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REVIEW ARTICLE

An overview of Dextromethorphan HBr and Promethazine HCl as potential antiallergic agents with special emphasis on reported analytical methods for estimation in bulk and formulation

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ABSTRACT
Antihistamines or antiallergics are a class of drugs that block the action of histamine, a chemical messenger in the body that plays a role in the immune response. Dextromethorphan HBr is a cough suppressant and an active ingredient in many over-the-counter cough and cold medications. Promethazine HCl is a phenothiazine antihistamine and antiemetic. It is used to treat a variety of conditions including allergic reactions, nausea, and vomiting. Both Dextromethorphan HBr and Promethazine HCl are available as oral medications in tablet and syrup form. In present article, we have reviewed Dextromethorphan HBr and Promethazine HCl as potential antiallergic agents with special emphasis on reported analytical methods for estimation in bulk and their formulations. There are many analytical methods reported for the estimation of these drugs in bulk or formulations. The analytical methods which were reported are mostly UV spectrophotometric method, HPLC, RP-HPLC, HPTLC, and LC-MS/MS. From present review we concluded that, there are very few analytical methods reported for the estimation of Dextromethorphan HBr and Promethazine HCl in bulk and formulations. Most of the methods were developed to estimate in combination with other drugs. Therefore we have selected these drugs to develop and validate HPLC method for the estimation in bulk and their pharmaceutical formulations.
Keywords: *Antihistamines; Dextromethorphan HBr; Promethazine HCl; Method development; Validation*

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INTRODUCTION

Antihistamines or antiallergics are a class of drugs that block the action of histamine, a chemical messenger in the body that plays a role in the immune response. They are commonly used to treat allergic reactions, such as hay fever, hives, and allergic asthma, as well as other conditions, such as nausea and motion sickness. There are two types of antihistamines: first-generation and second-generation[1]. First-generation antihistamines, also known as sedating antihistamines, are typically more potent but also more likely to cause drowsiness and other side effects. Examples include diphenhydramine (Benadryl) and chlorpheniramine (Chlor-Trimeton). Second-generation antihistamines, also known as non-sedating antihistamines, are generally less likely to cause drowsiness but may still cause other side effects. Examples include loratadine (Claritin), cetirizine (Zyrtec), and fexofenadine (Allegra).

The mechanism of action of antihistamines is by binding to histamine receptors, preventing the action of histamine on the body. Histamine is a chemical messenger that is released by cells in the body in response to an allergen. Histamine binds to receptors on other cells, which leads to the symptoms of an allergic reaction, such as itching, sneezing, and increased mucus production[2,3]. Antihistamines bind to the same receptors as histamine, but they do not activate the receptors. This prevents histamine from binding to the receptors and causes the symptoms of an allergic reaction to be less severe.It is important to note that

antihistamines do not cure allergic reactions, but they can relieve symptoms. They also do not prevent future allergic reactions. They are only effective in treating symptoms of the current allergic reaction[4–7].

Dextromethorphan HBr is a cough suppressant and an active ingredient in many over-the-counter cough and cold medications. It is a synthetic derivative of the opioid morphine, but it does not have opioid-like effects, such as pain relief or euphoria. Instead, it acts on the cough reflex in the brain to suppress coughing[8,9].Promethazine HCl is a phenothiazine antihistamine and antiemetic. It is used to treat a variety of conditions including allergic reactions, nausea, and vomiting. It works by blocking the action of histamine, a chemical that is responsible for many allergic symptoms, and by blocking the action of dopamine, a chemical that is involved in the regulation of nausea and vomiting[10–12].

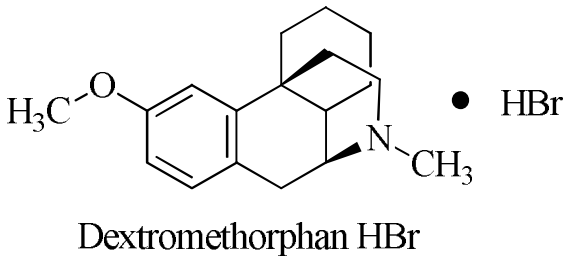
Both Dextromethorphan HBr and Promethazine HCl are available as oral medications in tablet and syrup form. They are also used as ingredients in combination products for the treatment of cough and cold symptoms. It is important to read the label carefully and follow the dosage instructions when using these medications, and consult a healthcare professional if you have any concerns.In present article, we have reviewed Dextromethorphan HBr and Promethazine HCl as potential antiallergic agents with special emphasis on reported analytical methods for estimation in bulk and their formulations.

