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A Review Using Continuous Flow Injection Analysis Technique in the Determination of Several Drugs

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Abstract

Continuous flow injection analysis (CFIA) is one of the simplest, easiest, and multilateral analytical automation methods in moist chemical analysis. This method depends on changing the physical and chemical properties of a part of the specimen spread out from the specimen injected into the carrier stream. The CFIA technique uses automatic analysis of samples with high efficiency. The CFIA PC compatibility also allows specimens to be treated automatically, reagents to be added, and reaction conditions to be closely monitored. The CFIA is one of the automated chemical analysis methods in which a successive specimen sample is to be estimated and injected into a vector stream from a flowing solution that meets the reagent and mixes at a specific point, the y-junction, before reaching the detector. However, CFIA does not have a separation method because the sample, carrier stream, and reagent all enter the system simultaneously and move together at a specific flow rate to the end of the system. It is also possible to inject a second specimen sample to be estimated before the first sample reaches the detector. For all the reasons mentioned, the CFIA technique analysis is appropriate, fast, and ideal for analyzing different samples. This general technique deals with solutions and is used for various tasks, including pH measurement, conductivity, colorimetry, titration, and enzyme assays. So, it was used in analytical chemistry to estimate many samples, including medicines, because they are essential substances for human life, and everyone widely uses them.

Keywords: Continuous flow injection analysis, Flow rate, Carrier stream, Pharmaceutical drugs, Pure and pharmaceutical preparations.

1. Introduction

The continuous flow injection analysis (CFIA) fast technique is an easy, simple, and versatile method in chemical analysis. It is considered one of the methods used to automate other methods; it depends on the chemical and physical factors of a scattered specimen region, from the blueness of the specimen inside the carrier stream and revealing [1]. The first to describe FIA in a patent

they filed in Denmark in 1974 were Ruzicka and Hansen. Since then, the technology has evolved into a discipline, covering 22 studies in addition to more than 20000 research papers that have become the scope of the method from a tool used to automate processes to a means to improve the performance of spectral and electrochemical instruments. The FIA analysis is defined according to Ruzicka and Hansen [2]. The FIA technique depended on consecutive injects for separated liquid specimens inside a movable, no-segmented persistent vector stream. The injected specimen forms a region, which is transferred towards the detector with the next continual reveal of the target analyte. Stewart, another FIA pioneer, knew FIA in 1981 [3] as the consecutive intromission for separated specimen solutions inside an undivided continuous stream together, following the possibility of detecting the analyzed substance. In 1988, Ruzicka and Hansen [4] recalled the nonattendance of air clips. They decided on the definition of a new FIA Data collection for concentration gusto component: a fluid injected from a specific area, scattered inside continuous unsegmented current for transporter [5].

The FIA passed through three generations. The first generation of FIA was in 1970, complemented via sequential flow injection analysis (SFIA) in 1990. As for the second generation, the recently appeared lab-on-valve (LOV) orderliness, also meaning the bead injection (BI), involves a regenerative bean use approach. The third generation has the clear advantages of automated miniaturization and offers new methods and chemical detections; the third generation revolutionized the concept of sample pre-treatment by facilitating online work and linking it with different detection techniques [6,7]. The FIA offers various advantages over manual methods:

- The reaction conditions are strictly controlled
- High precision, the mechanical performance of the measurements reduces analyzer error
- High productivity
- Low cost
- Low waste generation
- Compatibility with the computer
- Ease and simplicity
- Automatic processing of samples and solution
- Consumption of volumes from samples and reagents is low
- Its use wide as it can be linked to various devices
- In a closed system, the reaction takes place. Thus, the risk of material exposure, contamination, or sample loss is reduced, preserving the safety of analysts by preventing the risk of direct exposure to materials through taking reagents or products of toxic reactions unparalleled in handling any other technology [8].

2. Design of FIA

Figure 1 shows the simplest flow injection analyzer. The analyzer consists of a pump that drives the current carrier through a narrow tube, an injection valve, and a microreactor in which the specimen region gets distracted and reacts with the ingredients of the carrier stream. In the case of the FIA technique, the equilibrium physical (flow homogenization) has never been detected nowadays. Moreover, the chemical equilibrium doesn't need to be obtained at detection [9]. The reaction product is measured while it passes through the detector cell [10, 11].

