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A review of various analytical methods of promethazine hydrochloride in pharmaceutical formulation, biological matrixes and misuse.

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Abstract: A review of various analytical methods determination of promethazine hydrochloride in pharmaceutical formulation, biological matrixes and misuse. Promethazine HCL is a first-generation antihistamine belonging to the phenothiazine family. Due to it is significant important many analytical techniques have been developed for both quality control of the drug in pharmaceutical dosage forms and the detection of potential misuse by patients. this study aims to make a review for various analytical methods for promethazine hydrochloride in pharmaceutical formulation and biological material and to camper between various method and show which method is most applicable. Official methods for analysis of promethazine hydrochloride are BRITISH, EUROPEAN AND UNITED STATE PHARMACOPEIA. Various analytical methods have been reported for analysis of promethazine hydrochloride in pure dosage form, in combination with other drugs in biological fluid. Spectroscopic methods, chromatographic methods, electrochemical methods and bioanalytical method. This review caver the period from 2000 to now. Spectroscopic method is the most applicable method for analysis of promethazine HCL alone UV/VIS is method of choice within spectroscopic methods. Chromatographic methods are methods of choice for analysis of promethazine in combination with other drugs in formulation and biological fluid.

Keyword: promethazine hydrochloride analytical methods, pharmaceutical formulation, misuse, biological fluid

1. Introduction:

1.1 background:

Promethazine hydrochloride (PH) [N,N-dimethyl-1-(10H-phenothiazine-10-yl)propan-2-amine] hydrochloride, is a first-generation antihistamine belonging to the phenothiazine family(1) , fig (1)

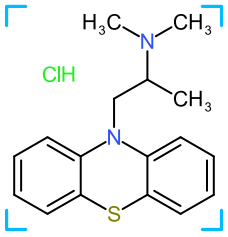

Figure 1- chemical structure of promethazine hydrochloride.

White or faintly yellowish, crystalline powder. Solubility Very soluble in water, freely soluble in ethanol (96 per cent) and in methylene chloride. mp About 222°C, with decomposition (2).

Promethazine which were introduced in the 1950's as antipsychotic drugs are still widely used in the treatment of moderate to severe mental illnesses including schizophrenia. The drug also is widely used as antihistaminic, antiemetic, antipruritic, analgesic and anticholinergic, and it has a strong sedative effect and anti-motion sickness (1). However, promethazine hydrochloride can cause adverse effects in humans, such as endocrinal, cardiac and reproductive alterations. Therefore, its determination in commercial formulations and biological samples is extremely important (3). The therapeutic importance of promethazine has prompted many researchers to develop and describe different methods for determination of promethazine in pharmaceutical formulations as well as body fluids (1). Promethazine disposition is characterized by a large volume of distribution and a high blood clearance (1.141 min-'). Less than 1% of the dose is excreted unchanged in the urine, therefore total body clearance is essentially metabolic clearance. In accord with this high clearance the oral availability of promethazine is only 25%.

The absorption of promethazine from the gastrointestinal tract exceeds 80% in most subjects. Minimal metabolism by the gastrointestinal mucosa is implicated(4).

2. Analytical methods for analysis of promethazine hydrochloride:

2.1 official methods:

2.1.1. British Pharmacopeia and European:

Potentiometric titration (2)

2.1.2. United State Pharmacopeia:

HPLC Chromatography(5).

2.2. Reported methods of analysis:

2.2.1. Spectroscopic Methods of Analysis:

2.2.1.1. Based on absorption

2.2.1.1.1. UV-visible methods:

Ultraviolet/visible (UV/VIS) spectrophotometry is often employed in pharmaceutical

Analysis due to the simplicity of the measurement and the relatively low cost of the instruments despite its simplicity, UV/VIS spectrophotometry is a well-established and powerful technique for analyzing single compounds such as bulk materials of active pharmaceutical ingredients (APIs) or excipients. A large UV/VIS spectra library of APIs is available as a reference to determine the identity and quantity of the analyzed sample. The limitation of this technique, however, is the poor selectivity for detecting drug mixtures as compounds with similar chromophores will have overlapping absorption spectra. To address this issue, derivative spectrophotometry and multivariate analysis have been implemented to resolve the overlapping bands and thus enable simultaneous detection of different drugs(6).

2.2.1.1.1.1 Direct UV-visible:

A UV spectrophotometric method for quantitative estimation of Promethazine HCl in phosphate buffer saline pH 7.4 has been developed The method is based on the ultraviolet light absorbance at 251 nm which is the maximum wavelength of the concerned drug(7).

2.2.1.1.1.2 Oxidative coupling reactions

A new spectrophotometric method has been developed based on the oxidative coupling reactions for determination of important phenothiazine drug which is promethazine HCl in pure

solutions and local pharmaceutical preparations. The Standard promethazine HCl was treated with organic reagent of P- Chloroaniline as a coupling reagent in the presence of oxidizing agent Ammonium Cerric (IV) Sulphate, the reaction leads to the formation a blue -greenish color product that has a maximum absorption at 306nm(8).

Visible spectrophotometric method has been developed for the determination of Promethazine Hydrochloride in pure form, pharmaceutical preparations and environmental water samples. The method is based on the oxidation of Promethazine hydrochloride by sodium hypochlorite in a Sulfuric acid medium to form a pinkish red colored product with an absorption maximum at 518 nm. Beer's Law was obeyed in the range of 2-28 µg/ml with molar absorptivity of 0.978×104 L.mol.-1.cm-1(9).

Molecular Absorption Spectrophotometric method for determination of trace amount of promethazine hydrochloride in pure and its pharmaceutical preparations were described. The method was based on the oxidation of promethazine hydrochloride by potassium dichromate in acid solution to form an intense yellow soluble product and the intensity of absorption has been measured for oxidant reagent potassium dichromate at λmax. 440 nm used Molecular Absorption UV-Vis. Beer's law is obeyed over the concentration range of 1-18 µg/mL(10).

A sensitive and rapid spectral method was developed to estimate promethazine hydrochloride based on the method of reduction of Fe3+tri-iron ion by promethazine and then complex formation of Fe2 + -Phen. It is soluble in water and stable for a period of time of at least 60 minutes and has maximum absorption at a wavelength of 514 nm(11).

A simple, rapid and sensitive spectrophotometric method for determination of trace amounts of Promethazine hydrochloric in aqueous solution is described. The method is based on using the oxidative coupling reaction of Promethazine hydrochloride with 2-Chloroaniline reagent in acid medium in the presence of N- bromoSuccinimide. The red color product is quickly converted to green color, water soluble, the product which exhibit maximum absorbance at 595 nm(12).

A simple and sensitive spectrophotometric method has been developed for the determination of some phenothiazine derivatives (promethazine and chlorpromazine) as pure and in dosage form. The method is based on oxidation of phenothiazines by N-chlorosuccinimide in hydrochloric acid medium to give red coloured species having maximum absorptions in the range 516.5-534.5nm(13).