Dextromethorphan HBr

Dextromethorphan is a cough suppressant found in many over-the-counter cold and cough medicines. It works by reducing the activity in the part of the brain that causes coughing. It is an active ingredient in many cough syrups and tablets, and it can also be found in some lozenges and capsules. Dextromethorphan is structurally related to levorphanol and morphine, but it does not have the same analgesic or addictive properties[13,14].

Dextromethorphan can be used to treat a number of conditions, including: coughs caused by colds, flu, or other viral infections, bronchitis or pneumonia, smoking or other types of lung irritation, certain medicines, such as ACE inhibitors or beta blockers.The mechanism of action of Dextromethorphan is not fully understood, but it is thought to work by affecting the cough reflex in the brainstem. It is thought to interact with a specific receptor called the sigma-1 receptor, which is involved in regulating the release of neurotransmitters that control the cough reflex.When used at the recommended dosage, Dextromethorphan is generally considered safe and effective. Common side effects include drowsiness, dizziness, and nausea. High doses of Dextromethorphan can cause more serious side effects, such as hallucinations, confusion, and even seizures[15–18].

It is important to note that taking Dextromethorphan in higher doses than recommended can be dangerous and even life-threatening. This is known as "Dextromethorphan abuse" or "robotripping" and can lead to a number of serious side effects, including hallucinations, confusion, and even seizures.In conclusion, Dextromethorphan is a cough suppressant that is commonly found in over-the-counter cold and cough medicines. It is effective in treating cough caused by various conditions, but it should only be used at the recommended dosage to avoid serious side effects. Misuse or overuse of Dextromethorphan can be dangerous and even life-threatening. The structure of Dextromethorphan is depicted in Figure 1. The IUPAC name of DXM is *(1S,9S,10S)-4-methoxy-17-methyl-17-azatetracyclo[7.5.3.01,10.02,7]heptadeca-2(7),3,5-triene*[16,17,19].



Dextromethorphan HBr

Figure 1. The structure of Dextromethorphan HBr

Different analytical methods reported for the estimation of Dextromethorphan HBr in bulk or formulation

High-performance liquid chromatography (HPLC) is a widely used method for the estimation of dextromethorphan HBr in both bulk and formulations. Several HPLC methods have been reported for the analysis of dextromethorphan HBr in bulk. These methods typically involve the use of a reversed-phase column, such as C18 or C8, and a mobile phase consisting of a mixture of water and organic solvent, such as methanol or acetonitrile. Detection is usually performed using a UV detector set at a wavelength of about 240 nm. HPLC methods for the estimation of dextromethorphan HBr in formulation are also widely

reported in the literature. These methods are similar to those used for bulk analysis, but they also involve the use of an appropriate sample preparation step, such as dilution or extraction, to prepare the sample for analysis.

A simple, rapid and economic UV spectrophotometric method has been developed and validated using a solvent 0.1N HCl to determine dextromethorphan HBr content in bulk and two different pharmaceutical solid dosage formulations, lozenges and chewable tablets. At the pre-determined λmax of 278nm, it was proved linear in the range of 5.0-30.0 µg/ml and exhibited good correlation coefficient (R2=0.9993)and excellent mean recovery (101.37-100.76%) and (100.66-101.17%) for lozenges and chewable tablets respectively. This method was successfully applied to the determination of dextromethorphan HBr content in lozenges and chewable tablets and the results were in good agreement with the label claim. The method was validated as per ICH guidelines for linearity, precision, accuracy, specificity, LOD and LOQ. The obtained results proved that the method can be employed for the routine analysis of dextromethorphan HBr in bulks as well as in the pharmaceutical formulations[20].

