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A COMPREHENSIVE REVIEW ON ANALYTICAL METHODS FOR THE ESTIMATION OF PARACETAMOL, A VERY COMMON ANALGESIC AND ANTIPYRETIC DRUG

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ABSTRACT

Acetaminophen (Paracetamol) is currently one of the most commonly used analgesic and antipyretic**.** Various analytical methods used for the estimation of paracetamol have been reviewed in this paper. These include Chromatography, Fluorimetry, spectroscopy and electrochemical methods to determine the amount of Paracetamol in bulk drug, pharmaceutical formulations and biological fluids.

KEYWORDS: Paracetamol, analytical methods, estimation, formulation, biological fluids.

INTRODUCTION

Acetaminophen (Paracetamol) is currently one of the most commonly used analgesic and antipyretic.[1] It is used extensively in the treatment of mild to moderate pain and fever. In case of an overdose, it may cause hepatic necrosis but it is a very safe analgesic at therapeutic doses.[2] It is used to reduce fever, cough and cold, and to reduce mild to moderate pain, including instances of tension headache, migraine headache, muscular aches, chronic pain, neuralgia, backache, joint pain, general pain and toothache.[3-5] It is also useful in osteoarthritis therapy and it is sometimes used for management of cancer pain[6] Recent research suggests that paracetamol may help to protect from changes leading to hardening of arteries that cause cardiovascular disease.[7] It also remains the analgesic of choice for people with asthma.[8] There is also some evidence to suggest that paracetamol may offer some protection against ovarian cancer.[9] Because paracetamol is being increasingly used for therapeutic purposes, its determination and quality control are of vital importance. Its determination in pharmaceutical dosage forms (quality control) and in biological fluids (overdose monitoring) remains great interest.

Chemically Paracetamol is N-(-4-hydroxyphenyl) acetamide, N-Acetyl-p-aminophenol with molecular formula $C_8H_9NO_2$ and molecular weight 151.17 g/mol. It is a white crystalline powder freely soluble in methanol, ethanol (95%), glacial acetic acid and insoluble in water and practically soluble in hot water. Its Melting point ranges from 168°C-172°C. Mechanism action of the drug is by inhibiting prostaglandin biosynthesis in conditions associated with low levels of cellular peroxides (pain, fever).Due to metabolic immaturity, neonatal clearance of paracetamol is different from adults. Sulphate conjugation is well developed in a neonate and is the major metabolic pathway for paracetamol clearance. Glucuronidation clearance is not well developed and plays a minor role in paracetamol clearance in neonates. With maturation these clearance pathways for paracetamol change. The usual adult ratio of 2:1 glucuronide to sulphate conjugates of paracetamol is achieved by 12 years of age. Acetaminophen usually is well tolerated at recommended therapeutic doses. Rash and other allergic reaction occur occasionally. The most serious acute adverse effect of overdose of acetaminophen is a potentially fetal hepatic necrosis. It is contraindicated in Patients who show hypersensitivity reaction to the salicylate.[10-12]

ANALYTICAL METHODS FOR PARACETAMOL

Many different analytical methods have been reported for the estimation of paracetamol in bulk and dosage form as well as in biological fluids.

For Estimation in Bulk Drug and Pharmaceutical Formulation

Spectroscopic methods

Ellcock C.T.H, Fogg A.G,[13] developed a colorimetric determination of Paracetamol by means of an indophenol reaction. The spontaneous oxidation of alkaline mixtures of p-aminophenol and phenol with molecular oxygen to form indophenols has been made the basis of this colorimetric procedure for the determination of paracetamol via its hydrolysis is product, p-aminophenol. In this method Paracetamol was determined by an

indophenols reaction after hydrolysis and oxidation with acidified hypochlorite.

