ has appeared at a significant higher temperature (Figure S4) at 168 °C. It seems that incorporation of TCNQ with ARP changes the crystal structure of ARP. Regardless of the behavior of the substances in the first heating round, they all appear to be deconstructed in the second heating round (Figure S5).

To understand the reasons for this alternation in the ARP crystal structure, the structures of ARP and ARP-TCNQ were drawn with the help of ChemBiodraw ultra and further converted to the 3D structure using ChemBiodraw 3D. All the designed structures were optimized by energy minimization using the MM2 method [22]. The energy-minimized structure of ARP is shown in Figure 4a. This structure is what previously has been reported as “Polymoroh 3” [19]. The predicted 2D structure for the ARP-TCNQ complex using spectroscopic and thermal analysis methods are shown in Figure 4b and its energy-minimized crystal structure is shown in Figure 4c. As it is clearly seen the structure of ARP-TCNQ shows complete deformation compared to that of ARP causing a significant change in its thermal behavior. This could be attributed to the incorporation of etheric oxygen of the butoxy chain with one of the TCNQ molecules.

The obtained structures not only reveal the causes of alternation in the thermal behavior of ARP-TCNQ but also clearly show the causes of missing functional groups in FT-IR spectra and the downfield shifting of aliphatic protons in ^{1}H-NMR assays.

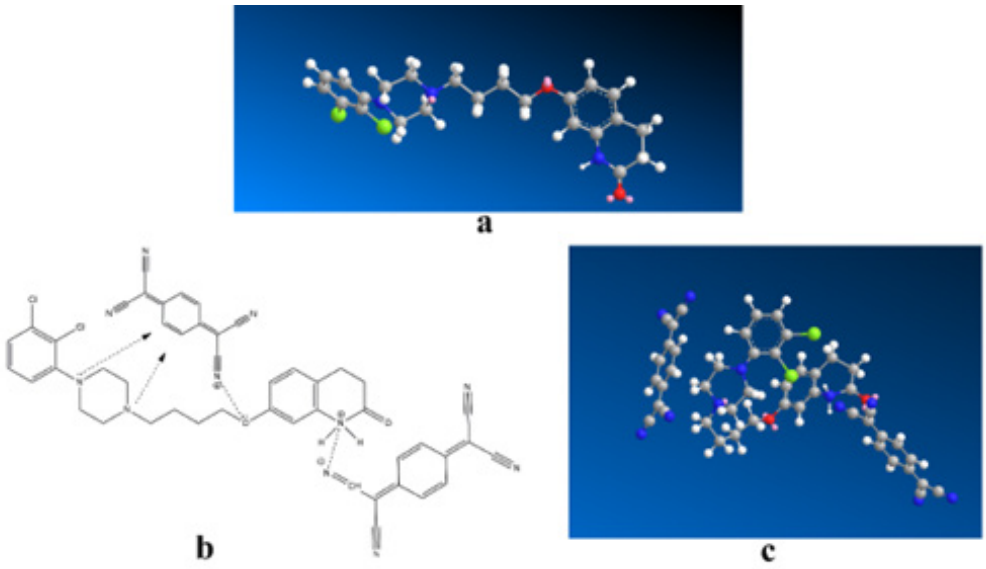

Figure 4. Energy minimized 3D structure of a: ARP, b: 2D structure of the predicted ARP-TCNQ complex, and c: energy minimized 3D structure of ARP-TCNQ.

Conclusion

As a result, a straightforward, quick, and precise spectrophotometric technique for figuring out the amount of aripiprazole (ARP) in tablet formulations was effectively created in this work. ARP reacts with 7,7,8,8-tetracyanoquinodimethane (TCNQ) to produce a colored product that can be measured at 392 nm, which is the basis of the approach. After optimizing several reaction-affecting variables, satisfactory linearity was shown in the 0.25–3 μg/mL range, as indicated by a correlation coefficient of 0.9994. The method's specificity, linearity, accuracy, precision, robustness, limit of detection (LOD), and limit of quantitation (LOQ) were all validated in accordance with the guidelines set out by the International Council for Harmonization (ICH).

Using elemental analysis, DSC, IR, and ^{1}H NMR spectroscopy, the synthesis of the charge-transfer (CT) complex and the interaction sites were verified. The technique was successfully used to measure ARP in pharmaceutical formulations, giving the pharmaceutical industry a useful tool for quality monitoring. Because of its simplicity and lack of expensive equipment or complicated sample preparation steps, the approach is suitable for ordinary laboratory analysis. Its resilience guarantees its dependability under a variety of analytical settings. Comparing this new spectrophotometric method to other methods, such LC-MS/MS and HPLC, which frequently call for more advanced equipment and significant sample preparation, reveals how efficient and economical it is. This technique can make a substantial contribution to improved therapeutic monitoring and quality assurance in the manufacturing of pharmaceutical products containing ARP by providing precise and accurate quantification of ARP. The results of this study highlight the significance of creating easily accessible analytical techniques for pharmaceutical analysis in addition to advancing the analytical capabilities for ARP determination.

Acknowledgement

The authors would like to thank Ali Raif Pharmaceuticals (Istanbul, Turkey) for providing the active ingredient and pharmaceutical preparation. This study was supported by Bezmialem Vakıf University Scientific Research Project Unit with project number 3.2019/8.

Declaration of Competing Interests

The authors confirm that they have no financial conflicts or personal relationships that could have influenced the work presented in this paper.