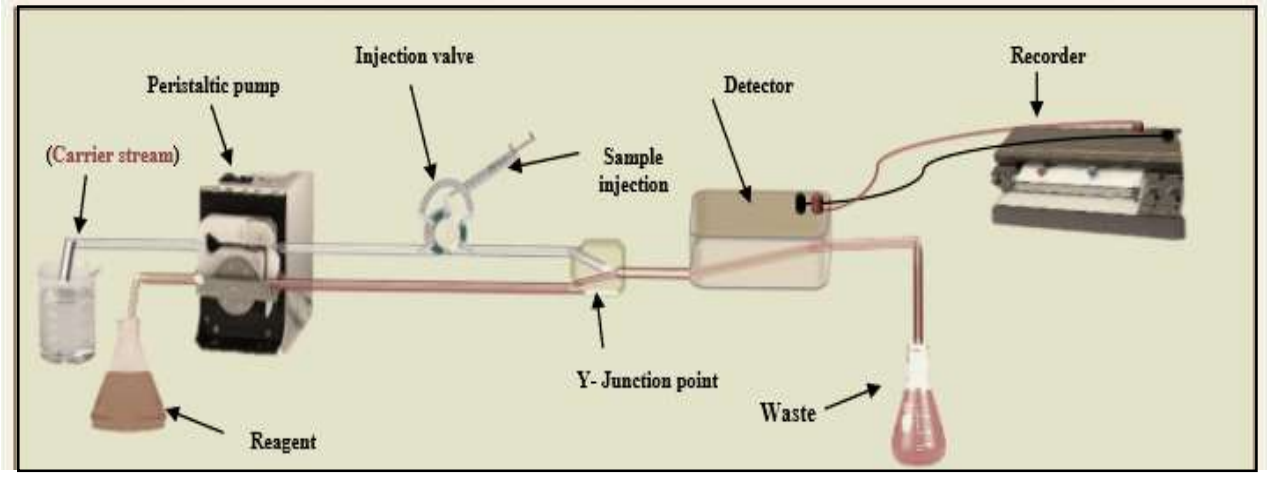

Figure 1. The design of the flow injection analysis system

3. Application of continuous flow injection analysis

Continuous flow injection analysis, in general, is a simple, easy, and low-cost technology commonly used and readily available in devices such as a peristaltic pump and a low-pressure injection valve. It provides more sampling, low reagent consumption, samples completed in preparation and detection, versatility and high accuracy, and various devices that can be used as detectors.

It offers increased sampling, lower reagent consumption, sample automation preparation and detection, better precision, and high versatility since various detectors may be employed. **Table 1** shows the use of the CFIA technique for the estimation of some drugs.

Table 1. Summarizes the use of CFIA technique to determine some drugs

Analyte ---------- **Type of sample**	**CFIA method**	**Comment**	**Linear range**	**LOD**	**Ref.**
Paracetamol ---------- **Drug**	CFIA-Merging zone	Utilizing the merging zone-CFIA technique with a hexagonal flow cell and a homemade photometric-dependent 704 nm LED, a photosilicon minidetectror was also studied. This method was dependent on the oxidation via Fe (III) solution for paracetamol, which leads to the configuration of Fe (II), which reacts together with potassium hexacyanoferrate (III) to configure prussian blue dye, and the estimation of this dye at 704 nm.	0.1-10 mmol/L	2 nmol/L	12
Ciprofloxacin ---------- **Pharmaceutical preparation**	CFIA – CL	This method is dependent on the indirect chemiluminescence (CL) reaction to improve the quantity of photons emitted during the oxidation of luminol-H_2O_2-OH- in the presence of ciprofloxacin as a sensitizer for the reaction.	0.01-1 mmol/L	6.01 ng/sample	13