2.2.1.1.1.3. Extractive-spectrophotometric:

Extractive spectrophotometric has been developed for determination of promethazine and perphenazine in pure forms and in their pharmaceutical formulations. Promethazine and perphenazine react in neutral medium with dipicrylamine and picric acid forming colored compounds, which are insoluble in water but quantitatively extracted into chloroform or benzene. The composition of the compounds of promethazine with dipicrylamine and picric acid was established. Working solutions were pre- pared by suitable dilution of the stock solution with distilled water and standardized by spectrophotometric method in UV range(14).

2.2.1.1.1.4. Ion pair complex formation:

Sensitive spectrophotometric method for trace amount determination of promethazine in drug formulation has been developed based on ion pair complex formation. This system relies on the instruction of colour ion-pair between complexes. Promethazine HCl is reacted in acidic medium with methyl blue dye resulting in the formulation of a colored product with a maximum absorption of 480 nm(15).

determination of promethazine hydrochloride in pharmaceutical preparation fanarkan by using molecular spectrum and iron metal. Through formation complex PRZH Fe(II) and extracted with Benzyl alcohol and absorbance was measured with ʎmax=475nm(16).

A molecular spectrophotometric method for determination of drug promethazine hydrochloride (PRZH) in some pharmaceutical preparations by chelating with Rhodium (II) has been developed. The complex has a maximum absorption at (472 nm). Benzyl alcohol was used as an organic solvent for extraction of chelating complex(17).

spectrophotometric method for the determination of promethazine hydrochloride (PH) in drug sample. The proposed method is based on the reaction of promethazine hydrochloride (PH) with iron(III) and a subsequent reaction with ferricyanide in an acetic acid medium to yield Prussian blue colored product with a maximum absorption at 700 – 720 nm(18)

A spectrophotometric method for determination of trace amounts of promethazine hydrochloric aqueous solution is described. The method is based on complication of promethazine hydrochloride with Indium (111) in presence of sodium hydroxide to form an intense product maximum absorption at 304nm(19).

2.2.1.1.1.5. charge-transfer complex:

The determination was based on the formation of a charge-transfer complex between chloranilic acid as a π-acceptor and the studied drug as n-donors in an acetonitrile-chloroform mixture. The

complexes formed were found to absorb at 520 nm. Beer's law is obeyed in the concentration range 25-150 µgml^{-1} (20)

2.2.1.1.1.6. Colorimetric:

A portable optical colorimetric sensor determined promethazine using the oxidation of promethazine by a potassium persulfate reagent entrapped within a sol-gel polymer network. The colored re- action product was detected with a portable spectrometer. The surface morphology of the optical colorimetric sensor was characterized by scanning electron microscopy and Fourier transform infrared spectroscopy(21).

2.2.1.1.1.7. Simultaneously estimation by UV-spectroscopy:

Simultaneous estimation of ondansetron hcl and promethazine hcl by UV spectroscopy in blluk drugs has been reported. The aliquot portion of standard stock solution of Ondansetron Hcl and Promethazine Hcl were diluted appropriately with Chloroform to obtain 10 µg/ml each respectively and the solutions were scanned in the range of 200-400 nm in 1.0 cm cell against chloroform as blank and the λ max for Ondansetron Hcl and Promethazine Hcl was found to be 310 nm and 250 nm respectively(22).

Simultaneous determination of promethazine, chlorpromazine, and perphenazine by multivariate calibration methods and derivative Spectrophotometry have been developed and validated based on Partial least-squares (PLS) regression, singular value decomposition-based PLS, and an artificial neural network (ANN) were tested as calibration procedures(23).

Five phenothiazine drugs namely, Promethazine HCl (PMH), Promethazine Theoclate (PMT), Chlorpromazine HCl (CPH), Trifluoperazine HCl (TFPH), Prochlorperazine Maleate (PCPM), in pure form and pharmaceutical formulations were assayed by a single chromogenic reagent Vanadium Pentoxide (V2O5) in an acidic medium, to form a red colored complex having maximum absorbance range from 500 to 525 nm(24).

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2.2.1.2. Spectroscopy based on emission:

2.2.1.2.1 atomic emission:

Flame Atomic Emission for determination of trace amount of promethazine hydrochloride in pure and its pharmaceutical preparations via Potassium Dichromate as Oxidant Reagent has been

developed. The methods was based on the oxidation of promethazine hydrochloride by dichromate in acid solution to form an intense yellow soluble product and the intensity emission measured of potassium at emission line of potassium 766 nm using flame emission spectrophotometer(10).

2.2.1.2.2 molecular photoluminescence:

Spectrofluorometric determination of certain biologically active phenothiazine in commercial dosage forms and human plasma. The method was based on condensation of malonic acid/acetic anhydride (MAA) under the catalytic effect of the tertiary amine moiety of the studied phenothiazine to provide a deep yellow to brown color with green florescence. Relative fluorescence intensity of the products was measured at λ_{exc} 398nm and λ_{em} 432 nm(26).

Spectrofluorometric determination of promethazine hcl in pure form and in drugs has been described with maximum excitation spectra 298.51nm(27).

2.2.1.3. Spectroscopy based on scattering:

2.2.1.3.1 Nephelometric techniques:

Nephelometery techniques is a technique in which an incident source of radiation is elastically scattered by a suspension of colloid particle, scattered radiation is measured at angle of 90° to the tradition source (28).

highly accurate nephelometric titration has been developed and validated for quantitative determination of promethazine hydrochloride. 5ml of 0.5% polyvinylpyrrolidone solution, place the beaker on a magnetic stirrer, immerse the nephelometric sensor in the beaker, and titrate with 0.01 mol l/L sodium tetraphenylboron solution. Record both the volume of the titrant and the relative intensity of the scattered light. Determine the end-point by the peak in the profile of relative intensity of scattered light versus the volume of titrant. Each ml of 0.01 mol/L sodium tetraphenylboron is equivalent to 3.2089 mg C17H20N2S·HCl(81).

.2.2.2. Chromatographic methods:

Chromatographic analysis is most sophisticated a method of choice for detecting multi-drug components in a sample simultaneously. While spectral derivatization, multivariate analysis, and the use of specific recognition elements for multiplexed optical/electrochemical measurements have been successful to detect binary or ternary mixtures of drugs, none of these can overcome

to chromatographic or separation-based detection techniques in term of the number of analytes they can resolve at the same time. In addition, the separation process allows for analytes stacking/preconcentrating into plugs or bands, which significantly improves the detection limit compared with direct detection methods. Various detectors such as optical detectors and mass spectrometry (MS) have been coupled to chromatographic systems to identify and quantify analytes(6).