CRediT authorship contribution statement

DD: Investigation, Experimental Design, and Formal Analysis, Manuscript writing, Conceptualization, Project administration, Supervision. **FB:** Investigation, Formal Analysis, Writing – original draft and review. **ET:** Investigation, Experimental Design. **AO:** Investigation, Experimental Design.

References

1. Erkmen, T.; Arıcıoğlu, F. Şizofreni'de İnflamatuvar Mekanizmaların Yeri. *MÜSBED* 2015, 5 (2), 134–139.
2. Stefan, M.; Murray, R. Atlas of Schizophrenia; 1st ed.; CRC Press: 2002.
3. T. İ., U. Nöropsikofarmakoloji Rasyonel İlaç Kullanımı; 1st ed.; 2007.
4. Üstünes, L. Rx MediaPharma® İnteraktif İlaç Bilgi Kaynağı. 2013.

5. Suzuki, Y.; Naito, T.; Kawakami, J. Validated LC–MS/MS Method for Simultaneous Determination of Aripiprazole and Its Three Metabolites in Human Plasma. *Chromatographia* 2017, 80 (12), 1805–1812.

6. Patel, D. P.; Sharma, P.; Sanyal, M.; Shrivastav, P. S. SPE-UPLC-MS/MS Method for Sensitive and Rapid Determination of Aripiprazole in Human Plasma to Support a Bioequivalence Study. *J. Chromatogr. B*, Analyt. Technol. Biomed. Life Sci. 2013, 925, 20–25.

7. Feng, S.; Enders, J. R.; Cummings, O. T.; Strickland, E. C.; McIntire, T.; McIntire, G. A Dilute and Shoot LC-MS/MS Method for Antipsychotics in Urine. *J. Anal. Toxicol*. 2020, 44 (4), 331–338.

8. Koller, D.; Zubiaur, P.; Saiz-Rodriguez, M.; Abad-Santos, F.; Wojnicz, A. Simultaneous Determination of Six Antipsychotics, Two of Their Metabolites, and Caffeine in Human Plasma by LC-MS/MS Using a Phospholipid-Removal Microelution-Solid Phase Extraction Method for Sample Preparation. *Talanta* 2019, 198, 159–168.

9. Liang, F.; Terry, A. V.; Bartlett, M. G. Determination of Aripiprazole in Rat Plasma and Brain Using Ultra-Performance Liquid Chromatography/Electrospray Ionization Tandem Mass Spectrometry. Biomed. *Chromatogr.* 2012, 26 (11), 1325–1332.

10. Shimokawa, Y.; Akiyama, H.; Kashiyama, E.; Koga, T.; Miyamoto, G. High-Performance Liquid Chromatographic Methods for the Determination of Aripiprazole with Ultraviolet Detection in Rat Plasma and Brain: Application to the Pharmacokinetic Study. *J. Chromatogr.* B 2005, 821 (1), 8–14.

11. Kalaichelvi, R.; Srinivasa, R. D. Validated RP-HPLC Method for Analysis of Aripiprazole in a Formulation. *Asian J. Chem*. 2009, 7 (3), 827–832.

12. Akamine, Y.; Yasui-Furukori, N.; Kojima, M.; Inoue, Y.; Uno, T. A Sensitive Column-Switching HPLC Method for Aripiprazole and Dehydroaripiprazole and Its Application to Human Pharmacokinetic Studies. *J. Sep. Sci.* 2010, 33 (21), 3292–3298.

13. Khaled, E. Spectrophotometric Determination of Terfenadine in Pharmaceutical Preparations by Charge-Transfer Reactions. Talanta 2008, 75 (5), 1167–1174.

14. Matos, M. S.; Gehlen, M. H. Charge Transfer Complexes of 9-Vinyl-Carbazole with π Acceptors in Homogeneous and in Micellar Solutions. *Spectrochim. Acta A Mol. Biomol. Spectrosc.* 2004, 60 (7), 1421–1426.

15. Job, P. Formation and Stability of Inorganic Complexes in Solution. *Ann. Chim.* 1928, 9, 113.

16. ICH, I. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Validation of Analytical Procedures: Text and Methodology Q2 (R1). 2005.

17. Li, J.; Liu, A.; Xia, G.; Nian, Y.; Shen, J. Spectroscopic Studies of Aripiprazole. Guang Pu Xue Yu Guang Pu Fen Xi 2007, 27 (5), 863–867.

18. Braun, D. E.; Gelbrich, T.; Kahlenberg, V.; Tessadri, R.; Wieser, J.; Griesser, U. J. Conformational Polymorphism in Aripiprazole: Preparation, Stability, and Structure of Five Modifications. *J. Pharm. Sci.* 2009, 98 (6), 2010–2026.

19. Mihajlovic, T.; Kachrimanis, K.; Graovac, A.; Djuric, Z.; Ibric, S. Improvement of Aripiprazole Solubility by Complexation with (2-Hydroxy) Propyl-β-Cyclodextrin Using Spray Drying Technique. *AAPS PharmSciTech* 2012, 13 (2), 623–631.

20. Arrondo, J. L. R.; Muga, A.; Castresana, J.; Goñi, F. M. Quantitative Studies of the Structure of Proteins in Solution by Fourier-Transform Infrared Spectroscopy. *Prog. Biophys. Mol. Biol*. 1993, 59 (1), 23–56.

21. Kaur, K.; Kaur, P.; Mittal, A.; Nayak, S. K.; Khatik, G. L. Design and Molecular Docking Studies of Novel Antimicrobial Peptides Using Autodock Molecular Docking Software. *Asian J. Pharm. Clin. Res.* 2017, 10, 28–31.