Methionine --- **Pharmaceutical preparations**	CFIA – CL	This method for estimation of methionine utilizes chemiluminescence for methionine, sodium hydroxide, and liminal for the generation of a chemiluminescence derivative of luminal.	0.6-20 mmol/L	5 µmol/L	14
Folic acid --- **Drugs**	CFIA- CL	Estimation of folic acid via chemiluminescence: CFIA depends on the formation of an adduct molecule of the formed derivative of luminol with folic acid in an alkaline medium.	0.003-0.45 mM	0.795 mmol/122µL	15
Metformin --- **Pharmaceutical preparation**	CFIA	Depending on the embedded Cu (II) in the bead of gel structure, it can be utilized to configure red– a magenta color complex (λ_{max}= 530 nm) via the direct reaction of the medicine together with the released Cu (II) from the bead of gel in the middle of alkaline.	0.001-1 mmol/L	0.5 µmol/L	16
Ciprofloxacin-HCl --- **Pharmaceutical formulations**	CFIA – Turbidimetric	This method is based on the estimation of ciprofloxacin in pure form and pharmaceutical formulations via coupling continuous flow injection analysis by turbidimetric at 0-180º and scattered light effect at two opposite positions at 0-90º. It is based upon the formation of a yellowish-white precipitate for complex ion pairs via utilizing potassium hexacyanoferrate in the middle of the water.	1-20 mmol/L	0.55 mmol/L	17
Promethazine-HCl --- **Pure and pharmaceutical preparation**	CFIA – Photometric	This method depended on the in situ detection of colored cationic radicals formed by the oxidation of medicine together with sodium persulphate to pinkish-red species and estimated by utilizing an Ayah 3SX3-3D analyzer.	0-7 mmol/L	3.97 µg/sample	18
Metformin hydrochloride --- **Drug**	CFIA – Micro photometric	This method is for the estimation of metformin hydrochloride via the complexation of the medicine with Cu (II). A colored complex was measured at 530 nm.	0-100 mM	662 ng	19
Amiloride --- **Pure and pharmaceutical preparations**	CFIA - Turbidimetric	A yellowish-white precipitate is formed for the amiloride-phosphomolybdic acid ion pair in the middle of the water. Turbidity was measured via the Ayah 6Sx1-ST-1D CFI analyzer by the attenuation of incident light from the surface precipitated particles in 0-180º.	0.005-10 mmol/L	23.14 µg/sample	20
Fe(III) --- **Drug samples**	CFIA – Turbidimetric	This method depends on the complex composition between Fe (III) and 8-hydroxyquinoline in a medium of ammonium acetate for the formation of a deep green precipitate. This complex was estimated utilizing a linear array Ayah 5SXI-T-1D analyzer.	0.1-8 mmol/L	4.8×10^{-9} M/sample	21

Chlorpromazine-HCl --- **Pure and pharmaceutical preparation**	CFIA – Turbidimetric	This is based on a reaction between Chlorpromazine-HCl and potassium hexacyanoferrate in a medium that is acidic for complex formation of a precipitate colored greenish-yellow.	3-30 mmol/L	0.12 µg/sample	22
Tetracycline-HCl --- **Pure and pharmaceutical formulation**	CFIA – Turbidimetric	This method depends on the complex formation of yellow precipitate for the tetracycline-phosphomolybdic acid as an ion pair complex in an aqueous medium. Turbidity was measured by a linear array Ayah 5SXI-T-1D analyzer at 0-180°.	0.25-25 mmol/L	96.18 pg/sample	23
Metoclopramide hydrochloride --- **Pure and pharmaceutical preparations**	CFIA	This method is dependent on the oxidation of medicine together with Ce (IV) sulfate in a medium from acid to form a red color complex, which is estimated utilizing a homemade Ayah 6SXI-T-2D solar cell.	0.05-16 mmol/L	0.332 µg/sample	24
Cyproheptadine hydrochloride --- **Pharmaceutical preparations**	CFIA – Turbidimetric	The method is dependent on the formation of an ion pair between CPH-HCl and hexacyanoferrate in an aqueous medium to form a yellow precipitate, utilizing the Ayah 6SXI-T-2D solar cell analyzer via the reflection of incident light from surfaces in 0-180°.	0.5-10 mmol/L	280.72 ng/100 µL	25
Vitamin B_1 --- **Pure and pharmaceutical Tablets**	CFIA – Turbidimetric	This method depends on the formation of an ion-pair complex between thiamin chloride and ammonium molybdate in the medium from aqueous to form a complex white precipitate.	0.1-2 mmol/L	1.579 µg/sample	26
Mebeverine --- **Pure form or pharmaceutical dosage**	CFIA-Quenched fluorescence	It is dependent on the fluorescence of fluorescein sodium salt and the quenching effect of fluorescence by mebeverine in an aqueous medium. Using a homemade instrument, a fluorometer and CFI analyzer together laser solid state at 405 nm.	0.05-10 mmol/L	114 ng/sample	27
Cefotaxime sodium --- **Pharmaceutical drugs**	CFIA - Turbidimetric	Estimation of cefotaxime sodium in pharmaceutical drugs It is dependent on the formation of a yellowish-white precipitate for the CFTS-K_3 [Fe (CN) $_6$] ion pair in a medium that is aqueous. Turbidity was measured by the Ayah 6SX1-T-1D solar cell CFIA analyzer by the attenuation of incident light at 0-180º.	1-50 mmol/L	63.739 µg/sample	28
Ketotifen fumarate --- **Pure And tablets**	CFIA - Turbidimetric	The method depends on the reaction of Ce (IV) sulfate together with ketotifen fumarate in a salt medium with sodium chloride to form a greenish-blue precipitate as an ion pair complex. Turbidity was measured via the attenuation of incident light at 0-180º.	0.1-50 mmol/L	1.136 µg/sample	29