2.2.2.1. Liquide chromatography:

High performance thin-layer chromatography combined with densitometry for determination of phenothiazine derivative (promethazine hcl) has been developed. To quantitative determination a chromatographic system composed of: LiChrospher Si 60 as the stationary phase, and mixture of acetone, methanol and ammonia (25%) (90:10:2, v/v/v) as the mobile phase was used. The plates were developed “face down” in horizontal Teflon DS chambers. The distance was 50 mm.The densitograms were obtained using Desaga CD-60 densitometer (Heidelberg, Germany) controlled by a Pentium computer with Windows Software ProQuant. In quantitative analysis meander scanning of 1.0mm wide paths at 247nm was used(35).

Determination of promethazine hydrochloride by densitometric method in substances and pharmaceuticals was provided. The following system was used for determination of analyzed compound: Merck HPTLC Silica gel 60 F254 chromatographic plates and mobile phase: diethylether - diethylamine (40: 1, v/v). Densitometric analyses were conducted using Shimadzu CS 9000 densitometer. Chromatographic plates were placed inside the chamber. Slit dimensions were 0.4 ◊ 0.4 mm. Measurement was made by zigzag scanning with the following width of deflection: 14 mm. Maximum wavelengths was 255 nm(36)

A sensitive LC-MS method for the determination of Promethazine hydrochloride in human plasma and urine has been developed and validated. Chromatographic and mass spectrometer conditions: An Diamonsil C18 (150 mmx4.6 mm ID, 5 um) analytical column were used with a mobile phase system to chromatographically separate. The mobile phase consisted of a mixture of methanol and water (pH 6), both containing 0.5 Mm ammonium acetate. Elution of analytes was carried out using a flow rate of 0.8 ml /min, the run time was set at 10 min. For optimum sensitivity, the following parameters were set: fragmentor voltage of 90V, capillary voltage 4000V, drying gas temperature 350°C, drying gas flow l3Umin and nebulizer pressure 50 psi. Mass spectrometric data were collected between 2.5 and 9.0 min(37).

High resolution mass spectrometry and Time of flight technology (LC-TOF)/ UHPLC high resolution mass spectrometry have been reported for Quantitative analysis of drugs in hair including promethazine hydrochloride. Analysis was performed on an Agilent 6550 iFunnel Q-TOF LC/MS system equipped with a Jetstream interface with positive electrospray ionization in combination with an Agilent 1290 Infinity UHPLC system. A capillary voltage of 3500 V was used to generate ions, and the fragmentor voltage was set at 380 V. The mass range was 50– 950 m/z with a scan rate of 3.0 spectra per seconds. Two reference masses (121.0509 and 922.0098) were constantly infused into the ion source performing mass correction in every scan. UHPLC was performed with a high-strength silica T3 column (150 x 2.1 mm, 1.8 µm) preceded with a high-strength silica T3 VanGuard precolumn (5 x 2.1 mm, 1.8 µm). A flow of 0.5 ml/min was used with mobile phase A (0.05 % formic acid in 10 mM ammonium format) and mobile phase B (0.05 % formic acid in acetonitrile). Column temperature was held constant at 60°C. 10 µl of the sample was injected(38).

the RP-UPLC method has been developed and checked. The uniform solution of 3.4% KH2

PO4 solution in water, 7.0 pH with dilute KOH, ACN, and MeOH in ratio of 40:40:20, used as a

mobile phase. The flow of 0.6 mL/min using photo diode array detector/UV detector by with wavelength of 254 nm and runtime 3 min(39)

A reversed phase high performance liquid chromatographic stability indicating assay method for the estimation of Promethazine hydrochloride in formulations. The separation was achieved on the LUNA C18 column 5µ (250 x 4.6 mm id), using phosphate buffer (pH 3.6): methanol, 70:30 as the mobile phase at 1 ml/min flow rate and 262 nm as detection wavelength. The retention time of was found to be 5.317 min(40).

A reversed phase high performance liquid chromatographic method for determination of promethazine in human serum has been developed, validated and applied to the pharmacokinetic study of promethazine. Promethazine and internal stander, chlorpromazine, were extracted from human serum by liquied-liquied extraction with n-hexane containing 0.8% isopropanol and analyzed on a capcell pak CN column with the mobile phase of acetonitrile-0.2M potassium dihydrogen phosphate (42:58 ,v/v, adjusted to pH 6 with 1M NaOH). Detection wavelength of 251nm and flow rate of .9ml/min were fixed(41).

Stability-indicating HPLC method has been developed for determination of promethazine hydrochloride (PMZ) in hot-melt extruded (HME) films and sustained release tablets. Chromatographic separation has been achieved on a 150 mm× 4.6 mm i.d., 3 mm particle size, C8 (2) column with acetonitrile-25mM phosphate buffer (pH 7.0), 50 : 50 (v/v) as mobile phase at a flow rate of 1 mL $min.^{-1}$ Quantitation has been achieved with UV detection at 249 nm based on peak area(42).

HPLC method for separation and determination of promethazine enantiomers has been developed. Promethazine has been separated and quantitated on a Vancomycin Chirobiotic V column (250 ´ 4.6 mm), using a mixture of methanol, acetic acid, and trimethylamine (100:0.1:0.1%, by volume) as a mobile phase at 20°C and at a flow rate of 1 mL/min. The UV-detector has been set to 254 nm. Acetyl salicylic acid (Aspirin®) has been used as an internal standard. The applied HPLC method allowed separation and quantification of promethazine enantiomers with good linearity (r > .999) in the studied range(43).

Liquid Chromatographic Method for the Simultaneous Determination of Promethazine and Three of Its Metabolites in Plasma Using Electrochemical and UV Detectors has been developed.

Chromatographic condition 5-µm CN column (250- × 4.6-mm i.d.) was used for the analysis. The mobile phase consisted of a mixture of methanol–0.15M ammonium acetate (pH5.0)–water (38:50:12) and was maintained at a flow rate of 0.9 mL/min.

The analytical wavelength for the UV detector was set at 236 nm, and the potential for the amperometric detector was set at +0.8 V(42).

An HPLC–ESI-MS method for simultaneous determination of fourteen metabolites of promethazine and caffeine and its application to pharmacokinetic study of the combination therapy against motion sickness have been reported. HPLC–ESI-MS method An Agilent 1200 series HPLC system was used. The LC separation was performed on an Agilent TC-C18 column (250 mm × 4.6 mm, 5 µm particle size) coupled with phenomenex C18 guard column (4.0 mm × 3.0 mm, 5 µm particle size). The aqueous mobile phase (phase A) was a mixture of water, tetrahydrofuran, glacial acetic acid and diluted ammonia water (99.6:0.2:0.1:0.1, v/v/v/v) (pH 3.8); the organic one (phase B) was acetonitrile. The following linear elution gradient was used (flow rate, 0.75 ml/min): 0–11 min, 3.5% B to 3.5% B; 11–22 min, 3.5% B to 8% B; 22–30 min, 8% B to 8% B; 30–40 min, 8% B to 53% B; 40–45 min, 53%B to 53%B. The equilibration time was 15 min. And the flow rate was reduced to 0.375 ml/min prior to MS detection using a T-

split. The column temperature was set at 25.0 ± 0.5 ◦C. In the condition of positive mode, internal reference masses m/z = 118.086255, 121.050873, 149.023320 were chosen, and m/z = 112.985599 was chosen in the negative mode(44).

