REVIEW ARTICLE

Indirect Pharmaceutical and Organic Compounds Analysis by Atomic Absorption Spectroscopy

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ABSTRACT

The organic and pharmaceutical compounds have been estimated using traditional methods such as weights and volumes of different types with different concentrations. Still, these methods did not respond to the possibility of estimating trace quantities of these compounds, as well as chemical interactions and the length of time of analysis, and this led to the emergence of an increasing need to estimate trace quantities or archaeological of such compounds in various samples of industrial, food and biological origin, such as blood, generation, etc., using automated and susceptible methods. Many of these methods have emerged in separating and estimating organic and pharmaceutical compounds, including atomic, partial, chromatic, electrochemical, and other spectral methods. The most notable was the direct and indirect estimation of the use of flame-atomic and thermal atomic absorption spectroscopy. This review discusses atomic absorption spectroscopy and its applications in medicines—furthermore, a study of literature consisting of data from 1968–2022.

Keywords: Atomic absorption spectroscopy, Electrothermal atomic absorption spectrometry, Pharmaceutical, Organic compounds, Impurities

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INTRODUCTION

The chemical analysis technique in atomic absorption spectroscopy (AAS) is one of the most established and sensitive methods developed in recent years. It has had many applications preferring AAS in terms of high sensitivity in determining very minimal concentrations. In addition to the low detection limit for most elements and with limits less than (sub-ng/L) and the ease of dealing with samples, especially when they are available in very small quantities, analyzes are not allowed to be carried out with high reliability or reliability as the size of 10–50 microliters is sufficient to complete the analysis compared with a flame ablation that needs at least 1-mL to complete the analysis. Despite these advantages, however, the effects of origin that are high, especially in low concentrations, systemic errors arising from time-dependent geothermal processes in the graphite furnace and interference with evaporation, dissociation, and radiation absorption phenomena are problems with this technique. For the enjoyment of this technique with several advantages, including use it to estimate no less than 70 elements and amounts up to 10–14 grams with high selectivity and sensitivity and not needing samples with large volumes, and although this technique is used to estimate the mineral components mainly, it is currently used indirectly in assessing organic compounds also are rapid and economical in terms of sample size and weight used in the analysis. The sensitivity of this technique is about to match the sensitivity of the analysis with mass spectrometry, neutron activation technology and is better than X-ray fluorescence technology.

Atomic Absorption Spectroscopy (AAS)

The flame atomic absorption mechanism is the same as the thermoelectric atomic absorption mechanism except for the sample entry system and the atomization cell. As the flame is used to scatter the sample solution. Also, analysis with this mechanism takes less time.[1,2] The electrothermal atomic absorption mechanism is identical to the flame atomic absorption mechanism, except for the sampling system and the atomic cell and its need for electronics and signal devices faster than in flame atomic absorption spectroscopy (FAAS).[3] L'vov[4,5] discussed a personal idea about evolution in electrothermal atomic absorption spectrometry (ET-AAS) regarding progress and problems in the theoretical side of technology. L'vov believes that this idea is an important achievement in the development of the theoretical description of sensitivity, limit detection, and the shape of the calibration

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curve and photometric error, preferring electrothermal ablation over flame ablation in:

- The concentration of the analyzed substance reaches the detection limit when using the flame.
- The concentration of the analyzer in the measurement solution is very small.
- The size and weight of the analyte are small.[6]

Determination of Active Substances in Pharmaceutical Preparations

The AAS has several advantages, including high selectivity and sensitivity, as well as not having to need samples of large volumes and specifying no fewer than (70) elements and their accuracy and speed in analysis, many researchers in the field of analytical and pharmaceutical chemistry have motivated the adoption of this technique and its widespread use In the direct and indirect estimation of the various compounds and pharmaceutical preparations as a technique added to other techniques used by international drug constitutions. The method of determination AAS depends on the interaction of organic pharmaceutical compounds with a specific metal ion to form a complex in the form of precipitates or salts-like complexes and chelating complexes that can be extracted in an elected organic solvent and then measure the metal content of these complexes by flame or electrothermal atomic absorption. The quantitative assessment of drugs and organic compounds is carried out through this measurement. Often metals are found in pharmaceutical preparations and medicinal drugs within their chemical composition and the form of a significant ingredient, impurities, and preservatives in salts or organic-metal compounds. These only need to be treated with intermediation or extract and estimate the metal directly with this technique. For example, therapeutic metals such as aluminium, antimony, arsenic, barium, bismuth, calcium, chrome, copper, gold, iron, manganese, mercury, platinum, potassium, silicon, sodium, titanium, and zinc. The technique of atomic absorption has received wide acceptance by the scientific community interested in drug analysis indirectly for two reasons. The first is the increase in the extent of use. The second is the exploitation of the sensitivity of this technique in estimating the active organic substances in drugs and drugs, which helped many drug indexes and constitutions to replace the methods of correction and weighted measures and even the colour spectroscopy by methods of atomic absorption by flame or electrothermal in the estimation of these compounds.[7]