The spectrophotometry method by double divisor ratio spectra derivative was developed to determine the levels of dextromethorphan hydrobromide in tablet dosage form using ethanol as solvent. The method is based on the use of the coincident spectra of the derivative of the ratio spectra obtained using a double divisor (sum of two spectra) and measuring at either the maximum or minimum wavelengths. Then, the method was applied to determine the levels of dextromethorphan hydrobromide in tablet dosage form.The application of double divisor ratio spectra derivative spectrophotometry method for the determination of dextromethorphan hydrobromide was performed on the first derivative at Δλ 2 (λ 286.1 nm). The selection of wavelengths based on wavelengths gives the best result. The mean % recoveries were found to be in 99.95%.The method is successfully applied to analyze dextromethorphan hydrobromidein pharmaceutical formulation with no interference from excipients as indicated by the recovery study. All validation parameters were within the acceptable range[21].A simple, rapid and precise spectrophotometric method has been developed for determining the enhancement in the aqueous solubility of Dextromethorphan. Method was based on the absorbance. Dextromethorphan maximum was found at 278nm with hydrotrope dextromethorphan in double distilled water as solvent. The linearity was obtained in theconcentration range of 10-120µg/ml with coefficient of correlation 0.9993.The %RSD in case of intra-day and inter-day was found to be 0.8182 and 0.9438, respectively. The value of LOD and LOQ was found to be 3.76 and 1.141, respectively[22].

A sensitive, stability-indicating gradient RP-HPLC method has been developed for the simultaneous estimation of impurities of Guaifenesin and Dextromethorphan in pharmaceutical formulations. Efficient chromatographic separation was achieved on a Sunfire C18, 250 × 4.6 mm, 5 µm column with mobile phase containing a gradient mixture of solvents A and B. The flow rate of the mobile phase was 0.8 mL min^{-1} with column temperature of 50°C and detection wavelength at 224 nm. Regression analysis showed an *r* value (correlation coefficient) greater than 0.999 for Guaifenesin, Dextromethorphan, and their impurities. Guaifenesin and Dextromethorphan formulation sample was subjected to the stress conditions of oxidative, acid, base, hydrolytic, thermal, and photolytic degradation. Guaifenesin was found stable and Dextromethorphan was found to degrade significantly in peroxide stress condition. The degradation products were well resolved from Guaifenesin, Dextromethorphan, and their impurities. The peak purity test results confirmed that the Guaifenesin and Dextromethorphan peak was homogenous and pure in all stress samples and the mass balance was found to be more than 98%, thus proving the stability-indicating power of the method[23].

Another RP-HPLC method was developed for the simultaneous determination of Doxylamine Succinate and Dextromethorphan HBr in pharmaceutical dosage forms. The estimation was performed by using Purospher® STAR RP18 end capped (250 x 4.6) mm, 5µ) column as stationary phase and ACN: Water (70: 30 v/v) pH adjust to 3.4 by using Glacial Acetic Acid as mobile phase with 1mL/min as flow rate of mobile phase. The effluents were monitored at 250nm. The retention time of Doxylamine Succinate andDextromethorphan HBr were found as 5.83 min and 7.72 min, respectively. The method shows linearity in the concentration range of 20.84-62.51µg/mL and 50.02 - 150.07µg/mL for Doxylamine Succinate and Dextromethorphan HBr respectively. This method was found free of any interference from any excipients. The recovery studies for Doxylamine Succinate and Dextromethorphan HBr in formulations was found to be in the range of 98.0-103.0% and 98-99%, respectively. This developed method was validated for specificity, precision, linearity, accuracy, LOD, LOQ and robustness. Recovery of Doxylamine Succinate and Dextromethorphan HBr in formulations was found to be in the range of 99.50-101.30% and 99-73- 100.7% respectively[24].A simple, accurate and precise RP-HPLC method was developed for the estimation of Paracetamol, Dextromethorphen and Ibuprofen in tablet dosage form. The separation is achieved on Kinetics C18, 250×4.6mm, 5 micron. Column with flow rate 1.20mL per

minutes in gradient modes using Buffer pH 2.5 (water modified with OPA) as a mobile base. Column oven temperature was maintained at 25 ^{0}C [25].

A RP-HPLC was developed for the simultaneous estimation of Dextromethorphan and Quinidine on Phenomenex C-8 column with the mobile phase of methanol and phosphate buffer (pH 2.5) in the ratio 60:40 v/v at flow rate of 1ml/min and detection at 230nm was used. In UV spectrometry, simultaneous equation method was based on measurement of absorbances at two selected wavelengths 278nm and 331nm for Dextromethorphan hydrobromide and Quinidine Sulfate respectively. Absorbance ratio method based on the measurement of absorbances at isobestic point and wavelength maxima of one drug, selected wavelengths were 278nm (λmax of Dextromethorphan) and 289nm (isobestic point). The peaks of Dextromethorphan and Quinidine were found to be well resolved with retention time of 4.3min and 2.8min, respectively, indicating the shorter analysis time. The linearity was established in the concentration range of 1-30µg/ml. Limit of Detection (LOD) and Limit of Quantification (LOQ) were found to be within limits for both Dextromethorphan and Quinidine. In UV-spectrometry, both methods obey the Beer Lambert's law in the concentration range of 30-150µg/ml for Dextromethorphan hydrobromide and 10-70µg/ml for Quinidine sulfate respectively[26].