Isocratic liquid chromatography method was developed for the simultaneous determination of diphenhydramine, promethazine, chlorpheniramine, and ephedrine in cold-cough syrups commonly available in the Kenyan market. The influence of the percentage of organic modifier, ion pairing agent, buffer concentration as well as pH and column temperature on the selectivity with respect to analytes was investigated. Optimum chromatographic separation was achieved using a C18 Gemini® NX column (250 mm ´ 4.6 mm, 5 mm) maintained at 40°C and a mobile phase comprising methanol – trimethylamine – 0.2 M ammonium acetate pH 5.0 – water mixture (50 : 0.15 : 40 : 9.85, v/v) delivered at a flow rate of 1.0 mL/min(45).

A direct plasma injection HPLC method has been developed for the determination of selected phenothiazines (promethazine, promazine, chlorpromazine) using a Hisep column. The method is easy to perform and requires 20 µL of a filtered plasma sample. The chromatographic run time is less than 11 min using a mobile phase of 15:85 v/v acetonitrile–0.18 m ammonium acetate pH 5.0 and UV detection at 254 nm(46).

High performance liquid chromatography method for determination of paracetamol and promethazine hydrochloride has been developed. The chromatography system used a reversed phase C18 column (HiQ Sil C18, 5µ, 250 mm x 4.6 mm). The sample was analyzed using Methanol: Water: Try ethyl amine, in the ratio of 90:10:0.1 v/v as a mobile phase at a flow rate of 1.0 ml/min and detection at 250 nm. The retention time for paracetamol and promethazine hydrochloride was found to be 2.853 and 5.107 min respectively, and recoveries from formulation were between 98 and 102 % (47).

2. 2.2.2. Gas chromatography:

Detection of pharmaceuticals in “dirty sprite” using gas chromatography and mass spectrometry has been reported. The injection volume was 1 µl and the injection port temperature was at 270$\dot{C}$ using a split-ratio of 50:1. The initial oven temperature was 120$\dot{C}$ which was increased to 300$\dot{C}$ at 7$\dot{C}$/min (total run time. 28.7 min). The carrier gas (helium) was set to 13.9 psi (1.2 ml/min), using constant flow mode. The transfer line temperature was 270$\dot{C}$. For MS screening in electron ionization (EI) mode at 70 eV, a mass range from m/z 50–650 was selected. Quantitative analysis was carried out in single ion monitoring (SIM) mode(48).

Simultaneously determination of the commonly abused prescription drugs in lean cocktail. Gas chromatography with flame ionization detection (GC-FID) was employed with a dilute-and-shoot sample preparation technique. The analysis was conducted using a 6890N gas chromatograph equipped with a flame ionization detector (FID) and a DB-5 capillary analytical column (30m×0.25mm i.d. × 0.25 mm film thickness). The gas types and their flow rates were as follows: He (carrier gas), 1.0 mL min^{-1};N2 (makeup gas), $25mLmin^{-1}$;H2, 30mLmin^{-1}; and oxidant gas, 300mL min^{-1} (49)

2.2.2.3. Capillary electrophoresis:

A new method based on CE–C4D for the simultaneous determination of paracetamol and promethazin in pharmaceutical samples was proposed. All electropherograms were performed using homemade CE equipment with two compact and high-resolution capacitively coupled contactless conductivity detectors (C4D). The detectors were positioned along the capillary at 10 cm from each end. The fused-silica capillary used in all experiments was 50 cm long (effective lengths of 10 and 40 cm) and 50 µm id x 375 µm od. Before use, the capillary was flushed with deionized water for 10 min, 0.1 mol L- 1 NaOH for 15 min, again with deionized water for 10 min and finally with BGE for 10 min. The samples were injected hydrodynamically for 1 s at 25 kPa. All experiments were carried out at +25 kV (inlet side) with cathodic direction of strong EOF. The capillary was rinsed for 3 min with BGE solution between each 20 injections to ensure a consistent and reproducible EOF(50)

A capillary zone electrophoresis (CZE) method with ultraviolet-visible detection has been established and validated for the determination of five phenothiazines: thiazinamium methylsulfate, promazine hydrochloride, chlorpromazine hydrochloride, thioridazine hydrochloride, and promethazine hydrochloride in human urine. Optimum separation was obtained on a 64.5cm 6 75 mm bubble cell capillary using a buffer containing 150mM tris(hydroxyethyl)aminomethane and 25% acetonitrile at pH 8.2, with temperature and voltage of 257C and 20kV, respectively(51).

capillary zone electrophoresis (CZE) for quantitative analysis of three phenothiazines: thiazinamium methylsulphate (TMS), promazine hydrochloride (PMH) and promethazine hydrochloride (PTH) in pharmaceutical formulations has been reported with following CZE coundtions: CE experiments were carried out with a HP3D CE instrument equipped with a diode-array detector. Data were collected using the software provided with the HP ChemStation, version A.09.01. Analytes were monitored at 254nm with a bandwidth of 30 nm. Separation was carried out in a silica fused capillary 58.5 cm×50?m i.d. (effective length 50 cm) in normal

mode, applying a voltage of 30 kV. For pH measurements, a pH meter (Crison model pH 2000, Barcelona, Spain) was employed. Samples injections were made in a hydrodynamic mode over 5 s under a pressure of50 mbar. Optimized background electrolyte solution was 100mM tris aqueous solution adjusted to pH 8.0 with hydrochloric acid and containing 15% (v/v) acetonitrile. When a new capillary was used, the capillary was conditioned 20 min with 1M NaOH solution, followed by 30 min with deionized water. At the beginning of each day, the capillary was prewashed for 2 min with 0.1M NaOH, 3 min with water and 7 min with running buffer. After each run, the capillary was postwashed for 1 min 0.1M NaOH, 4 min with deionized water and 3 min with buffer to maintain adequate reproducibility of run-to-run injections(52).

Chiral separation of promethazine by capillary electrophoresis with end-column amperometric detection has been successfully coupled to capillary electrophoresis for chiral separation of promethazine, with a carbon fiber microdisk electrode as working electrode. Baseline separation and sensitive detection were achieved under optimum conditions: 0.030 M Na2HPO4 and 0.015 M citric acid at pH = 2.50, 1.0 mM b-CD, 10 kV separation voltage, and detection potential 1.10 V (vs Ag/AgCl). The numbers of theoretical plates were higher than 700000, and the detection limit was 5×10^{-8}M(53).