Krishna K. Verma, Archana Jain.[14] developed spectrophotometric determination of paracetamol with iodylbenzene. Paracetamol (N-acetyl-4-aminophenol) has been determined spectrophotometricaly by its oxidation with iodylbenzene in acetone to produce the yellow-orange N-acetyl-1,4-benzoquinoneimine, which attains maximum colour intensity with in 1 min and absorbs maximally at 430 nm. The maximum molar absorptivity is 1.58×10^{3} l. $mole^{-1}$ cm^{-1}.

Martinez calatayud J, M. Pascual Marti M.C &.Sagrado Vives S.[15] developed a flow injection-spectrophotometric determination of paracetamol .The procedure is based on the oxidation of the analyte with potassium hxacyanoferrate(III) and reaction of the N-(hydroxyphenyl)-p-benzoquinonimine produced with phenol. Both reactions are carried at 80˚C and in aqueous ammoniacal solution. Concentration of paracetamol in 0.25-30 ppm range are determined.

Salah M. sultan.[16] developed a rapid spectrophotometric method for the determination of paracetamol. It is based on oxidation with dichromate for 15 min in 6*M* sulphuric acid at 80° and measurement at 580 nm.

Basilio Morelli[17] developed a spectrophotometric method for the determination of paracetamol in pure form and in tablets. The method depends on reaction of the drug with ammonium molybdate in strongly acidic medium to produce molybdenum blue. Beer's law was followed for concentrations of up to 6 μg ml^{-1} of paracetamol and the detection limit ($p = 0.05$) was 0.10 μg ml^{-1}. The molar absorptivity at 670 nm was 2.6×10^{4} 1 mol^{-1} cm^{-1} and the relevant Sandell's sensitivity of the reaction was 0.0059 μg cm^{-2} per 0.001 absorbance unit.

Martinez Calatayud j, Sagrao Vives S.[18] developed a flow injection-spectrophotometric determination of paracetamol. The procedure is based on the reaction of the analyte with potassium hexacynoferrate (III) previously retained in an anionic exchange column and the reaction of the N-(hydroxyphenyl)-p-benzoquinonimine so produced with phenol. The oxidation is carried out at room temperature and in aquous ammoniacal solution.

Issopoulos PB[19] developed a sensitive spectrophotometric determination of acetaminophen. A sensitive, accurate and precise spectrophotometric method is described for the determination of Acetaminophen in pure form and in pharmaceutical formulation. The principle involved is the reduction, of Fe(III)toFe(II) by the drug in the presence of o-Phenanthroline , when the orange-red coloured chelate complex $[Fe(II)\text{-}(o\text{-}Phen)_3]^{2+}$the ferroin complex was formed, and its absorbance was measured at 510nm. The calibration graph was rectilinear over the rang 0.25-10.0ppm.

Zouhair Bouhsain et al.[20] developed a procedure for the direct FTIR Spectrophotometric determination of paracetamol in pharmaceuticals. The method is based on the solubilization of paracetamol in a 10% v/v ethanol in CH2Cl2 solution and direct absorbance measurement at $1515cm^{-1}$, using the baseline established at 1900 cm^{-1} for measurement correction. The procedure can be carried out in both the stopped flow and flow injection modes(FI), in both instances the sensitivity is approximately 0.09 A ml mg^{-1}, the limit of detection being 8 μgml^{-1} in the stopped–flow mode and 33 μgml^{-1} in the FI mode.

Andrew D. Trafford et al.[21] developed a Near-infrared (NIR) reflectance spectroscopy to determine rapidly and non-destructively the content of paracetamol in bulk by collecting NIR spectra in the range1100–2500 nm and using a multiple linear regression calibration method.

Eustaquio. A et al.[22] developed a Near infrared transmittance spectroscopy to determine the paracetamol in a pharmaceuticals. Spectra were recorded on an instrument that measures the transmission of intact tablets over the wavelength range 600–1900 nm. Spectral data were processed by using two multivariate calibration methods, viz. stepwise multiple linear regression (SMLR) and partial least-squares regression (PLSR).