A simple, sensitive and accurate stability indicating HPTLC method has been developed and validated for estimation of Dextromethorphan hydrobromide in bulk and pharmaceutical dosage form. The drug was spotted on precoated silica gel 60 F254 aluminum plates using Toluene: Methanol: Triethylamine (8.5:1:0.5 v/v/v) as mobile phase. The retention factor (Rf) was found to be 0.60±1.92. The detection of band was carried at 225 nm. The drug was subjected to different stress conditions like acid, base, neutral hydrolysis, oxidation, thermal degradation and photolysis. The method was successfully validated according to ICH guidelines Q2 (R1). The data of linear regression analysis indicated a good linear relationship over the concentration range of 2000-20000 ng/band with correlation coefficient 0.991. The method found to be accurate as results of the recovery studies are close to 100 %[27].

The simultaneous determination of Dextromethorphan hydrobromide, Chlorpheniraminemaleate, and Potassium sorbate in cough syrup using the HPLC. The determination was carried out on the simulation sample consisting of three substances and prepared five different concentrations, with three replications for each concentration. The optimum HPLC conditions were obtained using the C18 column, with UV detection at 230 nm. The mobile phase of acetonitrile & phosphate buffer pH 2.5 (containing sodium-heptane sulfonate as ion-pair), with a gradient elution system, at a 1 mL/minute, while the flow rate column temperature is set at 35^{0}C. The results showed that the method has met the parameters set in the validation test with the recovery ranged from 98-102%, the precision test results (RSD) < 2%, and the linearity (r) ≥ 0.98. The method obtained was quite selective by confirmed identity with the maximum wavelength scanning of each analyte peak by PDA detector. The limit of detection (LOD) for Dextromethorphanhydrobromide, Chlorpheniramine maleate and Potassium sorbate were 3.13 µg/mL, 0.94 µg/mL and 0.12 µg/mL respectively and the limit of quantitation (LoQ) were 9.49 µg/mL, 2.85 µg/mL and 0.38 µg/mL respectively[28].

The LC-MS-MS method that can quantify Dextromethorphan and dextrorphan in oral fluid in a high-throughput toxicology laboratory setting have been developed. The developed method was validated according to the Scientific Working Group for Forensic Toxicology guidelines. The linear dynamic range was 5-100 ng/mL with a lowest limit of quantitation (LLOQ) of 5.0 ng/mL for Dextromethorphan and dextrorphan. Overall, the results of the accuracy and the precision values were within the acceptance criteria for both drugs. In addition, selectivity, matrix effect and recovery were calculated for the LC-MS-MS method. Authentic samples (n = 59) were tested to evaluate the applicability of the method. Thirty samples were found to be positive for Dextromethorphan and dextrorphan and two samples were found to be positive for Dextromethorphan only[29].A simple method using LC-MS/MS was developed and validated for determination of dextromethorphan and dextrorphan in human oral fluid. Following protein precipitation, chromatographic separation used a phenyl column with isocratic elution (1 ml/min) of 10 mM ammonium-formate buffer and acetonitrile (65:35; v/v) with 0.1% formic acid. Retention times were 2.6 min for dextrorphan and 5 min for dextromethorphan. Total run time was 7 min. The intra- and inter-assay deviations (accuracy) for dextrorphan (1-100 ng/ml) and dextromethorphan (5-1000 ng/ml) ranged from -13.6 to 8.8% and -9.6 to 5.7%, respectively. Precision variations were ≤7.5%. Matrix effect was ≤11.8%[30].

Promethazine HCl

Promethazine is an antihistamine and sedative medication that is used to treat a wide range of conditions, including allergies, nausea, vomiting, and motion sickness. It is also sometimes used as a mild sedative or to help with sleeping. Promethazine is available in both prescription and over-the-counter forms[31,32].The mechanism of action of promethazine is similar to that of other antihistamines. It works

by binding to histamine receptors in the body, preventing the action of histamine and reducing the symptoms of an allergic reaction. Histamine is a chemical messenger that is released by cells in the body in response to an allergen. It binds to receptors on other cells, which leads to the symptoms of an allergic reaction, such as itching, sneezing, and increased mucus production. Promethazine blocks the histamine from binding to the receptors and causes the symptoms of an allergic reaction to be less severe[16,19].