ACE instrument coupled with chemiluminescence (CL) detection was designed for the determination of promethazine hydrochloride (PTH) and promazine hydro- chloride (PMH) in real samples. An important enhancement of the CL emission of luminol with potassium ferricyanide was observed in the presence of these phenothiazines; so this system was selected for their detection after CE separation. Parameters affecting the electrophoretic separation were optimized in a univariate way, while those affecting CL detection were optimized by means of a multivariate approach based on the use of experimental designs(54).

A simultaneous determination method of PMZ, PMZSO, DOPMZ and DMPMZ by improved CE coupled with end-column CEL was established. The parameters about CE separation and CEL detection were investigated in detail. The optimum experimental conditions were detection potential 1.20 V (vs. Ag/AgCl), 40 mmol/L of phosphate buffer solution (pH 6.5) containing 6 mmol/L Ru$(bpy)_3{}^{2+}$ in CEL detection cell, separation buffer of 21.5% isopropyl alcohol aqueous solution (v/v) containing 20 mmol/L phosphate (pH 5.0), separation voltage of 14 kV, sample injection time of 7 s and sample injection voltage of 12 kV(55).

simultaneous determination of promethazine (PRO) and codeine (COD) have been developed based on capillary electrophoresis with capacitively coupled contactless conductivity detection (CE–C4D). The electrophoretic analyses were performed using homemade equipment with two compact and high-resolution capacitively coupled contactless conductivity detectors (CE–C4D). A fused silica capillary with dimensions of 50 um inner diameter, 375 um outer diameter, 40 cm long, and effective length of 10 cm was used. Before analyses, the capillary was preconditioned with 0.1 mol L-1 NaOH solution (15 min), deionized water (10 min) and background electrolyte (10 min). The samples were injected hydrodynamically for 0.6 s at 25 kPa and the separation potential adopted was 25 kV(56).

2.2.2.4. Miscellaneous:

2.2.2.4.1. Sequential injection chromatography for biofluidic analysis:

A new SIC method for promethazine assay is provided. The method was optimized, validated, and applied to human urine and serum, in addition to pharmaceutical formulations Trifluphenazine was used as an internal standard. The separation was conducted onto C18 monolithic column (4.6×25mm) using 30mmol=L phosphate: acetonitrile (50:50, v=v) at pH 4.0. The detection was carried out by miniaturized fiber optic spectrometric devices set at 250nm(57).

Chemometric optimization of a SIA promethazine hydrochloride assay method, based on its oxidation by acidified cerium (IV), was optimized. Three chemometric approaches were applied: (i) factorial design for screening the potential interacting variables, (ii) univariate for optimizing insignificantly interacting variables and (iii) simplex for optimizing potentially interacting variables. The optimum experimental conditions were 30 µl of 0.38 mol/l sulphuric acid, 30 µl of 3.99×10−3 mol/l cerium (IV), 20 µl of promethazine hydrochloride and 20 µl/s flow rate(34).

2.2.3. bioanalytical methods

2.2.3.1. Liquid phase microextraction

Liquid phase microextraction (LPME) was a novel microextraction technique introduced by Jeannot and Cantwell in 1996, it is simple, fast and inexpensive. Single drop microextraction (SDME) and hollow fiber-liquid phase microextraction (HF-LPME) are the two sampling modes of LPME. Compared to conventional liquid–liquid extraction (LLE), SDME would provide higher enrichment factor, superior selectivity, and significantly reduced solvent consumption.

Nevertheless, the microdrop suspended on the needle of microsyringe is easily dislodged during extraction, especially the case when samples are stirred vigorously.

Hollow fiber-liquid phase microextraction (HF-LPME) combined with gas chromatography (GC) has been developed for the analysis of four phenothiazine drugs (promethazine, promazine, chlorpromazine and trifluoperazine) in human urine samples(58).

2.2.3.2. Solid phase microextraction (SPME):

Solid-phase microextraction is a recently developed technique, which integrates sampling, extraction, concentration and sample introduction into a single solvent-free step. With a polyacrylate coated fiber, SPME was also applied for LC/MS/MS determination of 11 phenothiazine drugs with heavy side-chains in human whole blood and urine samples(58).

Simultaneous determination of ten antihistamine drugs in human plasma using pipette tip solid phase extraction and gas chromatography/mass spectrometry has been developed. Ten antihistamine drugs, diphenhydramine, orphenadrine, chlorpheniramine, diphenylpyraline, triprolidine, promethazine, homochlorcyclizine, cyproheptadine, cloperastine and clemastine, have been found to be extractable from human plasma samples using MonoTip C18 tips, inside which C18- bonded monolithic silica gel was fixed. Human plasma (0.1 mL) containing the ten antihistamines was mixed with 0.4mL of distilled water and 25 mL of a 1M potassium phosphate buffer (pH 8.0). After centrifugation of the mixture, the supernatant fraction was extracted to the C18 phase of the tip by 25 repeated aspirating/dispensing cycles using a manual micropipettor. The analytes retained on the C18 phase were then eluted with methanol by five repeated aspirating/dispensing cycles. The eluate was injected into a gas chromatography (GC) injector without evaporation and reconstitution steps, and was detected by a mass spectrometer with selected ion monitoring in the positive-ion electron impact mode. The separation of the ten drugs from each other and from impurities was generally satisfactory using a DB-1MS column (30mT0.32mm i.d., film thickness 0.25 mm)(59).

2.2.3.3. Solid phase extraction:

A method based on magnetic graphene oxide dispersive solid phase extraction (MGO-D-SPE) combined with ion mobility spectrometry (IMS) was firstly introduced for simultaneous determination of ephedrine, pseudoephedrine, diphenhydramine, promethazine and terfenadine in saliva and urine matrices. The prepared MGO was characterized by Fourier transform infrared (FT-IR) spectroscopy and thermo gravimetric analysis (TGA)(60). Quantitative determination of phenothiazine derivatives in human plasma using monolithic silica solid-phase extraction tips

and gas chromatography–mass spectrometry has been developed, a recently introduced C18 monolithic silica SPE tip, the MonoTip C18, for extraction from human plasma. The drugs could be extracted within 5min from 0.1-mL plasma samples, eluted with methanol, and the eluate injected directly into a gas chromatograph prior to mass spectrometry analysis(61).

