

Spectrophotometric Determination of Pharmaceutical by Oxidative Coupling of 4-Aminoantipyrine: A Short Review

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Abstract: During the 1990's, pharmaceutically active compounds such as lipid regulating drugs, analgesics, antibiotics, antiseptics, hormones and chemotherapy and beta-blocking heart drugs were detected in wastewaters, streams and ground-water resources across. A simple, sensitive and selective spectrophotometric methods have been developed for the quantitative estimation of some antibiotic drugs. The method involves the formation oxidative coupling of drug using 4-aminoantipyrine. The method (Oxidative coupling) is based on the condensation of aminoantipyrine with phenols in the presence of an alkaline oxidizing agent to yield coloured product the absorbance of which is monitored at wavelengths.

Key words: Pharmaceutically, antibiotics, antiseptics, wastewaters, spectrophotometric, oxidative coupling, alkaline

INTRODUCTION

Over the last 20 years, pharmaceuticals have been receiving increasing attention as potential bioactive chemicals in the environment (Rivera-Utrilla *et al.*, 2013; Kummerer, 2009). Although, pharmaceuticals have been present in water for decades, their levels in the environment have only recently begun to be quantified and acknowledged as potentially hazardous to ecosystems (Fent *et al.*, 2006; Jjemba, 2006). Pharmaceuticals are continuously introduced into the environment and are prevalent at small concentrations (Rivera-Ustrila *et al.*, 2013) which can affect water quality and potentially impact drinking water supplies, ecosystem and human health (Sires and Brillas, 2012). The pharmaceuticals are mainly excreted in urine and faeces as such or as metabolites. They are carried to wastewater treatment plants where they pass through various treatment processes. The removal in wastewater treatment plants has been, however, shown to be incomplete and thus the pharmaceuticals are found as contaminates in surface waters throughout the world (Lindqvist *et al.*, 2005; Aljeboree and Alshirifi, 2018a-c; Ziylan and Ince 2011). These sources of pharmaceuticals in the environment have been extensively reviewed (Kaur *et al.*, 2016). Therapeutic groups most commonly detected in

water are anti-inflammatories and analgesics, antidepressants, antiepileptic, lipid-lowering drugs, β -blockers, antiulcer drugs and antihistamines, 7 antibiotics (Rivera-Utrilla *et al.*, 2013; Aljeboree and Alshirifi, 2018a-c; Bush, 1997).

The 4-aminoantipyrine 4-amino-1, 5-dimethyl-2-phenyl-1, 2-dihydro-3H-pyrazol-3-one (Fiamegos *et al.*, 2002) is an aromatic substance a yellow crystalline powder has analgesic, antipyretic and anti-inflammatory properties (Aljeboree and Alshirifi, 2018a-c; Saber and Mautner, 2012). The formula is C₁₁H₁₃N₃O, molar volume is 168.3 L/mol and relative molecular mass is 203.24 g/mol. Aljeboree and Alshirifi (2018a-c), Wang *et al.* (2013) and Elgemeie *et al.*, (2017) it is useful chromogenic reagent for the determination of various phenols in aqueous solution (Fiamegos *et al.*, 2002) for biochemical reactions producing peroxides or phenols. 4-aminoantipyrine stimulates liver microsomes and is also used to measure extracellular water. The derivatives derived from 4-aminoantipyrine have shown various pharmacological activities such as antipyretic, anti-inflammatory, analgesic, anti-oxidant, anti-fungal properties and anti-microbial. Elgemeie *etal.* (2017); Adam (2013) due to accurate efficacy, use easily, diverse dosage forms and low prices, analgin plays an important role in clinical medicine. Analgin is used in developing countries (Wang *et al.*,