Promethazine is also a sedative medication and it works by affecting the brain chemicals that are responsible for causing sleep. It blocks the action of certain neurotransmitters such as dopamine and norepinephrine, which can cause drowsiness and relaxation. Promethazine is used to treat a variety of conditions, including: allergic reactions, such as hay fever, hives, and allergic asthma, nausea and vomiting, including that caused by chemotherapy, motion sickness, and insomnia, sedation before and after surgery.Common side effects of promethazine include drowsiness, dizziness, and dry mouth. High doses or long-term use of promethazine can cause more serious side effects, such as confusion, agitation, and even seizures. It can also cause blurred vision, so it is important to be careful when operating heavy machinery or driving while taking this medication[15,17,18].

In conclusion, Promethazine is an antihistamine and sedative medication that is used to treat a wide range of conditions, including allergies, nausea, vomiting, and motion sickness. It works by blocking the action of histamine and certain neurotransmitters, such as dopamine and norepinephrine, which causes drowsiness and relaxation. While it is generally considered safe and effective when used as directed, it can cause serious side effects if misused or overused. The structure of Promethazine is depicted in Figure 2. An IUPAC name of Promethazine is *N,N-dimethyl-1-phenothiazin-10-ylpropan-2-amine*[17].

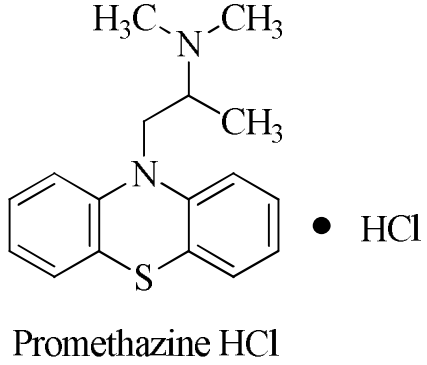


Figure 2. The structure of Promethazine

Different analytical methods reported for the estimation of Promethazine HCl in bulk or formulation

The estimation of Promethazine HCl by UV spectrophotometric method is a simple and rapid method that can be used for the quantification of Promethazine HCl in tablets, capsules, and injectable solutions. The method is based on the measurement of the absorbance of the drug at a specific wavelength using a UV-visible spectrophotometer. The basic principle of the method is that Promethazine HCl has a characteristic absorption spectrum in the UV-visible region. The absorbance of the drug is measured at a specific wavelength, usually around 275 nm, where the drug has maximum absorbance. By using a standard curve, the concentration of the drug in the sample can be determined[33,34].

The procedure for the method involves preparing a series of standard solutions containing known concentrations of Promethazine HCl and measuring the absorbance of each solution at the specified wavelength. A standard curve is then constructed by plotting the absorbance of the solutions against the corresponding concentrations. The sample solutions are then prepared, and their absorbance is measured at the specified wavelength. Using the standard curve, the concentration of Promethazine HCl in the sample can be determined.

A new spectrophotometric method was developed based on the oxidative coupling reactions for determination of 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 306 nm. The variables of reaction conditions including optimum volumes of both reagent and oxidizing agent, acidity of the reaction medium, order of addition and stability time were studied. The obtained results of the proposed method shows that a Beer law is obeyed in the range of 7-40ppm with a correlation coefficient (r^2) of 0.9981. While the molar absorptivity (ξ) of 1.861x103 $L.mol^{-1}.cm^{-1}$,sandal sensitivity(s) of 0.172µg.cm^{-2}, limit of detection (LOD) of 4.02ppm and limit of quantification(LOQ) of 13.39ppm were obtained[33].

Another visible spectrophotometric method has been developed for the determination of Promethazine HCl 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 0.978×10^4 $L.mol.^{-1}.cm^{-1}$. The relative standard deviation of the method was less than 2% and accuracy (average recovery) was 100±0.98%. The optimum conditions for all color development are described and the proposed method has been successfully applied for the determination of Promethazine HCl in pharmaceutical preparations and water samples. The common excipients and additives did not interfere in the proposed method[35].