2.2.4. Electrochemical method of analysis:

2.2.4.1. Voltammetric Methods of Analysis

A voltammetric method based on square wave voltametric method for determination of promethazine using DNA modified multiwall carbon nanotube paste electrode and MWCNT electrode were been developed for the determination of PMZ in pharmaceutical formulations and biological fluids(62) ,(63). The electrochemical oxidation of promethazine hydrochloride was made on highly boron-doped diamond electrodes(64). The AuNPs-PG were employed as the modifier of glassy carbon paste electrodes (CPE/AuNPs-PG), which were applied as sensitive electrochemical sensors to the determination of the antihistamine drug promethazine hydrochloride (PMZ)(65). Designing hybrid barium tungstate on functionalized carbon black as electrode modifier for low potential detection of antihistamine drug promethazine hydrochloride(66). A multi-walled carbon nanotube modified paste electrode (MWCN-PE) was used for determination of promethazine (PMZ) in drug formulations and blood plasma by cyclic voltammetry (CV) and differential pulse voltammetry (DPV) methods(67). Ultrasonication-aided synthesis of nanoplates-like iron molybdate: Fabricated over glassy carbon electrode as an modified electrode for the selective determination of first generation antihistamine drug promethazine hydrochloride(68). A highly sensitive electrochemical biosensor for the detection of trace amounts of promethazine has been designed. Double stranded (ds)DNA molecules are immobilized onto a pretreated glassy carbon electrode (GCE(ox)) surface(69). Promethazine determination in plasma samples by using carbon paste electrode modified with molecularly imprinted polymer (MIP): Coupling of extraction, preconcentration and electrochemical determination(3). A $(SiPy^{+}Cl^{-}/CuTsPc)_5$ layer-by-layer film was employed for the electroanalytical determination of promethazine hydrochloride (70). A new Schiff base of bis-N -(2-mercaptophenyl) salicylaldimine(MPSI) has been immobilized on a bare gold electrode as a novel self-assembled monolayer (SAM) sensor for determination of promethazine hydrochloride (PMZ)(71). A novel electrochemical platform for nanomolar detection of antihistamine promethazine hydrochloride, based on a novel ternary nanocomposite sonochemically prepared using a zinc-graphene oxide (GO-Zn) complex and a nanosheets-stacked spherical ZnO(72).

Dynamic electrocatalyst for the selective detection of promethazine hydrochloride has been reported based on a cost-effective method for fabricating the electrochemical sensing detector for promethazine hydrochloride (PHCusing cashew like cobalt tungstate (CW). The CW was synthesized using a simple co-precipitation method and was characterized using FTIR, Raman, XRD, FE-SEM, XPS, EDAX, and elemental mapping analysis. Also, the electrochemical activity and potential impact of the CW were scrutinized by CV and used towards the oxidation of PHC(73).

2.2.4.2. Potentiometric Methods of Analysis:

Portable system of programmable syringe pump with potentiometer for determination of promethazine in pharmaceutical applications has been developed and validated based on the oxidation of promethazine by cerium in an acidic medium. The parameters were optimized and the related optimum working conditions were; for supporting electrolyte concentration sulfuric acid, ranges from 1×10^{-3} mol $L^{-}1$to$5 \times 10^{-3}3$ mol L^{-1}, cerium(IV) concentration ranges from 5×10^{-5} mol $L^{-1}$to 1×10^{-3} mol L^{-1}, DC current of 5 µA and flow rate of 20 µAs^{-1} (74).

A molecularly imprinted polymer with recognition sites for promethazine was prepared and then used to fabricate the promethazine-selective potentiometric sensor, creating the first MIP-based promethazine sensor. It was found that the MIP com- position as determined by the nature of the monomers used for the MIP preparation had a considerable effect on the final sensor performance. After optimization of the parameters influencing the sensor performance, the sensor was successively used for promethazine determination in pharmaceutical products and serum samples over a wide concentration range, from 5.0×10^{-7} to 1.0×10^{-1}M, with a low detection limit of1.0×10^{-7}Mand a response time of~50 s(75).

Promethazine Potentiometric Membrane Sensor for Promethazine Hydrochloride Pharmaceutical Analysis; Computational Study a potentiometric liquid membrane sensor for simple and fast determination of promethazine hydrochloride in pharmaceutical formulation and urine was constructed. For the membrane preparation, PM-Tetraphenylborate complexes were employed as electroactive material in the membrane. The wide linear range (10^{-5}-10^{-2}2molL^{-1}), low detection limit (1.0×10^{-5} mol L^{-1}), and fast response time (~5s) are characterizations of the proposed sensors(76).

2.2.4.3. Amperometric method of analysis:

Amperometric determination of promethazine in tablets using an electrochemically reduced graphene oxide modified electrode has been developed. This modified sensor was prepared by

chemical oxidation of graphite powder followed by product exfoliation in ultrapure water using an ultrasonic bath. Then, the resultant graphene oxide was electrochemically reduced in 0.10 mol L^{-1} acetic acid–sodium acetate (pH = 5.0) on a glassy carbon electrode surface(77).

A Facile One-pot Sonochemical Synthesis of Ni Doped Bismuth Sulfide for the Electrochemical Determination of Promethazine Hydrochloride have been reported. Prior to the electrode fabrication, the material was characterized using suitable spectrophotometric techniques. In addition, the modified electrode was fabricated using optimized volume of well characterized Ni-Bi2S3. Then, the fabricated sensor was applied for the determination of PMTZ using CV and aerometric techniques. The Ni-Bi2S3/GCE delivered the excellent electrocatalytic performance and detected the PMTZ with very lowest limit of detection (LOD) of 0.4 nM(78).

simultaneous determination of promethazine (PRO) and codeine (COD) have been developed. based on batch injection analysis with multiple pulse aerometric detection (BIA–MPA)(56)

2.2.4.4. Ion-Selective Electrode:

Determination of Promethazine in Various Pharmaceutical Samples using Promethazine Selective Poly (Vinyl Chloride) Membrane Electrode has been reported. A promethazine hydrochloride and ammonium phosphomolibdtae ion-pair compound was used as electroactive material for selective determination of promethazine in various samples. The electrode of the composition of PVC: PM-PMD: DBP of 33: 3: 64 (%, w/w)(79).

2.2.4.5 Conductmetric titration:

Ion-Pair Formation in Pharmaceutical Analysis. Conductimetric Determination of, Promethazine in Pure Form, Drug Formulations and Urine. Potassium ferricyanide and sodium tetraphenylborate were used as titrants for the conductimetric determination of promethazine HCl, through ion-associate complex formation(80).

2.2.5. kinetic method of analysis:

2.2.5.1. Enzyme-catalyzed analytical kinetic methods

Enzyme-catalyzed analytical kinetic methods have been extensively used for substrate, enzyme, inhibitor and activator analysis in several areas of analytical chemistry such as in clinical, pharmaceutical, agricultural, industrial applications and process monitoring. Horseradish peroxidase (HRP; EC 1.11.1.7) is one of the most important oxidases in biology. Having the function of active molecular oxygen, HRP can enhance the oxidation of H2O2 directly into H2O.

A new spectrophotometric method for trace amount of promethazine hydrochloride determination was developed based on inhibitory effect of promethazine hydrochloride on hemoglobin-catalyzed reaction(25)

2.2.5.2. Flow injection analysis:

An analytical technique in which samples are injected into a carrier stream of reagents, or in which the sample merges with other streams carrying reagents before passing through a detector(28).