2013). Sutcliffe (2003), however, AAP usually produces side effects such as the risk of agranulocytosis (Lang *et al.*, 2009). Although, AAP is scarcely ever administered as an analgesic because of side effects as a raw material, it is mostly used to produce 4-aminoantipyrine derivatives which have better biological activities (Cunha *et al.*, 2005). The toxic effect of AAP on experimental animals was reported (Vinagre and Collases, 2007). AAP can reduce blood flow (Sunderji *et al.*, 1984) and 13,14-dihydro-15-keto prostaglandin F₂ alpha concentration after it is infused into the blood. AAP can form stable complexes with heme (Vinagre and Callares, 2007). Several works have reported the degradation of 4-AA by ozonation (Munoz *et al.*, 2009; Simerson and Kelly, 1948) and Advanced Oxidation Processes (AOPs) such as UV/H₂O₂ (Gomez *et al.*, 2008) and photoelectrocatalysis with a TiO₂/ITO anode AOPs are eco-friendly technologies that involve the generation of Reactive Oxygen Species (ROS) like the strong oxidant hydroxyl radical (\bullet OH) which can destroy many organics including drugs and their metabolites that tend to be resistant to conventional methods (Cavalcante *et al.*, 2016). However, there exists no previous information on the ability of a powerful electrochemical AOP (EAOP) like Electro-Oxidation (EO) to remove 4-AA from water. However, using to determination is based on the oxidative coupling of phenols with AAP by oxidants such as H₂O₂, persulfate and K₃Fe(CN)₆ to yield highly colored diagnostic quinoneimine dyes (Munoz *et al.*, 2009). On the other hand, coupling reaction of phenols with 4-aminoantipyrine is a well-established process for the determination of oxidants such as hydrogen peroxide, in industrial analytes (Ribeiro *et al.*, 2009; Vojinovic *et al.*, 2004). The same reaction can also be used for the determination of glucose in blood by using phenol, AAP and glucose oxidase (De-Oliveira *et al.*, 2005). Interestingly, Cu²⁺ ions have been reported to act as an oxidant in the coupling of catechol with 4-aminoantipyrine (Mohamed *et al.*, 2004). However, no studies have been carried out on the construction of Cu²⁺-selective probes employing this useful reaction. In this study, we report a new colorimetric signaling system for Cu²⁺ ions based on a metal ion-induced coupling of phenols with 4-aminoantipyrine. Upon treatment with Cu²⁺ ions, coupling of phenols with 4-aminoantipyrine smoothly proceeded to form a new quinoid dye with a prominent color change from colorless to pink. Since, AAP is widely used for different applications, AAP as an aromatic pollutant exposes in the environment.

MATERIALS AND METHODS

The problem of pharmaceutical pollution: The pollution produced by pharmaceutical products in surface and

ground waters has been acknowledged by many countries as an environmental problem and has led to the establishment of a research field known as pharmaceuticals in the environment. The pharmaceutical industry uses the designation active pharmaceutical ingredients to describe products that are pharmacologically active, resistant to degradation, highly persistent in aqueous medium and potentially able to produce adverse events in water organisms and have a negative impact on human health (Rivera *et al.*, 2013).

Therapeutic groups most commonly detected in water are: anti-inflammatories and analgesics (paracetamol, acetylsalicylic acid, ibuprofen and diclofenac), antidepressants (benzodiazepines), antiepileptics (carbamazepine), lipid-lowering drugs (fibrates), β -blockers (atenolol, propranolol and metoprolol), antiulcer drugs and antihistamines (ranitidine and famotidine), antibiotics (tetracyclines, macrolides, β -lactams, penicillins, quinolones, sulfonamides, fluoroquinolones, chloramphenicol and imidazole derivatives), other substances (cocaine, barbiturates, methadone, amphetamines, opiates, heroin and other narcotics) (Rivera-Utrilla *et al.*, 2013 Bush, 1997).

The following characteristics of pharmaceuticals, most of which have a molecular mass <500 Da (Lipinski *et al.*, 1997), differentiate them from conventional industrial chemical contaminants: they can be formed by large and chemically complex molecules that vary widely in molecular weight, structure, functionality and shape; they are polar molecules with more than one ionizable group and the degree of ionization and its properties depend on the pH of the medium; they are lipophilic and some of them are moderately soluble in water; pharmaceuticals such as erythromycin, cyclophosphamide, naproxen and sulfamethoxazole can persist in the environment for more than a year and others, e.g., clofibrac acid can persist for various years and become biologically active through accumulation and after their administration, the molecules are absorbed, distributed and subject to metabolic reactions that can modify their chemical structure (Rivera-Utrilla *et al.*, 2013).