Ayora Canada M.J et al.[23] developed a simple flow-through UV optosensing device for the determination of paracetamol, based on its transient retention and concentration on a suitable active solid support (Sephadex QAE A-25 anion-exchange resin) packed in the flow cell and continuous monitoring of its native absorbance on the solid phase at 264 nm. The sample was injected into a 0.08-M NaCl carrier stream at pH 11 by using a simple monochannel. A very good linear response was found in the concentration range 0.5-8.0 mg/ml.

Andres Criado et al.[24] reports a continuous flow-based spectrophotometric method for the determination of paracetamol in pharmaceuticals. Dilute samples containing paracetamol are continuously hydrolysed in an alkaline medium, using a household microwave oven, to *p*-aminophenol, which reacts with *o*-cresol in 3.5 M NaOH. The blue derivative thus formed exhibits an absorbance maximum at 620 nm. The detection limit of the method is 0.2 μg ml^{-1} and the system obeys Beer's law from 0.6 to 20 μg ml^{-1}.

Koos. J et al.[25] developed a simple method for the rapid determination of paracetamol in pharmaceutical formulations. The method involves oxidation of paracetamol by potassium hexacyanoferrate (III) and a subsequent reaction with phenol in the presence of

ammonia. The blue complex formed is measured at 630 nm. The calibration curve is linear up to 60 mg/ml.

Ihssane. B et al.[26] developed a spectrophotometric determination of paracetamol in pharmaceutical Preparation Using Hetrerocyclic Coupling Agent . The method is based on the hydrolysis of the amide to amino group followed by diazotization and coupling reaction with 8-quinolonol. The resulting coloured azo dyes exhibit maximum absorption at 498nm. The experimental conditions were optimized and Beer's law was obeyed over the applicable concentration ranges of 1-25 µg/ml.

Buddha Ratna Shrestha and Raja Ram Pradhananga[27] developed a spectrophotometric Method for the Determination of Paracetamol which is based on the reaction of Paracetamol with 1-napthol or resorcinol which give an azodye and the concentration of paracetamol was investigated spectrophotometrically. The azodyes formed with both 1- napthol and resorcinol as coupling agents follow Lambert Beer's law in the range of 0 to 10 µgmL-1 of paracetamol. The molar absorptivity and Sandell's sensitivity for azodye coupled with 1-napthol were found to be 1.68×104 Lmol-1cm-1 and 9.0 ngmL-1cm-2, respectively. The molar absorptivity and Sandell's sensitivity for azodye coupled with resorcinol were found to be 2.86×104 Lmol-1cm-1 and 5.3 ngmL-1cm-2, respectively. Both coupling agents had been applied successfully in the analysis of paracetamol in pharmaceutical preparation.

Pavan Kumar. G V et al.[28] developed a simple and accurate method for the determination of paracetamol in pharmaceutical formulations. Paracetamol was dissolved in 4M sulphuric acid and treated with 10.0 mg of sodium bismuthate in the presence of 1M HCl and 1M acetic Acid. It exhibited a stable bluish-violet colour. The coloured compound showed a λmax at 550 nm. Beer's law was obeyed in the range of 100-300µgmL-1 in 1M HCl and300-800 µgmL-1 in 1M acetic acid medium, with detection limits of 0.03µgmL-1 in 1M HCl and 0.05 µgmL-1in 1 M acetic acid medium respectively.

Martinez Calatayud.J et al.[29] reported a flow-injection spectrofluorimetric determination of paracetamol . It is based on the oxidation of the analyte with potassium hexacyanoferrate(III) immobilized on an anion-exchange resin. The fluorescence being enhanced with *N,N*-dimethylformamide. Concentrations of paracetamol in the range 0.04–17.60 mg $l^{-1}$are determined with a relative standard deviation of 1.5%. The injection rate is 25 samples h^{-1}.