Ketotifen fumarate --- **Pure and pharmaceutical Preparation**	CFIA - Turbidimetric	The method was based on the reaction between phosphomolybidic acid and ketotifen fumarate in a medium of sodium chloride to form a yellowish- green precipitate as an ion pair complex. Turbidity was measured at 0-180º.	0.5-50 mmol/L	4.255 µg/sample	30
Mefenamic acid --- **Pure and pharmaceutical Preparation**	CFIA – Turbidimetric	This method depends on the reaction between Ce (IV) sulfates and mefenamic acid in an aqueous medium to form a bluish-green precipitate. Turbidity was measured via the reversal of incident light at 0-180º.	0.3-7 mmol/L	7.35 µg/sample	31
Mefenamic acid --- **Pure and pharmaceutical preparation**	CFIA – Turbidimetric	Estimation of mefenamic acid in pure form and pharmaceutical preparation by turbidimetric measurement at 0-180º via the Ayah 6SX1-ST-2D CFIA analyzer. The method depends on phosphomolybidic acid and mefenamic acid reacting with water to make a blue precipitate that is made up of ion pairs. The reflection of incident light at 0-180° served to measure turbidity.	0.3-7 or 0.3-10 mmol/L	4.92 µg/sample	32
Zinc (II) ion --- **Pure and pharmaceutical preparation**	CFIA – Turbidimetric	This method is dependent on the formation of an ion pair complex among folic acid and ammonium molybdate in an aqueous medium to obtain a gray precipitate complex utilizing the Ayah-6SX1-ST-2D solar cell CFI analyzer.	5-16 mmol/L	79.05 µg/sample	33
Ciprofloxacin --- **Pure or pharmaceutical dosage**	CFIA-Quenched fluorescence	This project is dependent on the fluorescence of fluorescein sodium salt, and it's quenched by ciprofloxacin hydrochloride in an aqueous medium using a fluorometer CFI analyzer together with a laser solid state at 405 nm.	10-100 mmol/L	8.12 µg/sample	34
Folic acid --- **Pure and pharmaceutical formulations**	CFIA - Turbidimetric	This way is dependent on the formation of ion pair complex among folic acid and ammonium molybdate in an aqueous medium to obtain a gray precipitate complex utilizing Ayah-6SX1-ST-2D solar cell CFI analyzer.	0.01-0.6 mmol/L	131.994 ng/µg	35
Ibuprofen --- **Pure form and drugs**	CFIA – Turbidimetric	Estimation for Ibuprofen in pure form and drugs by CFIA. The method is based on the reaction of Ibuprofen with potassium chromate to form a precipitate using a homemade ASNAG fluorometer.	5-30 mmol/L	1.630 µg/sample	36
Vitamin B_9 --- **Pure and pharmaceutical formulations**	CFIA	This method depends on the oxidation of vitamin B_9 via Ce (IV) sulphate in sulphuric acid medium to form a red colour complex. Utilizing a homemade Ayah 6SXI-T-2D solar cell analyzer.	0.1-5 mmol/L	5.544 µg/sample	37