RESULTS AND DISCUSSION

Anti-inflammatory and analgesic drugs discussed in this review: The NSAIDs constitute a heterogeneous group of drugs with analgesic, antipyretic and anti-inflammatory properties that rank intermediately between corticoids with anti-inflammatory properties on one hand and major opioid analgesics, on the other. Considering the contamination level of anti-inflammatory and analgesic drugs in aqueous environment, aspirin, ketoprofen, ibuprofen, diclofenac, naproxen, paracetamol,

Table 1: Basic information of selected NSAIDs.

NSAIDs	Formula	Mass	pKa	LogKow	CAS No.	Solubility	References
Diclofenac	C ₁₄ H ₁₁ Cl ₂ NO ₂	296.2	4.91	4.51	15307-79-6	2	Scheytt <i>et al.</i> (2005)
Aspirin	C ₉ H ₈ O ₄	180.0	3.50	1.20	50-78-2	4600	Cantabrana <i>et al.</i> (1995)
Ibuprofen	C ₁₃ H ₁₈ O ₂	206.3	4.51	4.51	15687-27-1 4	21	Vieno <i>et al.</i> (2007)
4-AAP	C ₁₁ H ₁₃ N ₃ O	203.24	4.07		83-07-8	0.1	Aljeboree and Alshirifi (2018a-c), Wang <i>et al.</i> (2013)
Ketoprofen	C ₁₆ H ₁₄ O ₃	230.3	4.15	3.18	4-53-1 4	144	Anonymous (2009)
Paracetamol	C ₈ H ₉ NO ₂	151.2	9.38	0.46	103-90-2	12900	Chen <i>et al.</i> (2002)

4-aminoantipyrine and mefenamic acid can be considered as the most significant ones. Their main physicochemical characteristics are given in Table 1.

Aspirin: The 2-acetoxybenzoic acid is one of the most popular pain killers, this compound as well as its derivatives is known to exhibit high toxicity to a wide range of aquatic organisms in water bodies (Cleuvers, 2004).

Paracetamol: N-(4-hydroxyphenyl)acetamide is one of the most frequently detected pharmaceutical products in natural water. As an example, it was detected in a concentration as high as 65 Lg L-1 in the Tyne River (UK) In addition, by chlorination in WWTPs 2 of its identified degradation compounds were transformed into unequivocally toxicants (Bedner and MacCrehan, 2006).

Ibuprofen: (IBP), (RS)-2-(4-(2-methylpropyl)phenyl) propionic acid, a non-steroidal anti-inflammatory, hugely global consumed is one of the most common drugs found in water (Guedidi *et al.*, 2013) has a high acute toxicity, quite similar toxicological consequences in aquatic environment have been shown by the intermediates formed by biological treatment (Feng *et al.*, 2013). Possibly presenting a potential hazard for human health (Guedidi *et al.*, 2013).

4-Aminoantipyrine: The (4AAP, Formula I) is a metabolite of aminophenazone and is an aromatic substance with analgesic, antipyretic, antiphlogistic and anti-inflammatory properties (Chen and Chen, 2009; Adam 2013; Lang *et al.*, 2007; Mishra and Kumar, 2011; Teng *et al.*, 2011). Although, today 4AAP is scarcely ever administered as an analgesic drug because of its side effects, it is still used as a precursor of 4AAP derivatives which have better biological activities (Cunha *et al.*, 2005).

Ketoprofen: (RS)-2-(3-benzoylphenyl)propanoic acid is metabolized mainly in conjugation with glucuronic acid (a cyclic carboxylic acid having structure similar to that of glucose) and excreted mainly in the urine 85% (Feng *et al.*, 2013).