JoseLuis vilchez et al.[30] developed a spectrofluorimetric method for the determination of paracetamol . It is based on the oxidation of the analyte to give the fluorophore 2,2′-dihydroxy-5,5′-diacetyldiaminebiphenyl. Sodium hypochlorite was used as an oxidizing reagent and the optimum pH was found to be 10.0 (sodium carbonate-boric acid buffer solution). The linear concentration range was 0.1–100.0 µg ml^{-1} .The detection limit was 0.01 µg ml^{-1} and the relative standard deviation was 1.2%. The method has been satisfactorily applied to the determination of paracetamol in pharmaceutical formulations and biological fluids.

Gregorio AlapontA et al.[31] developed the system Luminol–H_2O_2–$Fe(CN)_6^{3-}$ for the indirect determination of paracetamol. The method is based on the oxidation of paracetamol by hexacyanoferrate (III) and the subsequent inhibitory effect on the reaction between luminol and hydrogen peroxide. The procedure resulted in a linear calibration graph over the range 2.5–12.5 µg ml^{-1}.

Altair B et al.[32] demonstrated the native fluorescence of paracetamol (PA) in the solid state , allowing the development of a rapid, simple and rugged method for direct analysis of pharmaceutical formulations. It is easily adaptable to any spectrofluorimeter, and no chemical treatment of the sample is needed. The fluorescence measurements (λ_{ex} = 333 nm; λ_{em} = 382 nm) are performed directly on the powdered sample, the active substance being diluted in lactose, maize starch, polyvinylpyrrolidone, talc and stearic acid. The influence of the ingredients of PA formulations is discussed. Fluorescence intensity is linearly dependent on PA concentration within the 100–400 mg g^{-1} range. The analytical frequency is 200 h^{-1}. Detection and quantification limits were estimated within the 13.0–16.7 and 43.1–55.7 mg g^{-1} ranges for samples with different ingredient proportions. The method was applied to pharmaceutical formulations and the relative standard deviation of results was <2.7% ($n = 20$) for all tested ingredient proportions. Results were compared with those obtained by a method recommended by the British Pharmacopoeia and no statistical difference between methods was found at the 95% confidence level.

Hossein Tavallali and Yahya Hamid[33] developed spectrofluorometric determination of Paracetamol in pharmaceutical formulations .A simple and sensitive method for determination of paracetamol, based on the oxidation reaction between paracetamol and cerium (IV) for determination of paracetamol has been described. The fluorescent species is the reduction product of cerium (IV) and has excitation and emission wavelength at 255 and 348nm respectively. The fluorescent intensity of the system is linear over the range of 150-750 µg/l of paracetamol with detection limit and relative standard deviation(RSD) of 20 µg/l, and 1.22% respectively.

Chromatographic methods

Sinan Suzen et al.[34] developed a reverse-phase high-performance liquid chromatographic method for the determination of acetaminophen in pharmaceutical formulations. A C18 stationary phase is used with a methanol-water (1/2 v/v) mixture at the flow rate of 1.78 ml/min with the spectrophotometric detection at 193.3

nm. Sulphamethoxazole is used as an internal standard and analysis is completed within 5 minutes.

Nadia M. Mostafa[35] developed a stability indicating method for the determination of paracetamol in its pharmaceutical preparations by TLC densitometric method. This method consists of dissolving the drug in methanol and then spotting the solution on a thin layer of silica gel G254. Paracetamol was separated on silica gel using the mixture of the mobile phase, ethyl acetate: benzene: acetic acid in a ratio (1:1:0.05 v/v/v). Absorbance measurements (detection of reflectance) of the separated drug were carried out at 250 nm. Calibration curves were established in the concentration range of 5–20 mcg/spot for paracetamol. Quantitation is achieved by comparing the area under the peaks obtained from scanning the thin layer chromatographic plates in a spectrodensitometer. The method has been successfully applied to pharmaceutical preparations (capsules) and the results obtained were statistically compared with those obtained by applying the reference method.

S. S. Narwade[36] developed an HPLC method for the estimation of paracetamol in Pharmaceutical formulations. It is very sensitive less time consumable but sharp peaks recorded. stainless steel column 20cm x 4.6mm packed with ocadesilance bonded to porous silica 10 micrometer is used. Flow rates 0.2ml /min. at 20 micrometer loop injector & spectrophoto-meter set at 272 nm. Retention time of std 4-ammino phenol & sample solution 4.388 & 4.542 respectively.