Flow injection spectroelectroanalytical method for the determination of promethazine hydrochloride in pharmaceutical preparations has been reported. It is based on the in situ detection of a colored cationic radical formed during electroxidation at a gold electrode in sulfuric acid medium (0.1 mol l−1). The determination of promethazine hydrochloride in pure form or in pharmaceutical formulations was investigated, considering the amperometric and the absortiometric signal(29) .

Promethazine-HCl Determination Using Entrapped Persulphate in Water Crystals by Flow Injection / Stopped - Flow Technique and Ayah 3SX3-3D Solar Cell Micro Photometer have been reported. In this study, the use of stopped- flow technique comprising the entrapment of sodium persulphate inside the water crystal gel bead for the determination of PM-HCL in pure and Pharmaceutical preparation. A single water gel bead (or many) located in a specially designed cell , which aims to the libration of sodium persulphate from this water gel bead to the carrier stream for the oxidation of PM-HCL in an aqueous medium . The oxidation product yields a pinkish red color measured at 515 nm. This procedure is involved using a homemade FI microphotometer which is equipped with three different light emitting diode [Blue (470 nm), Green (525nm), and Red (635nm)] as a sources and solar cell as a detector(30) A bead injection spectroscopy- flow injection analysis (BIS-FIA) system for the spectrophotometric detection of promethazine and trifluoperazine is developed. The sensor is based in the oxidation of the phenothiazines by Fe(III) which is later determined by formation of the complex between Fe(II) and Ferrozine, $[FeFz3]^{4-}$ (31).

Ionophore-Based Potentiometric Sensors for the Flow-Injection Determination of Promethazine Hydrochloride in Pharmaceutical Formulations and Human Urine have been reported.Plasticised poly(vinyl chloride)-based membranes containing the ionophores (α-, β- and γ-cyclodextrins (CD), dibenzo-18-crown-6 (DB18C6) and dibenzo-30-crown-10 (DB30C10) were evaluated for their potentiometric response towards promethazine (PM) in a flow injection analysis (FIA) set-

up. Good responses were obtained when β- and γ-CDs, and DB30C10 were used. The performance characteristics were further improved when tetrakis (4-chlorophenyl) borate (KTPB) was added to the membrane. The sensor based on β-CD, bis (2-ethylhexyl) adipate (BEHA) and KTPB exhibited the best performance among the eighteen sensor compositions that were tested. The response was linear from 1 * 10−5 to 1 * 10−2 M, slope was 61.3 mV decade−1, the pH independent region ranged from 4.5 to 7.0, a limit of detection of 5.3 * 10−6 M was possible and a lifetime of more than a month was observed when used in the FIA system(32).

Chemiluminescence assay of promethazine hydrochloride using acidic permanganate employing flow injection mode operated with syringe and peristaltic pumps. The method was based on the chemiluminescence emission intensity produced as a result of its oxidation reaction with permanganate in sulfuric acid medium. Reaction variables were thoroughly investigated employing chemometrical methods with few number of experiments. The optimum system and chemical conditions were 2.1519×10^{-4}mol l^{-1}permanganate in 0.01 mol l^{-1}sulfuric acid when operating the peristaltic pump at a flow rate of 45 mls^{-1} and injecting the drug by a syringe pump operated at a speed of 40 mls^{-1}(33)

3.Result:

A review of analytical method of analysis of promethazine hydrochloride with eighty-one reference has been reported and illuminated in tables and charts below.

method for analysis of promethazine alone	frequency	percent%
spectroscopic methods	19	35.18519
chromatographic methods	13	24.07407
kinetic methods	5	9.259259
Electrochemical methods	17	31.48148
total methods	54	100

Table (1)

analytical method for analysis of promethazine in combination with other drugs	frequency	percent of each method %
spectroscopic methods	3	15
chromatographic methods	12	60

electrochemical methods	1	5
kinetic methods	1	5
bioanalytical methods	3	15
total methods	20	100

Table (2)

percent of each method = frequency /total*100

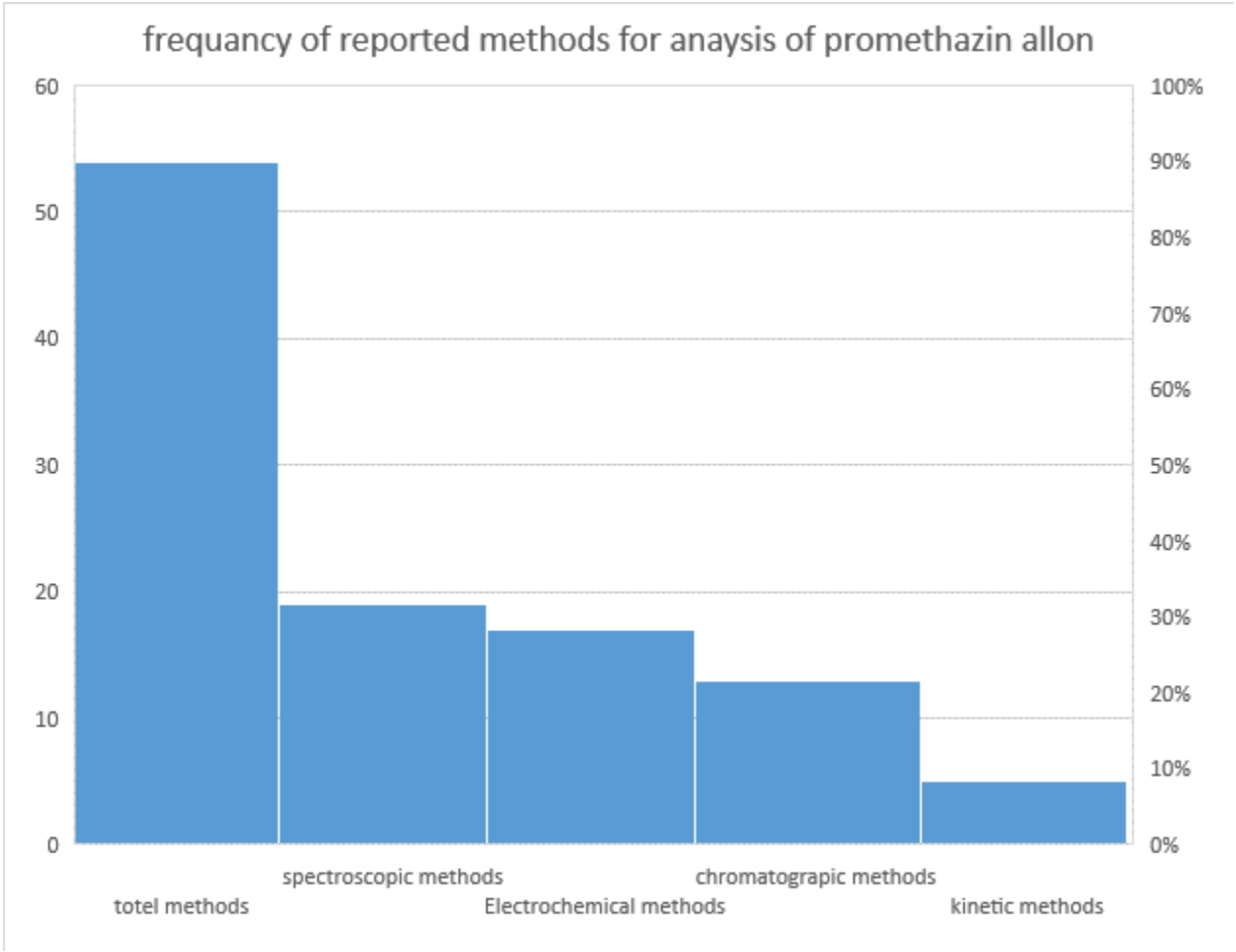

Figure (2)