Different physical properties of the co-crystals 4AAP: 4-Aminoantipyrine is an active pharmaceutical ingredient

with powerful anti-inflammatory, antipyretic and analgesic properties. Its amino functional group is highly reactive and it will react readily with ketones and aldehydes at room temperature. Due to its chemical reactivity it has been widely used as a nitrogen scavenger species against hydroxyl radicals (Santos *et al.*, 2010). Although, 4AAP has many recognized therapeutic benefits, the use of 4AAP has been associated with agranulocytosis. In order to reduce adverse effects in cases of drugs with considerable side effects a number of derivatives using the 4AAP backbone have been made (Bailey, 1983; Fiamegos *et al.*, 2002). In addition, the pharmaceutical industry often turns to the synthesis of salts and co-crystals where the different physical properties of the co-crystals may enhance the bioavailability of the drug to date, 251 derivatives of 4AAP have been reported in the Cambridge Structural Database (Groom and Allen, 2014) where the modifying adduct has attached to the amino nitrogen atom. Yet, despite the drive to synthesize salts and co-crystals of pharmaceuticals such as 4AAP, only 5 molecular salts of 4AAP have yet been reported, Yang *et al.*, (2012) of which 2 are simple salts with halide counter-ions. No co-crystal of 4AAP has ever been reported. The scarcity of salts of 4AAP and the complete absence of any co-crystals of the species are presumably due to the fact that it reacts covalently with the potential co-former rather than co-crystallizing on a supramolecular basis.

Firstly, in the “Knowledge-based approaches to co-crystal design 4AAP (Wood *et al.*, 2014). Wood stresses the importance of choosing a suitable synthon. 4AAP possesses amine and carbonyl functional groups which can undergo hydrogen bonding. Both amine and carbonyl functional groups form robust heterosynthons with carboxylic acids and so, carboxylic acids were therefore, chosen as the co-formers in all our attempts at co-crystallization. Secondly, solvent choice is critical in determining whether a salt or co-crystal will be formed. A polar solvent stabilizes ionic species through charge-charge or charge-heteroatom interactions whereas non-polar solvents inhibit the formation of charged species, since, they cannot interact with the ions (Levy, 2008). Thirdly, the effect of pKa on co-crystal formation has recently come into the spotlight. Childs *et al.* states that the absolute separation of the pKa values of a molecule and its potential co-former

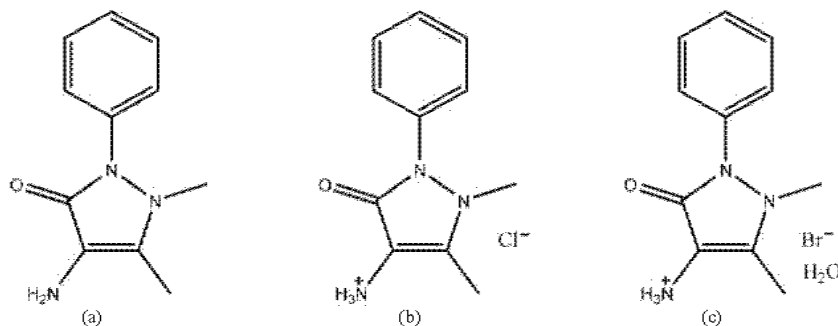


Fig. 1: The structure of 4-aminoantipyrine and its reported simple salts: a) 4-aminoantipyrine (SIKBAR), (LOYXEE); b) 4-aminoantipyrine-4-aminium chloride (HUKTIS) and c) 4-aminoantipyrine-4-aminium bromide monohydrate (PAXSOY)

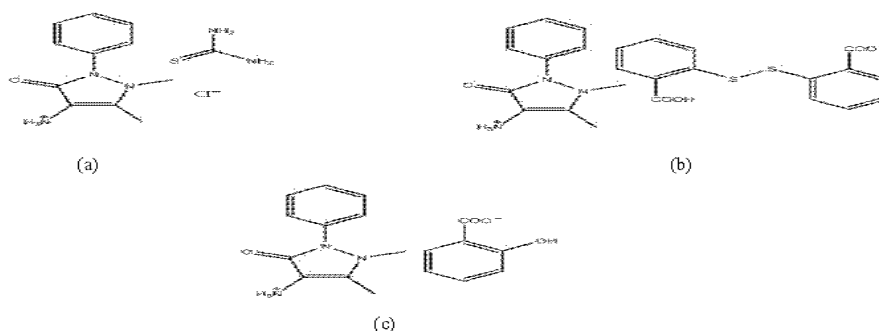


Fig. 2: Previously synthesized salts of 4-aminoantipyrine: a) 4-aminoantipyrine-4-aminium thiourea chloride (EVOLLIL); b) 4-aminoantipyrine-4-aminium 2, 2'-dithiodibenzoate (PUGHEF), (PUGHEF01) and c) 4-aminoantipyrine-4-aminium salicylate (DUHYOV)