Mohan Thippeswamy et al.[37] developed a new method for estimation of Paracetamol in pharmaceutical dosage form by reverse phase- high performance liquid chromatography using a reversedphaseC18 column (250 mm X 4.6 mm i. d, 5 µm particle size) with isocratic elution. A mixture of Acetonitrile: 10 mm potassium dihydrogen orthophosphate buffer(15:85 v/v), pH 2.5 was used as a mobile phase at the flow rate of 1.0 ml/min and detectorwave length at 210 nm. The retention time of paracetamol was found to be 5.7 minutes. The linearity of paracetamol was in the range of 25.00 to 60.00µg/ml. This method showed an excellent linear response with the correlation coefficient (R2) value of 0.999 for the paracetamol. The recovery of the drug was ranged from 99.51 to 100.68%. An intra-day and inter-day precision study of the new method was less than the maximum allowable limit (% RSD<2.0).

Electroanalytrical methods

Chengyin Wang et al.[38] developed differential pulse voltammetry for determination of paracetamol at a pumice mixed carbon electrode with the pumice weight percent of 6% (m/m) in 0.1 mol^{-1} H_2SO_4. The anodic peak potential is *ca*. 0.640 V (*us*.SCE). There is a good linear relationship between the peak current paracetamol concentration in the range of 6.0×10^{-8}_1.0×10^{-6} mol l^{-1}, and 2.0×10^{-6}-9.8×10^{-5} mol l^{-1} with the detection limit of 2.0×10^{-8} mol l^{-1},Compared with the carbon paste electrode.

Kanita Tungkananuruk et al.[39] developed a method using cyclic voltammetry for the determination of acetaminophen in paracetamol tablets. The peak current from acetaminophen in 0.10 mol L^{-1} phosphate buffer pH 7.0 was measured with a glassy carbon electrode versus Ag/AgCl. The optimum step potential and scan rate were found to be 0.0005 V and 0.1000 V/s, respectively. The linear calibration range was 3-240 µg ml^{-1}, and the detection limit and recovery were 3.0 µg ml^{-1} and 99.1%, respectively.

Natasa Pejic et al.[40] proposed a new procedure for kinetic determination of paracetamol in pharmaceuticals . The method is based on potentiometric monitoring of the concentration perturbations of the matrix reaction system being in a stable non-equilibrium stationary state close to the bifurcation point. In the case considered as the matrix system, the Bray–Liebhafsky oscillatory reaction is used. The response of the matrix system to the perturbations by different concentrations of paracetamol is followed by a Pt-electrode. Proposed method relies on the linear relationship between maximal potential shift, ΔE_m, and the logarithm of added paracetamol amounts. It is obtained in optimized experimental conditions for variable amounts of paracetamol in the range 0.0085 and 1.5 µmol. The sensitivity and precision of proposed method were quite good (0.0027 µmol as the limit of detection and 2.4% as R.S.D.).

ShangGuan X et al.[41] developed a differential pulse voltametric determination of paracetamol at a carbon ionic liquid electrode. The electrochemical behavior of paracetamol in 0.1 M acetate buffer solution (pH 4.6) was investigated at a traditional carbon paste electrode (TCPE) and a carbon ionic liquid electrode (CILE) fabricated by replacing nonconductive organic binders with a conductive hydrophobic room temperature ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate (B mim PF(6)).The results showed that the CILE exhibited better reversibility for the electrochemical redox of paracetamol. The method has been applied to the determination of paracetamol in tablet and urine samples and the average recovery of paracetamol was 98.5% and 99.3%, respectively.

He N,Xu L, Wang T, Du J, Li Z,[42] developed a method for the determination of paracetamol with a novel and sensitive electrochemical sensor based on porous – carbon paste electrode . It was demonstrated this exhibits high sensitivity towards Paracetamol in comparison with polypyrrole modified carbon paste electrode (PCPE), carbon nanotube modified carbon paste electrode (CPE), and a detection limit as low as 0.05 mM was obtained.