Determination of Impurities in Medications

Quality control of medicinal drugs and pharmaceutical preparations is one of the crucial statutes in this industry to control the limits of toxic substances in the final product that enter the drug through raw materials, auxiliary factors, preparation devices and vessels in which these medicines are packed, such as lead, arsenic, mercury, copper, iron, zinc and the rest of the other elements subject to prescribed limits.[8,9] Accordingly, it requires a high sensitivity to estimate lead and mercury, and these can be achieved using the electrothermal application or by generating hydride. The lead, cadmium, and thallium are evaluated in the drug and active substance tablets.[10-12] Aluminium is estimated in preparations against hemorrhage with electrophoresis, as clotting factors are obtained from human blood plasma by depositing it with aluminium hydroxide. The trace concentration of mercury is determined in pharmaceutical products such as sulfacetamide and nicotinamide.[13-15]

Determination of Organic Compounds and Pharmaceuticals by AAS

The indirect estimation of pharmaceutical and organic compounds results from their interaction with metallic elements, forming precipitated or extracted complexes as a first stage and then measuring the metallic content of these complexes with AAS technology. Through this measurement, the quantification of drugs and organic compounds is achieved. Medications can be estimated directly if they contain molecules on a metal atom within their chemical composition.[16] Despite the use of analytical atomic spectroscopy with emission and absorption methods in estimating some organic and pharmaceutical compounds in global pharmaceutical indexes such as british and american pharmacopoeias, the use of the indirect atomic absorption method in evaluating these compounds is increasing and replacing many of the traditional and mechanical techniques that were previously followed Because of the simplicity and speed of this method as well as its high accuracy, sensitivity and low detection limits.[16] Christian and Feldman[17] pointed out in 1968 that some negative ions and organic compounds could be estimated indirectly by AAS technology, and Kirkbright and Johnson[18] presented in 1973 a list of research related to this technology performed before 1973 and pointed out the great interest in developing indirect methods of AAS technology. For two reasons: the first is the increase in the extent of use, and the second is the exploitation of the sensitivity of this technique in estimating the organic compounds as in Table 1. Therefore, instances where a compendial procedure is usable or necessary no longer restrict applying the different AAS techniques. Now, only by the technical requirements chosen and the sensitiveness requirements of a given study are the number of analytes monitored in the pharmaceutical application of AAS restricted. In any case, it is clear that the conventional narrow testing approach to element analysis of pharmaceutical products has become unsatisfactory, in compliance with the publication of the european medicines evaluation agency (EMEA) guideline and chapter 232 proposed by the USP. Table 2 offers a wider list of papers related to pharmaceutical studies.

Direct Assessment of Organic and Pharmaceutical Compounds Using AAS

Some of the organic and pharmaceutical compounds contain in their composition a specific metal and thus can be directly estimated using AAS such as vitamin B12. It has one atom of cobalt for every part of the compound. The vitamin B12 rating was performed by measuring its cobalt content at 240.7 nm and

Table 1: Results derived from the literature to analyze some organic chemical compounds by measuring indirect atomic spectroscopy.