plays a critical role in determining whether the supramolecular synthesis of two such molecules will result in a salt or in a co-crystal (Cruz-Cabeza, 2012). More recently, Lemmerer *et al.* presented empirical evidence to suggest that an absolute ΔpK_a separation of <3 ($[\Delta pK_a] = [pK_a(\text{base}) - pK_a(\text{acid})]$) will greatly enhance the formation of a co-crystal rather than a salt (the “Rule of Three”) (Lemmerer *et al.*, 2015). Our strategy, therefore was to attempt co-crystallizations of carboxylic acids with 4AAP and to take into account the calculated pK_a values of the co-formers as well as considerations of the polarity of the solvent. Co-crystallizations were first attempted with a derivative of 4AAP (namely 4-aminoantipyrine-N-acetamide) of which there are several reported co-crystals in an attempt to find suitable solvents and co-formers as a proof of concept exercise.

The crystal structure of 4AAP has been reported by Li *et al.* (2013) and by Mnguni and Lemmerer. (2015) (Fig. 1a). 4AAP has a pK_a of 4.07 ± 0.65 (based solely on the calculated pK_a for the species in aqueous solution).

Its exocyclic nitrogen atom is readily protonated and forms a chloride salt in the presence of hydrochloric acid and a bromide salt when refluxed in an aqueous dibromomethane solution (Fig. 1b and c) (Chitradevi *et al.*, 2015). The crystal structure of these two salts have been reported by Chitradevi *et al.* (2015) prepared a three-component salt (Fig. 2a) by acidifying the 4AAP with an aqueous solution of hydrochloric acid and then refluxing with thiourea (pK_a 14.91 ± 0.29) in ethanol ($[\Delta pK_a] = 10.84$) (Ziylan and Ince, 2011). A molecular salt of 4AAP and 2, 2'-dithiobenzoic acid was synthesized first by Fazil *et al.* (2012) and was crystallized from ethanol and from a 50% ethanol/water mixture, respectively (Fig. 2b). Huo commented that the components were selected as building blocks for creating a co-crystal but proton transfer was observed in the ethanol medium. The calculated pK_a of 2, 2'-dithiobenzoic acid is 3.02 ± 0.36 which is much closer to the 4.07 pK_a of 4AAP (with $[\Delta pK_a] = 1.05$) and therefore more likely to co-crystallize than co-formers with larger pK_a separations. However, the polar solvent (ethanol) lends itself to salt

formation as the polar solvent stabilizes the ionic species through charge-charge and charge-heteroatom interactions. Finally, a salt of 4AAP with salicylic acid (pKa 3.01±0.10) was prepared in aqueous solution by Chitradevi *et al.* (2015) ([ΔpK_a] = 1.06)11 (Fig. 2c).

Van Staden *et al.* (2005) found a sequential injection spectrophotometric determination of the ritodrine hydrochloride is described. The method is based on the condensation of 4-aminoantipyrine with phenols in the presence of an alkaline oxidizing agent to yield a pink coloured product the absorbance of which is monitored at 503 nm. A linear concentration range of 3.1-123.5 $\mu\text{mol L}^{-1}$ and a detection limit (as 3 σ -value) of 1.0 $\mu\text{mol L}^{-1}$ were obtained. The precision was 2.4 and 2.3% Relative Standard Deviation (R.S.D.) at 6.2 and 15.4 $\mu\text{mol L}^{-1}$, respectively Van Staden *et al.* (2005).