Ying Zhang et al.[43] developed a highly sensitive method for determination of paracetamol by adsorptive stripping Voltametry paste electrode modified with nanogold and

glutamic acid. A reliable and simple sensor was fabricated by modifying a carbon paste electrode with nano sized gold particles and poly glutamic acid for determination of paracetamol (PAR). The modified electrode exhibited an effective catalytic response to the oxidation and reduction of PAR with good reproducibility and stability. The determination was carried out by differential pulse adsorptive stripping voltammetry after a 30 s accumulation time with an open circuit potential and under stirring. The calibration curve is linear in the range from 0.05-70µM of PAR (with a correlation coefficient of 0.9990), and the sensitivity is 1.51µA·μM^{-1}.

Nada F. Atta, Ahmed Galal and Shereen M. Azab[44] investigated a highly sensitive and simple method for the determination of acetaminophen using gold nanoparticles modified carbon paste electrode. It displayed excellent electrochemical catalytic activities towards the oxidation of Paracetamol. Under optimized experimental conditions in differential pulse voltammetry (DPV) technique, the sensitivity of ACOP was improved greatly and gave a linear response over the ranges 5.0×10−8 to 2.7 ×10−4 mol L−1 with a detection limit of 1.46 x 10-8 mol L−1. This procedure was successfully applied for the assay of paracetamol in pharmaceutical formulations.

Yogeswaran Umasankar et al.[45] developed a method for the determination of Acetaminophen Present in Pharmaceutical Drug Using Functionalized Multi-Walled Carbon Nanotube Film. Carboxylic acid functionalized multi-walled carbon nanotube (f-MWCNTs) was synthesized by simple acid treatment of pristine multi-walled carbon nanotube. The surface morphology of f-MWCNTs showed the existence of functional groups on the outer sidewalls of f-MWCNTs. These functional groups, –OH and C=O species of carboxylic acid on f-MWCNTs were confirmed by Fourier transform infrared spectroscopy. The f-MWCNT was applied to modify the glassy carbon electrode (GCE) to study the electrocatalysis of acetaminophen. The electrochemical studies showed better diffusion coefficient with stable signal, enhanced effective area and reduced charge transfer resistance results in presence of f-MWCNTs film on GCE. The f-MWCNTs film modified GCE also showed enhanced electrocatalysis towards acetaminophen. The sensitivity of f-MWCNTs film towards acetaminophen (9.6 µA µM-1 cm-2) was higher than the value obtained for bare GCE (0.33 µA µM-1 cm-2). Similarly, the limit of detection of acetaminophen at f-MWCNTs film (39.8 nM) was lower than other electrodes. The DPV and selectivity studies revealed that f-MWCNTs modified GCE can be efficiently applied for acetaminophen determination in real samples.

Abdul Rauf Khaskheli, Jan Fischer[46] developed a differential pulse voltammetric determination of paracetamol in tablet and urine samples at a micro-crystalline natural graphite–polystyrene composite film modified electrode.The experimental parameters, such as pH of Britton–Robinson buffer and potentials for regeneration of the electrode surface, were optimized. Under optimized conditions in Britton–Robinson buffer (pH 4.0), linear calibration curves were obtained in the range of 0.02–100 µmol l^{-1} of paracetamol. The limit of determination was 0.034 µmol l^{-1} which shows high sensitivity of the developed method. The method was applied for the determination of paracetamol in pharmaceutical formulations and in human urine model samples.