Organic compounds	*Basis of the method used*	*Solutes*	*Results obtained*	*Ref.*
Oxygen compounds				
Anthranilic acid	Reaction with cobalt (II) Followed by Extraction into (MIBK)	Co	L.R = 3-22 µg/mL^{-1} Recv% = 99.5	(19)
P-Amino benzoic acid	Reaction with copper in the presence bathe -phenanthroline, then extraction into (MIBK)	Cu	L.R = 13.7 - 38 µg/mL^{-1} Recv% = 100.6	(20)
EDTA	Complexation reaction with Nickal (II) followed by pH adjustment to Release the Ni	Ni	D.L = 4 µg/g^{-1}	(21)
Ketones	Reaction with copper acetate, followed by extraction into benzene	Cu	Recv range% = 96.7–102.2	(22)
Nitrogen compounds				
Urea nitrate	Reduction by cadmium metal and measured the cadmium ion by (AAS)	Cd	Recv% = 97.5 RSD% = 1	(23)
Nitro benzene	Formation of ion- association complex with bipyridylo-copper(II) (CuDp) and Phenanthrolino Copper(II)(CuPh) followed by extraction into(MIBK)	Cu	—	(24)
L-Histidine	Reaction with salicylaldehyde to give Schiff base, which reacts with copper(II), followed by extraction with (MIBK)	Cu	Recv% = 98.5 S.D = 0.7	(25)
Sulfur compounds				
Thioesters (sulfides)	Reaction with periodate and the excess of periodate precipitated by addition of $AgNO_3$ and the AgI_2 Dissolve in acetone measure	Ag	Recv% = 99.3 S.D = 2-6	(26)
Sulphapyridine	Precipitate the Ag or Cu-Sulpha Pyridine complexes, and measured the excess of the metals	Ag Cu	Recv% = 99.7 Recv% = 100.1	(27)
Carbohydrates				
Lactose Sucrose Glocose	Reaction with Periodic acid and precipitate the resultant iodate with $AgNO_3$, then dissolve the ppt. in aq. Ammonia to measured	Ag	D.L = 0.89 µg/mL^{-1} D.L = 1.93 µg/mL^{-1} D.L = 0.21 µg/mL^{-1}	(28)
Organo Metalic compounds				
Methyl mercury	Extract methyl mercury in toluene from the sample, then reduce Hg++ By $SnCl_2$ and measure the mercury by cold vapour technique	Hg	Recv% = 70-80 DL = 2 ng/g^{-1}	(29)
Tributyl tin(Bu3SnH)	Reduction by Na-borohydride then measured by hydride generation AAS	Sn	D.L = 2 ng	(30)
Dimrthylorsinic acid (DMAA)	Preconcentration by Cation- exchanger resin, then determination of As	As	D.L = 0.02 ng/mL^{-1} Recv% = 100 ± 6%	(31)
Gold containing drugs: Myocrisine solganal	Diluted in water, the aspirated direct in air-acetylene flame	Au	Recov range% = 97.6–100	(32)

using the oxygen-acetylene flame. Ribocarbo and cykloplatin platidiam medications contain Pt22 in their composition.

Indirect Estimation of Pharmaceutical Organic Compounds Using AAS Technology

Christian and Feldman[17] pointed out in 1968 that some negative ions and organic compounds could be estimated indirectly using AAS. Kirkbright and Johnson[18] in 1973 presented a list of research on this technology completed before this year. He pointed to the great interest in developing the indirect methods of AAS for two reasons. The first is the increased use, and the second is the exploitation of the sensitivity of this technique in estimating organic compounds. In 1984, Clark, Yacoub[45] showed a particular interest in analyzing organic drug

Table 2: Preparing samples and quantitative methods of pharmaceuticals using AAS techniques.