Aljeboree and Alshirifi (2018a-c) found a highly sensitive in the presence of optimum methods by using spectrophotometric to described for the determination of phenylephrine hydrochloride in aqueous solutions. The method is based on the oxidative coupling reaction of phenylephrine hydrochloride with 4-aminoantipyrine and potassium ferricyanide to form dirty ping water soluble stable product at λ_{503} nm (Aljeboree and Alshirifi, 2018a-c).

Aljeboree and Alshirifi (2018) found a spectrophotometric sensitive, selective and inexpensive method for the determination of phenolic drug phenylephrine hydrochloride. The method depended on the oxidation of phenylephrine hydrochloride by potassium ferricyanide and coupling of reagent 4-aminoantipyrine to give intensely colored absorbs light strongly in the spectral region of 503 nm. Beer's law was obtained in the concentration range of 5-100 mgL^{-1} . Good linearity ($r^2 = 0.9992$) under the optimum condition. Calculation the standard error, Limit of Detection (LOD) (signal/noise = 3), Limits of Quantitation's, LOQ, accuracy and precision (R.S.D., %) better than 1% (Aljeboree and Alshirifi, 2018a-c).

Hong *et al.* (2015a, b) they found selective Cu^{2+} signaling by the oxidative coupling of anilines with 4-aminoantipyrine was investigated. The Cu^{2+} -assisted reaction between N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3, 5-dimethylaniline sodium salt and 4-aminoantipyrine resulted in the pronounced color change from colorless to bluish green, with a detection limit of 2.1×10^{-6} M in 90% aqueous acetonitrile (Hong *et al.* 2015a, b).

Ana *et al.* found a spectrophotometric method for the determination of glucose in blood sample is proposed. This method is based on selective oxidation of β -d-glucose in the presence of phenol, 4-aminoantipyrine and peroxidase, produces a red

compound ($\lambda_{\text{max}} = 505$ nm). Beer's law is obeyed in a concentration range of 10-100 $\mu\text{mol/L}$ glucose with an excellent correlation coefficient ($r = 0.9991$) at pH 6.5 with a Relative Standard Deviation (RSD) <3%. The flow rate of 2.0 mL/min and injecting 200 μL sample volumes was adopted. The detection limit of the method is 5.7 $\mu\text{mol/L}$ (Ana *et al.*, 2015).

Ribeiro *et al.* (2009) found the determination of Hydrogen peroxide (H_2O_2) and the evaluation of scavenging capacity against this species were performed using five colorimetric reactions which were adapted to flow injection analysis. The reactions chosen were based on the oxidation of iodide (I⁻ method), on the formation of titanium-peroxide complex (TiP method), on the formation of titanium-xylene orange-peroxide complex (TiXoP method) on the oxidation of 3, 3', 5, 5'-tetramethylbenzidine (TMB method) and on the co-oxidation of the phenol-4-sulfonic acid and 4-aminoantipyrine (PSA/4-AAP method) (Ribeiro *et al.*, 2009).

Van Staden *et al.* (2005) found a fully automated sequential injection spectrophotometric method for the determination of phenylephrine hydrochloride with 4-aminoantipyrine in the presence of potassium ferricyanide. The absorbance at 503 nm. A linear range 0.5-17.5 mgL^{-1} . The detection limit (as 3 σ value) was 0.09 mgL^{-1} and repeatability was 0.8 and 0.6% at 2.5 and 5 mgL^{-1} , respectively (Beyene and Van Staden, 2004).

Koshy and Mitchner (1963) they found 2 colorimetric methods are described for phenylephrine hydrochloride using potassium ferricyanide and 4-aminoantipyrine as reagents. Using 2% sodium borate as the medium, a sufficiently stable color is obtained. This method is suitable for the analysis of phenylephrine in common tablet formulations without prior separation. A second procedure using tris(hydroxymethyl) aminomethane (Tham) buffer, pH 9 and isopropyl alcohol as medium gives a color stable for over 1 h (Koshy and Mitchner, 1963).