Spectrophotometric techniques were developed for the determination of single and binary mixture promethazine hydrochloride and paracetamol. Normal and first derivative (^1D) used for single drug at λ 249.5 and 243.0 for promethazine hydrochloride and 243.5 and 225 for paracetamol. The simultaneous determination of binary mixture were accomplished by first derivative (^1D) and second derivative (^2D) spectrophotometric technique with applying zero crossing at valley (V=216.5) and Peak (P=258.8) nm for (promethazine hydrochloride) and (V=274.0 and P=299.2 nm for paracetamol).The correlation coefficient for calibration curves not less than 0.999 and the relative standard deviation not exceed to 0.214. The recovery of individual constituents under established conditions in the ranges from 97.00% to 101.97 %. Linearity is maintained within a wide concentration range from 4.00-30.00mg/L for promethazine hydrochloride and paracetamol. Standard addition method used for pharmaceutical tablets. A good accuracy and precision of simultaneous determination of promethazine hydrochloride and paracetamol were confirmed by statistical analysis[36].

Two cost effective spectrophotometric methods are developed and validated for quantitative determination of paracetamol and promethazine hydrochloride in tablet dosage form. Method I is based on the simultaneous equation and Method II on the absorbance ratio.The absorption maxima were found to be at 244 nm and 254 nm in distilled water for both the drugs. Beer's law is obeyed in the concentration range of 5-25 µg/ml for paracetamol and promethazine hydrochloride with correlation coefficient within range of 0.996-0.998. The simultaneous equation method is based on the additivity of absorbencies and the absorbance ratio method involves determination of the ratio of absorbance at 254 nm, the absorption maxima of promethazine and isoabsorptive wavelength 248 nm. The accuracy was assessed by recovery studies[37].A new, sensitive, rapid, simple, specific and economical procedure has been developed for determination Promethazine HCl in phosphate buffer saline pH 7.4. This analytical method for the determination of Promethazine HCl in phosphate buffer saline pH 7.4 can be used to estimate the amount of promethazine HCl penetrated and dissolved in the blood vessels *in vitro* by penetration study. The method is based on the ultraviolet light absorbance at 251 nm which is the maximum wavelength of the concerned drug. This method can be successfully applied for determination of drug in phosphate buffer saline pH 7.4[38].

A highly sensitive and simple catalytic spectrophotometric method for the determination of promethazine hydrochloride based on inhibitory effect of promethazine hydrochloride on the hemoglobin-catalyzed the reaction of H2O2 and acid chrome blue K (ACBK) was developed. The concentration of promethazine hydrochloride is linear with the percentage inhibition (I %) of system under the optimal experimental conditions. The calibration graph is linear in range 6.23×10^{-8} to 1.56×10^{-5}mol L^{-1} with the detection limit of 9.32×10^{-10}mol L^{-1}. This method can be used for the determination of promethazine hydrochloride in tablets and injection solution of promethazine hydrochloride with satisfactory results[39].A sensitive spectrophotometric method for determination Promethazine HCl in aqueous solution based on reduction of Fe^{3+} to Promethazine HCl have been developed. The Fe^{2+} formed complexed with 1,10-Phenanthroline at pH 3.10 to produce a red-colour, water soluble and stable complex, which exhibits maximum absorption at 514 nm. Beer's law obeyed in the concentration range from 2-16 µg/ml of Promethazine HCl. The molar absorptivity is 34015.4 $L.mol^{-1}.cm^{-1}$ and Sandell's sensitivity index of 0.0094 $\mu g.cm^{-2}$, a relative standard deviation was not more than 1.34%, and D.L 0.138 µg/ml[40].

A simple and rapid stability-indicating HPLC method was developed for determination of promethazine hydrochloride in hot-melt extruded (HME) films and sustained release tablets. Chromatographic separation was achieved on a 150 mm x 4.6 mm i.d., 3 microm 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 was achieved with UV detection at 249 nm based on peak area. The method was validated in terms of linearity, precision, accuracy, robustness specificity, limits of detection and quantitation according to ICH guidelines. Specificity was validated by subjecting the drug to acid, base, oxidative, reductive and dry heat degradations. None of the degradation products obtained by forced degradation interfered with the promethazine hydrochloride peak. The method was successfully applied for assessing

the stability of the drug in the HME films and sustained release tablet formulations. In addition, uniformity of promethazine hydrochloride content in HME films was also determined using the method developed. Excipients present in either of the dosage forms analyzed did not interfere with the analysis indicating the specificity of the method. Due to its simplicity and accuracy, the method is suitable for application to various dosage forms[41].