Hanieh Ghadimi, Ramin M.A Tehrani, Abdussalam Salhin Mohamed Ali[47] developed a novel glassy carbon electrode (GCE) modified with a composite film of poly (4-vinylpyridine) (P4VP) and multiwalled carbon nanotubes (P4VP/MWCNT GCE) for the voltammetric determination of paracetamol (PCT). This novel electrode displayed a combined effect of P4VP and MWCNT on the electro-oxidation of PCT in a solution of phosphate buffer at pH 7. Hence, conducting properties of P4VP along with the remarkable physical properties of MWCNTs might have combined effects in enhancing the kinetics of PCT oxidation. The P4VP/MWCNT GCE has also demonstrated excellent electrochemical activity toward PCT oxidation compared to that with bare GCE and MWCNT GCE. The anodic peak currents of PCT on the P4VP/MWCNT GCE were about 300 fold higher than that of the non-modified electrodes. By applying differential pulse voltammetry technique under optimized experimental conditions, a good linear ratio of oxidation peak currents and concentrations of PCT over the range of 0.02–450 µM with a limit of detection of 1.69 nM were achieved.

For Estimation in Biological Fluids

Spectroscopic methods

Patrica C. Damiani, Maria E. ribone & Alejandro C.olivieri[48] developed a rapid Determinaton of Paracetmol in Blood Serum Samples by First-Derivative UV Absorption Spectroscopy. It involves no sample pretreatment,extracton or derivatization procedure ,other than a standard deproteinizing technique with trichloroacetic acid.The results can be applied to both therapeutic and toxic levels of paracetamol.

Parojcic.J, Karljikovic-Rajic K, Duric Z, Jovanvic M, Ibric S.[49] developed a second-order derivative UV Spectrophotometric method for direct determination of paracetamol in urine . In the present study the UV spectra of investigated samples were recorded over the wavelength range 220-400 nm (lambda step 0.21 nm ; scan speed 60 nm/min) and second order derivative spectra were calculated. Second-order derivative spectra of different blank urine samples displayed the presence of a zero-crossing point at 245-247 nm.The zero-order absorption spectra of paracetamol in water displays maximum absorbance at 243 nm, while in second derivative spectra, a minimum peak at 246 nm was observed.

Fathima Shihana, Dhammika Dissanayake, Paul Dargan and Andrew Dawson[50] developed a modified low-cost colorimetric method for paracetamol (acetaminophen) measurement in plasma. The paracetamol assay used in this study was based on the Glynn and Kendal colorimetric method with a few modifications to decrease the production of nitrous gas and thereby reduce infrastructure costs. Preliminary validation studies were performed using spiked aqueous samples with known concentrations of paracetamol. Subsequently, the results from the colorimetric method for 114 stored clinical samples from patients with paracetamol poisoning were compared with those from the current gold-standard high-performance liquid chromatography method.The recovery study showed an excellent correlation ($r2 > 0.998$) for paracetamol concentrations from 25 to 400 mg/L. The final yellow color was stable for at least 10 min at room temperature. There was also excellent correlation with the high-performance liquid chromatography method ($r2 = 0.9758$). This colorimetric paracetamol assay is reliable and accurate and can be performed rapidly, easily, and economically.

Chromatographic methods

Hackett. L.P, Dusci L.J.[51] described a procedure that gives quantitative extraction of paracetamol from serum together with derivatisation and gas chromatography. This provides a simple method that facilitates the rapid estimation of the drug in serum in the range 5-500mg/litre.

Demotes-Mainard F, Vincon G, Jarry C, Albin H.[52] described a Plasma determination of paracetamol using HPLC. Paracetamol is extracted with diethylether in the presence of an internal standard, beta-hydroxyethyl theophylline. The extracts are analysed using reversed phase chromatography (Radial Pak C18 column), the mobile phase consisting of a buffer mixture of 0.01 mol/l acetate (PH4)-acetonitrile (920-80, v/v). The method is simple, rapid, precise and sensitive (lower level of sensitivity 0.13 mol/litre). it was used successfully in a pharmacokinetic studies.