Beyene and Van Stedan (2004) found A simple, fast, economical and automated sequential injection spectrophotometric. The method is based on the condensation reaction of etilefrine hydrochloride with 4-AAP in the presence of alkaline potassium hexacyanoferrate and the absorbance of the colored product measured at 503 nm. The detection limit (as 3 σ value) was 0.1 mg L^{-1} and precision was 2.7 and 1.5% at 1 and 2 mgL^{-1} , respectively, (Beyene and Van Stedan, 2004).

Kim *et al.* (2015) found a new Cu^{2+} -selective chromogenic probe system based on the oxidative coupling of phenols with 4-aminoantipyrine was

developed. Cu^{2+} ions promoted facile coupling of phenols with 4-AAP to yield quinoneimine dyes. The phenol-4-aminoantipyrine probe system showed chromogenic Cu^{2+} signaling by prominent color change from colorless to pink with a detection limit of 8.5×10^{-7} M. The signaling of Cu^{2+} ions in practical samples using tap water and simulated semiconductor wastewater was also tested (Hong *et al.*, 2015a, b).

Hassan *et al.* (2015) found the method is based on the oxidative coupling reaction of barbituric acid with 4-AAP and potassium iodate to form purple water soluble stable product at λ_{510} nm. Good linearity for both methods was obtained ranging from $2\text{-}60 \mu\text{g mL}^{-1}$, $5\text{-}100 \mu\text{g mL}^{-1}$ for batch and FI techniques, respectively. The limit of detection (signal/noise = 3) of $0.45 \mu\text{g mL}^{-1}$ for batch method and $0.48 \mu\text{g mL}^{-1}$ for FI analysis was obtained (Hassan *et al.*, 2015).

Hong *et al.* (2015a, b) found a new Cu^{2+} -selective probe was developed based on the Cu^{2+} -induced sequential hydrolysis and oxidative coupling reactions of 4-aminoantipyrine-appended 8-hydroxyquinoline derivative 1Cu^{2+} -assisted hydrolysis of the enamine moiety of Schiff base 1 afforded its constituents, 4-aminoantipyrine and 8-hydroxyquinoline-2-carboxaldehyde (Hong *et al.*, 2015a, b).

Beyene and Van Staden (2004) found a fully automated sequential injection spectrophotometric method for the determination of phenylephrine hydrochloride in pharmaceutical preparations is reported. The method is based on the condensation reaction of the analyte with 4-AAP in the presence of potassium ferricyanide. The absorbance of the condensation product was monitored at 503 nm. The detection limit (as 3 σ value) was 0.09 mgL^{-1} and repeatability was 0.8 and 0.6% at 2.5 and 5 mgL^{-1} , respectively (Beyene and Van Stedan, 2004).

Nakano *et al.* (1994) found a kinetic-catalytic method is described for the determination of iron, based on its catalytic effect on the oxidative coupling of 4-AAP with *N,N*-dimethylaniline to form an indamine dye ($\lambda_{\text{max}} = 555 \text{ nm}$) in the presence of hydrogen peroxide with photometry detection (Nakano *et al.*, 1994).

Chung *et al.* (1993) they found a spectrophotometric flow injection method for the determination of H_2O_2 in aqueous solution is presented. The technique is based on the oxidative condensation reaction between 1-Anilino-naphthalene-8-Sulfonic Acid (ANSA) and 4-aminoantipyrine (AAP) in the presence of H_2O_2 . A detection limit of $0.3 \mu\text{M}$ was achieved with a linear dynamic range extending to $50 \mu\text{M}$. The typical relative standard deviation is 1.5% or better. The structure of the reaction product has been identified (Chung *et al.*, 1993).

CONCLUSION

Due to research advancement and discoveries in the field of medical science literature indicates that pharmaceuticals use and release into the environment are unavoidable these pharmaceutical (biologically active) compounds were not fully metabolized by the body and excreted out in wastewater. The release of pharmaceutical compounds into environment causes disturbance of aquatic flora and fauna, a risk to human health and development of multi-drug resistant microbial strain method for the determination of drug by colorimetric spectrophotometric the oxidative coupling reaction of 4- aminoantipyrine in the presence of oxidative reagent in the any medium to give colored chromophore which is spectrophotometric ally estimated at wavelength.

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