Another RP-HPLC method has been developed for the estimation of paracetamol and promethazine HCl using water, methanol and acetic acid in 79:20:1 v/v/v ratio as eluting phase on Kromasil Silica column keeping flow rate at 1mL/min and detection at 249 nm. Both drugs observed linearity between 10-50µg/ml and successfully resolved within 6 minutes (3.565 and 5.641 minutes for paracetamol and promethazine respectively) with percent recovery between 98-101%. Tailing factor was within the range and number of theoretical plates was more than 2500. Method was validated as per ICH guidelines and the results indicate that these drugs could be quantified simultaneously without excipient interference and thus suitable for routine analysis of drugs in combination[42].Few more article reported another HPLC method reported for the estimation of paracetamol and promethazine HCl.The chromatography system used a reversed phase C18 column (HiQSil 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%. The method can be used for estimation of combination of these drugs formulations[43].

The HPLC method for determination of promethazine HCl in promethazine and bile tablets have been developed and reported.The HPLC system consisted of DiamonsilTMC18 (5 µm 250 mm×4.6 mm),and mixture of 0.02 mol·L^{-1}potassium dihydrogen phosphate buffer solution(dissolve 2.72 g potassium dihydrogen phosphate in 700 mL of water, adjust to pH3.0 by H_3PO_4,dilute with water to 1000mL)-acetonitrile- methanol(55:20:25)as mobile phase,at the flow rate of 1.0 mL·$min^{-1}$and the detection wavelength of 249 nm and the injection volume was10 µL.The linear range of promethazine HCl was5.3-84.6 µg·mL^{-1},the correlation coefficient was 0.9998(n=6).The average recovery was 99.90%, (RSD=0.62%,n=5). The method was simple, sensitive and accurate[44].One more RP-HPLC method was developed using Column 5 micron and reverse step with linear gradient elution is accomplished in Symmetry Shield RP8 (4.6 mm x 150 mm). Mobile phase A was 3.4% in the 7.0 pH water, modified to dilute potassium hydroxide solution. In contrast, the 60:40 mixture of acetonitrile and methanol combination as mobile phase B. The handled phase with a continuous flow rate of 1.0 ml $min^{-1}$was provided by choosing the wavelength 254 nm using a PDA/UV detector. The temperature of the column oven and sampler was 25^0C and 4^0C, respectively. The injection amount chosen was 10.0 µL. The method was linear in the quantitation limit range (LOQ) to 150 percent concerning the specification impurity concentration limit. Both impurities and promethazine HCl have a correlation coefficient of greater than 0.999. The LOQ for all known impurities and promethazine HCl has a specification limit of between 10 to 30%. The relative response factor for all four known impurities was calculated. The unexplained peaks are very different; the effects obtained are similar to the original values. There were no significant changes improvements to the suitability parameters, such as tailing factor, theoretical plates, and % RSD in robustness studies[45].

CONCLUSION

Antihistamines, also known as antiallergics, are a group of medications that inhibit the activity of the chemical messenger histamine, which is produced naturally by the body and is involved in the immunological response. Dextromethorphan HBr is a cough suppressant that is also an active ingredient in several over-the-counter drugs that are used to treat coughs and colds. Antihistamine and antiemetic properties are exhibited by the phenothiazine compound known as promethazine HCl. It is prescribed for the treatment of a wide variety of disorders, such as allergic responses, nausea, and vomiting. Oral drugs in the form of tablets and syrup are available for administration of both dextromethorphan HBr and promethazine HCl. In this paper, we discuss the possible antiallergic drugs dextromethorphan HBr and promethazine HCl. We place a particular emphasis on published analytical methods for estimate in bulk and their formulations. There have been several different analytical methods documented that can be used to determine the amount of these medications in formulations or bulk. The majority of the published analytical methods include UV spectrophotometric method, HPLC, RP-HPLC, HPTLC, and LC-MS/MS. As a result of this analysis, we have come to the conclusion that there are only a small number of analytical methods that have been described for the determination of dextromethorphan HBr and promethazine HCl in bulk and formulations. The majority of these techniques were designed to estimate the presence of

the drug in conjunction with other substances. As a result, we have chosen these medications so that we can develop and validate an HPLC method for the estimation of their pharmaceutical formulations as well as the bulk drug.

CONFLICTS OF INTERESTS

Authors declared that there is no conflicts of interests exist.

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