Baclofen --- **In pharmaceutical formulation**	CFIA – Spectrophotometric	A spectrophotometric method for the estimation of baclofen in the pharmaceutical formulation was developed by combining a spectrophotometric detector with flow injection analysis. This method is based on the oxidation of Fe (II) to Fe (III) via baclofen, which also forms complexes in an acidic solution measured at 700 nm.	0.05-25 mmol/L	0.01 mmol/L	38
Cefotaxime sodium --- **Pure and pharmaceutical preparation**	CFIA-Fluorescence	The project for estimation of cefotaxime sodium in the form of pure pharmaceutical preparation by fluorescence measurement in ± 90º by 2 × 4 solar cells of a new homemade ISNAG fluorometer. It is dependent on the quenching of fluorescence of calcein.	10-50 mmol/L	501.314 µg/sample	39
Ibuprofen --- **Pure form and drugs**	CFIA – Turbidimetric	This method is based on the reaction between Ibuprofen and sodium nitroprusside to form a precipitate utilizing an ISNAG fluorometer.	0.5-15 mmol/L	33.934 µg/sample	40
Indomethacin --- **Pure form and drugs**	CFIA – Turbidimetric	The determination of indomethacin in its pure form and drugs by CFIA diverged light. This method depends on the reaction of indomethacin with phosphotungstic acid to form a moff-white precipitate using a homemade ISNAG fluorometer.	0.01-5 mmol/L	320.222 ng/sample	41
Indomethacin --- **Pure form and drugs**	CFIA – Turbidimetric	The method depends on the reaction of the indomethacin with potassium hexacyanoferrate to form an off-white precipitate, utilizing the ISNAG- fluorometer.	0.01-5 mmol/L	698.76 ng/sample	42
Ciprofloxacin hydrochloride --- **Pure and pharmaceutical preparation**	CFIA-Fluorescence	Estimation of ciprofloxacin hydrochloride via fluorescence resonance energy transfer from erythrosine B which used a carrier stream. The method was based on using the FIA system of a new homemade ISNAG fluorometer with fluorescence measurement at ± 90º via a 2 × 4 solar cell.	0.01-0.4 mmol/L	1.736 µg/sample	43
Propranolol --- **Pure and pharmaceutical preparations**	CFIA – Turbidimetric	This method relied on a reaction between propranolol and phosphotungstic acid in a medium of water to produce a yellow precipitate. A long-distance chasing photometer (NAG-ADF-300-2) that contains two cells was applied for turbidity measurements.	0.007-13 (cellA) 5-15 (cell B) mmol/L	207.4792 ng/160 µL 1.2449 µg/160 µL	44
Propranolol --- **Pure and pharmaceutical preparations**	CFIA – Turbidimetric	A method was utilized to determine propranolol together with Bi (III) to prove the efficiency of the long-distance chasing photometer (NAG-ADF-300-2) using continuous flow injection. This project is based on a reaction between propranolol and Bi (III) in a medium of water to obtain a yellow precipitate.	0.1-25 (cell A) 1-40 (cell B) mmol/L	51.8698 363.0886 ng/200 µL	45

Atenolol --- **Pure and pharmaceutical preparations**	CFIA – Turbidimetric	Utilizing the long-distance chasing photometer NAG-ADF-300-2, which contains two cells, for turbidity measurements optimum parameters were studied to increase the sensitivity of the developed method. The method depended on the reaction between atenolol and ammonium molybdate reagent in a medium of distilled water, utilizing the technique CFIA.	0.1-3.5 (cell A) 0.3-3.5 (cell B) mmol/L	133.1680 532.6720 ng/100 µL	46
Atenolol --- **Pure and pharmaceutical preparations**	CFIA	The method depended on the reaction of atenolol with povidone iodine reagent in the medium of distilled water by using a continuous flow injection analysis technique. A long-distance chasing photometer (NAG-ADF-300-2) that contains two cells was applied for measurements.	2-19 (cell A) 5-19 (cell B) mmol/L	146.4848 ng/55 µL 2.6600 µg/200 µL	47
Methyldopa --- **Pure and pharmaceutical formulations**	CFIA – Turbidimetric	This method is dependent on the formation of an ion-pair compound between methyldopa and potassium hexacyanoferrate in an acidic medium to obtain a yellow precipitate complex utilizing the NAG-ADF-300-2 analyzer.	0.05-35 (cell A) 0.05-25 (cell B) mmol/L	1.4292 µg/200 µL	48
Warfarin --- **Pure form and pharmaceutical formulations**	CFIA – Turbidimetric	Formation of a turbid precipitated output yellow colour due to the reaction between warfarin and potassium dichromate. Using a homemade analyzer (NAG Dual and Solo 0-180^{o}) which contained two consecutive detection zones measuring cells 1 and 2 is described.	2.0-16 (cell 1) 0.7-16 (cell 2) mmol/L	0.58 0.55 mmol/L	49
Promethazine-HCl --- **Pure form and pharmaceutical formulations**	CFIA – Turbidimetric	This study is based on the reaction between promethazine-HCl acid and cadmium iodide in the presence of ammonium acetate to form a white precipitate. The attenuation of incident light at 0-180o served as a proxy for turbidity.	0.25-25 (cell A) 0.1-20 (cell B) mmol/L	360.5574 275.5830 µg/sample	50
Promethazine-HCl --- **Pure and pharmaceutical drug tablets**	CFIA – Turbidimetric	This method uses a low-cost analyzer, the NAG-ADF-300-2 homemade instrument. This work depends on the reaction between promethazine-HCl and phosphomolybdic acid in the presence of ammonium chloride to form a brownish-yellowish ion pair complex and precipitate.	0.5-30 mmol/L	2.1659 0.4332 µg/sample	51
Mesalazine --- **In pharmaceutical forms**	CFIA – Spectrophotometric	In this method, using a manifold with three channels, mesalazine was determined by an oxidative coupling reaction with o-coumaric acid after oxidation with sodium periodate in a basic medium. A blue-color complex was formed and measured at 659 nm.	5-150 µg/mL	4.94 µg/mL	52