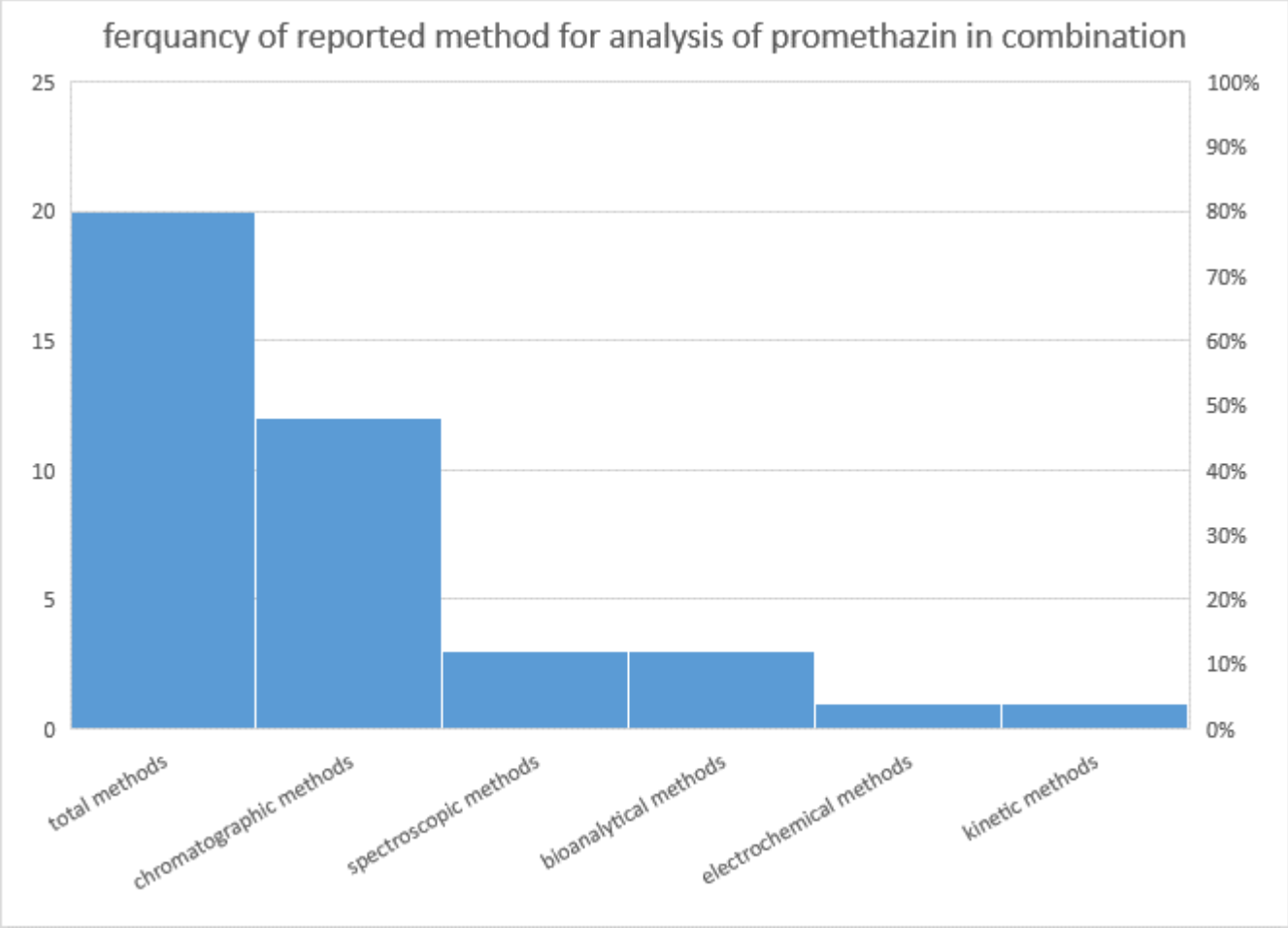

Figure (3)

4. Discussion:

Various analytical method has been used for analysis of promethazine hydrochloride either official method or reported methods in literature. spectroscopic methods, chromatographic methods, electrochemical methods, and bioanalytical methods.

Spectroscopic methods include UV/visible spectroscopy, flam emission spectroscopy, Spectrofluorometric /Chemiluminescence and represented as highest method developed and validated for analysis of promethazine alone in formulation. UV/visible is predominant methods within spectroscopic methods due to availability, vary rapid method, economically inexpensive.

Chromatochraphic methods have developed and reported are liquid (LC, UPLC, HPLC), gas, capillary electrophoresis and Sequential injection chromatography. And hyphenated techniques such as liquid chromatography –mass spectroscopy. Chromatographic method is most sophisticated method for analysis

of promethazine hcl in combination with multiple compound but it is more expensive and lack of availability in simple laboratory for this reasons has represented as first method for analysis of promethazine hcl in combination with other drugs. HPLC is official method for analysis of promethazine hcl in USA pharmacopeia.

Bioanalytical methods (solid phase extraction, solid phase microextraction and liquid phase microextraction) for analysis of promethazine hydrochloride in biological fluid this method used for extraction of promethazine from biological material then determination these methods have used for analysis of promethazine in combination with other drugs and biological material.

Electrochemical methods (voltammetry methods, Potentiometric Method, Amperometric method of analysis, Ion-Selective Electrode and Conductimetric) have been represented as second methods for determination of promethazine hydrochloride alone in pharmaceutical preparation due to selectivity

5.Conculsion:

This review caver the period from 2000 to now. Various analytical methods have been reported for analysis of promethazine hydrochloride in pure dosage form, in combination with other drugs in biological fluid. Spectroscopic method is the most applicable method for analysis of promethazine HCL alone have been reported in literature. UV/VIS is method of choice within spectroscopic methods. Chromatographic methods are methods of choice for analysis of promethazine in combination with other drugs in formulation and biological fluid.

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