Drug	*Sample preparation*	*Solutes*	*Results obtained*	*Ref.*
Furaltadone methandone trazodone	Precipitate the ion-association complexes with $[Cd(SCN)_4]^{-2}$, and measured the excess of metal	Cd	7.2–72.16 µg/mL 6.9–69.18 µg/mL 8.1–81.6 µg/mL	(33)
Captopril	Formating of ion-association complex with PdI_4^{-2} and using cationic-ion exchanger resin to effluent the un-reacted Pd(II) and measured	Pd	R = 0.9936 1–40 µg/mL S.D = 0.039	(34)
Atropine diphenhydramine. Talazoline Levamisole	Precipitate the ion-association complex with potassium tetra iodomercurate $K_2[HgI_4]$, and measured the excess of metals.	Hg	13.6–138.8 µg/mL 5.6–58 µg/mL 3.6–39.6 µg/mL 4.8–48 µg/mL	(35)
Pizotifen Ketotifen Loratadine	Formation of ion-association complexes with $[Co(SCN)_4]^{-2}$, followed by extracted into the organic solvent	Co	10–74 µg/mL 12–95 µg/mL 10–93 µg/mL	(36)
Pindolol Propranolol Levamisole.	Precipitateion-association complexes with $[Mn(SCN)_4]$ and measured the exsess of metal.	Mn	1.14–17.07 µg/mL 1.18–17.75 µg/mL 1.08–16.24 µg/mL	(37)
Cefotaxime	After alkali-hydrolysis react with silver nitrate ($AgNO_3$), and lead acetate ($(CH_3COO)2Pb$), precip. the complexes and measured the excess of metals	Ag Pb	14.2–57 µg/mL 13.3–53.4 µg/mL	(38)
Ephedrine Cinchonine Chlorpheniramine	Precipitate ion-association complex with ammonium Reinecke, and the unreacted chromium measured by (Atomic emission spectroscopy)	Cr	1.6–52 µg/mL 2.64–85.8 µg/mL 3.12–101.4 µg/mL 5.52–180.4 µg/mL 2.72–75.85 µg/mL	(39)
Amylocaine bromhexine	Formation of ion-association complexes with ammonium reinecke followed by extracted into 1.2-dichloroethane	Cr	3–120 µg/mL RSD % = 1 RSD = 3%	(40)
Amodiaquine Chloroquine Primaquine	Participate in the ion-association complexes with $[Co(NO_3)_4]^{-2}$, $[Cd(SCN_3)_4]^{-2}$ and ammonium Reinecke and measured the unreacted metals	Cd Co Cr	0.155–3.87 µg/mL	(41)
Enalapril Ramipril	Formation of copper II - enalapril Complex followed buy extracted into chloroform. Formation of the ternary complex [Fe III,$(SCN)^{-2}$, ramipril], followed by extracted into methylene chloride	Cu Fe	19–32 µg/mL	(42)
Lignocaine Amprolium	Formation of ion-association complex with $[Co(SCCN)_4]^{-2}$ and measured the unreacted metal Formation of ion-association complex with ammonium Reinecke and measured the excess of the metal	Co Cr	0.135–135.4.4 µg/mL RSD% = 0.92 Recv% = 99.18–48 0.158–157.6 µg/mL RSD% = 0.92 Rec% = 100.12–0.34	(43)

compounds using ET-AAS. Lowering the metal determination limits using graphite furnaces was reflected in compounds indirectly estimated. The following is a quick review of some drugs, pharmaceutical preparations, and their interactions with metals. They were used in FAAS and can be used to analyze these compounds with ET-AAS release:

A- Sulfonamides[27]

These compounds interact quantitatively at pH = 8 with silver or copper ions to form a precipitate of the metal sulfonamides. The precipitate is isolated, and the excess designation is made of silver or copper in the filtrate by FAAS.

B-Ethambutol[46]

This drug interacts with copper ions in the basal circumference (pH = 8-11-5) to form a recoverable copper complex with the methyl isobutyl ketone solvent.

C-Chloramphenicol[47]

This compound, whether pure or in its preparations such as plankton, eye drops, and capsules, reacts with cadmium metal, as the cadmium metal is quantitatively reduced by chloramphenicol.

Determination Pharmaceutical of by Using Indirect FAAS

Rasheed and co-workers study the development of new analytical methods to determine the trifluoperazine hydrochloride (TFPH) drug compound (used in the treatment of schizophrenia) in some pharmaceutical preparations by

the indirect FAAS. TFPH determination at pharmaceutical trace concentrations. This approach included synthesizing and extracting a TFPH-Pt(IV) complex at a particular pH in an organic solvent. FAAS measured the complex's platinum absorptiveness, and the TFPH concentration was calculated indirectly.[48] For studies of low concentration TFPH, an indirect FAAS approach was proposed with good accuracy and precision in pharmaceutical preparations. The process depends on forming a metal complex into an orange-yellowish liquid between TFPH and palladium (II).[49]

Determination Pharmaceutical of by Using Indirect ET-AAS

Rasheed and co-workers conducted several studies on estimating drugs indirectly using ET-AAS technology. Desferrioxamine (DFOM) is one of the compounds widely introduced in the 1960s as a drug for treating excess iron in the blood and aluminium poisoning associated with chronic dialysis and aging diseases. A new ET-AAS method has been established to determine DFOM in pharmaceuticals as DFOM–Au (III).[50] The reaction has been utilized to estimate this drug using ET-AAS's technique indirectly after fixing the best conditions by identifying the gold with the ET-AAS using a graphite tube coated with zirconium. The second method has been developed; DFOM was evaluated as DFOM-V (V) after being extracted with benzyl alcohol and evaluated in pharmaceutical preparations.[51] The gold and vanadium elements were chosen to estimate the drug for the clear response to the reaction, the distinctive color of the reaction, and the biological significance of both gold and vanadium. But the gold complex with the drug is unknown, which means that a new complex has been prepared in this research and drug analysis. And they mentioned that three methods could be used to estimate organic compounds using a technique, including:

Direct Measurement Method

Some organic compounds already contain a specific metal and can thus be estimated using AAS as the Vitamin B12 estimate, which contains one atom of cobalt per compound.[52]

Precipitation Method

In this way, the organic compounds are estimated by depositing them by a specific metal (such as Ag, Cu, Ni), then by AAS technology, and this estimation is done either by dissolving the precipitate or by the leachate, as in estimating some organic compounds containing sulfur using silver.[53]

Solvent Extraction of the Complexes

In this method, the organic compounds interact with a known increase of the metal ion to form chelate complexes or form ion-association complexes that are subsequently extracted by a suitable organic solvent. The absorbance of the metal present in these extracted complexes is measured by flame technique or by a graphite furnace. And it is possible to calculate the non-reactive increase of the metal in the aqueous layer and then estimate the organic compounds indirectly, as in evaluating the alcohols using chromium.[54]

Liquid-Liquid Extraction

The extraction process (liquid-liquid) is one of the widely used separation methods, and this method is distinguished from others by its simplicity (requires no more than a separating funnel), speed (only needs a few minutes), and inclusiveness (it can be applied to low and high concentrations of the same accuracy). It is selective from aqueous solutions to organic and vice versa, and it also has cleanliness. That is, it is free of associated pollution. This method depends on the solute distribution between two solvents (two phases) that are not immiscible. In general, one phase is aqueous, and the other is organic. And the solute that dissolves in each of the two phases is distributed between them in a certain percentage. The required separation is accomplished by this method when setting chemical parameters (such as pH), masking agent and the appropriate solvent. To achieve a suitable extraction of the metal ions in a suitable organic solvent, a complex, non-charged component is formed. The metal water molecules are replaced by components dissolved in the organic phase. To reach this state, one of the following two systems can be followed: First, the chelate extraction system; second, the ion-association complex extraction system. The extraction process includes three successive stages: Firstly, the formation of the uncharged complex; secondly, the distribution of the extract complex; thirdly, the interactions of the complex in the organic layer.[55]

Using Extraction with AAS Technology

The main objective of using the liquid-liquid extraction method in AAS is to increase the estimated components' concentration or remove chemical interference.[55] Because of the many advantages of this method, it has increased its use with AAS technology in other fields, including:

- Estimating some of the extracted components through their effect on the extraneous elements as a blocking agent and estimating the EDTA.
- Redox processes.
- Estimating some thermally stable inorganic components after converting them into volatile chelating complexes, as in the interaction of the elements Fe (III), Cr (VI), Cu (II) with derivatives (acetylacetone).
- Estimating the extracted components through their equivalent of the combined metal, as in estimating salicylic acid.
- Magnification reactions, as in determining phosphates with molybdophosphoric acid.

Use of Extraction with Electrothermal Ablation (ET-AAS)

In addition to the improvements introduced to the AAS method by flame ablation method, the use of extraction with ET-AAS added new features:

- The use of very small volumes of the extracted organic solvent (up to 1-µL) has led to more safety and security requirements and increased the possibility of dealing with a more significant number of organic solvents.

- Avoid the problems resulting from fluctuations in the flame by using organic solvents ionizing from the ablation process.
- Removing the solvent completely before dissolving the analyte resulted in removing the problems of partial absorption of the structure and the absence of the roots phenomenon.
- The presence of a thermocouple avoids the problems resulting from using organic solvents with flame.

CONCLUSION

The review will provide insight into the various applications of AAS in pharmaceutical and organic compound analysis. In addition to the quality of products and patient safety perspectives, the need to analyze pharmaceutical and organic compounds' elements are growing insignificantly. The analytical problems involved with the analyte matrix are critical for the effectiveness of the study in choosing the sample preparation and estimating some influential functional groups within the pharmaceutical compounds (hydroxamic group) using the electrothermal AAS and molecular absorption spectroscopy and investing these interactions in developing rapid and sensitive analytical methods and low detection scores to estimate drug compounds of industrial and biological importance using: Indirect AAS technology. The AAS technique allows all elements to be monitored at concentrations between sub-ppb and percentage levels.

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