Kotal P, Perlik F, Vlachova E, Kordac V.[53] reports the determination of paarcetamol in the serum by means of high-performance liquid chromatography. Prior to analysis, the sample is purified by deproteination with perchloric acid. The analysis is carried out isocratically on the reverse phase (SEPARON SIX C18, 5 microns,150××3.7mm).The mobile phase consists of 40% methanol in 0.4% phosphoric acid. The detection is performed at 254nm. The calibration curve is linear in the region 6.62-331mumol.l^{-1}(1.0-50.0 micrograms.ml^{-1})with 95% reproducibility. The sensitivity of detection is 1.3mumol.l^{-1}(0.2mg.ml^{-1}).

Whelpton, R, Fernandes, K, Whilknson, K. A.and Goldhill, D. R.[54] developed a method for the determination of paracetamol (acetaminophen) in blood and plasma using high performance liquid chromatography with dual electrode coulometric quantification in the redox mode. Samples were prepared by precipitation with trichloroacetic assay solution and the drug quantified by reversed phase liquid chromatography with dual electrode electrochemical detecton in the redox mode (oxidation at +0.25V followed by reduction at -0.15V). The limit of detection was 0.1 mg/L for a10μL sample of blood or plasma, the coefficient of variation at this concentration being 11.4%.

Speed DJ, Dickson S.J, Cairns E.R, and Kim N.D.[55] described analysis of Paracetamol Using Solid-Phase Extraction, deuterated Internal Standards, and Gas Chromatography-Mass Spectrometry A rapid method for determining paracetamol (acetaminophen) inwhole blood and liver tissue samples is described. Blank plussingle-point calibration gives reliable quantitation at therapeuticand higher concentrations. Whole blood and liver tissue samplescontaining a deuterated internal standard were extracted using Bond Elut Certify columns. Butyl derivatives were formed usingn-iodobutane and tetramethyl ammonium hydroxide under mildconditions and were extracted into ethyl acetate as a cleanup step.Recovery was better than 90%, and sample preparation time wasless than 2 h. Gas chromatograph run time was less than 20 min.SIM of two ion pairs formed by electron impact ionization resultedin intraday coefficients of variation (CV) less than 3.03% (7.48%in liver) and interday CVs less than 8.93% (for midtherapeuticconcentrations in whole blood). Linearity was observed fromsubtherapeutic to high, fatal levels. This method has been appliedto forensic cases and has significantly reduced analytical time whileimproving casework quality.

Bose D et al.[56] developed a rapid determination of Acetaminophen in Physiological Fluids by Liquid Chromatography Using sodium dodecyl sulfate at pH 7 as Mobile Phase.Acetaminophen is determined in serum and urine samples without any pretreatment step in a C18 column. Acetaminophen is eluted in less than 5 min with no interference of the protein band. The use of electrochemical and UV detection is compared. Linearities ($r > 0.999$), as well as intra- and interday precision, are studied in the validation of the method. Limits of detection (LOD) are also calculated to be 0.56, 0.83, and 0.74 ng/mL in micellar solution, serum, and urine using electrochemical detection.

Electro analytical methods

Christie. I et al.[57] performed direct electrochemical determination of paracetamol in plasma. A simplified, reagentless method for the determination of paracetamol (0–2 mM) in plasma is described, based on the electrochemical oxidation of paracetamol. The technique has been adapted for assay in biological fluids by the use of a perm selective cellulose acetate membrane, and an outer diffusion-limiting, microporous polycarbonate

membrane treated with dimethyldichlorosilane to impart biocompatibility. The results obtained agreed well with those obtained by a routine enzymic method. The limit of detection is 0.1 mM paracetamol.

CONCLUSION

After the scrutiny of literatures it has been observed that many methods are reported for the estimation of paracetamol in its formulation and in biological fluids. For determination in formulation and in biological fluids different techniques available include Chromatography, electrochemical, spectrophotometry, and fluorimetry. It can be concluded that UV Spectrophotometry and HPLC are the most simple and easy methods for paracetamol estimation in pharmaceutical formulations while HPLC can be widely used for paracetamol estimation in biological fluids like plasma, urine and serum. Thus, this current review gives details of the analytical methods available on paracetamol which can be helpful for further research work studies on it.

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