Methyldopa --- **Pure and pharmaceutical formulations**	CFIA	A new, simple, sensitive, and fast-developed method was utilized for the estimation of methyldopa in pure form and pharmaceutical formulations via CFIA. The idea behind this method is that methyldopa and ammonium ceric (IV) nitrate will combine to form a burgundy color complex in water using an NAG-ADF-300-2 analyzer.	0.05-8.3 (cell A) 0.1-8.5 (cell B) mmol/L	952.8000 ng/200 µL 3.3348 µg/200 µL	53
Cefotaxime sodium --- **Pharmaceutical drugs**	CFIA – Turbidimetric	This method uses a handmade ISNAG-fluorimeter. The reaction between cefotaxime sodium and vanadium oxide sulfate produces a precipitate complex.	0.01-20 mmol/L	0.334 g/sample	54
Chlorpromazine-HCl --- **Pure form and pharmaceutical formulations**	CFIA – Turbidimetric	This method is based on precipitation reactions. Together, the NAG-ADF-300-2 analyzer was utilized to estimate chlorpromazine-HCl via attenuation of light at two steps: the first step at 110 mm and the second step at 60 mm with a 100 mm separation distance. The chlorpromazine-HCl reaction together mixes two reagents, sodium nitrite and sulfanilic acid, to form a yellowish-white precipitate.	0.5-45 (cell A) 1-43 (cell B) mmol/L	0.9984 49.9239 µg/sample	55
Ciprofloxacin-HCl --- **Pure form and pharmaceuticals**	CFIA – Turbidimetric	This method was based on the interaction between Ciprofloxacin-HCl and ammonium metavanadate as a precipitating agent to form an ion-pair association yellow precipitate in the salt medium. The assessment of Ciprofloxacin-HCl using CFI.	0.0-50 mmol/L	0.221 g/sample	56
Oxymetazoline and Vancomycin hydrochloride --- **Pure and pharmaceutical preparations**	CFIA – Spectrophotometric	The CFI-Spectrophotometric method is used for the determination of oxymetazoline (oxy) and vancomycin hydrochloride (van) in pure and dosage forms. The sulfadimidine using a safe chromogenic reagent via diazotization coupling together oxymetazoline and vancomycin hydrochloride to configure azo dyes was measured at 498 nm for oxymetazoline and 441 nm for vancomycin hydrochloride.	5-200 (oxy) 6-200 (van) µg/mL	2.19 (oxy) 1.79 (van) µg/mL	57
Mebeverine hydrochloride --- **In pharmaceutical formulations**	CFIA – Turbidimetric	This method was developed with a low-cost flow injection method and a specific turbidimetric method for the determination of mebeverine hydrochloride in pharmaceutical formulations by using a homemade NAG Dual and Solo (0-180º) analyzer, which contains two cells, for turbidity measurements.	1.0-6.5 (cell 1) 0.7-6.5 (cell 2) mmol/L	0.28 0.21 mmol/L	58

4. Conclusions

Continuous flow injection analysis is one of the most important, simple, low-cost techniques. It is used to analyze different types of drugs, solid, liquid, or capsule-shaped, with a meager detection

limit, high sensitivity, and a wide range of linearity compared to other techniques. In addition, FIA technology can automate other methods, making it possible to measure the sample and determine whether the product of the reaction is a residue or a clear solution. One of the advantages of this technique is that the response occurs within a closed system, so it is considered one of the green chemistry techniques that reduce the risks of exposure to hazardous materials and their inhalation by the analyzer.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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Ethical Clearance

This study has been approved by the Scientific Committee at the University of Baghdad/ College of Education for Pure Sciences (Ibn Al-Haitham).

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