Survey Spectrophotometric Method for Determination of Phenothiazine Drug

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Abstract: The main purpose of this study is determination of phenothiazine drug by spectrophotometry method. A new simple and sensitive spectrophotometric method for some phenothiazine derivatives has been developed. The proposed method is based on the reaction of phenothiazine derivatives promethazine hydrochloride, chlorpromazine hydrochloride, triflupromazine hydrochloride, prochlorperazine, and trifluoperazine with potassium iodate followed by reaction of liberated iodine with leuco crystal violet and measurement of the color of the oxidized LCV at 634 nm. An extensive survey of the literature published in various analytical and pharmaceutical chemistry related journals has been conducted and the instrumental analytical methods which were developed and used for determination of some drugs. The method showed a good linearity. The optimum conditions and other analytical parameters were evaluated. The proposed methods have been applied successfully to the analysis of phenothiazine derivatives in pure form and in their dosage forms, and no interferencewas observed from common excipients present in pharmaceutical formulations. The results obtained were in a good agreement with those obtained from a previously published method of the investigated drug.
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1. Introduction

Simple, rapid, cost-effective, sensitive and extractive spectrophotometric methods were developed for the determination of drugs. Phenothiazines are a very significant class of organic compounds with potent physiological activity. Phenothiazines are neuroleptics used for the treatment of moderate and severe mental and emotional conditions. They are also used as antipsychotics, anticholinergics and antihistamines. Many phenothiazine derivatives and their formulations are officially in British pharmacopoeia and Indian pharmacopoeia. The increasing use of phenothiazine derivatives in medicine has boosted the development of several methods for their determination in pure form and in pharmaceutical formulations.

The aim of this work was to develop simple, sensitive, reliable and inexpensive spectrophotometric methods for MSN quantitation in bulk form and in its commercial ampoules. The first method is time consuming and care must be taken with the second one since many organic compounds absorb in this region of the spectrum. The methods used for their determination include spectrofluorometry, conductometry, fluoroimmunoassay, HPLC, HPTLC polarography, GLC, chemiluminescence, and capillary zone electrophoresis. The official methods presented in the British pharmacopoeia for phenothiazines consist of nonaqueous potentiometric titrimetry or spectrophotometry in the ultraviolet region, depending upon the derivative.

Reviewing the literature revealed that, up to the present time nothing has been published concerning the spectrophotometric determination of nalbuphine and naltrexone and little detection has been reported for the determination of morphine and tramadol by spectrophotometric methods. For these reasons, the present study describes simple, sensitive and economical spectrophotometric methods for the analysis in pure and pharmaceutical preparations.

Many drugs are easy to determine by spectrophotometry based on color charge transfer (CT) complexes formed between electron acceptors, either π- or δ-acceptors and drugs as electron donors either n or π donors. This paper reports simple, direct, sensitive and precise spectrophotometric methods for the determination of drugs. Different analytical methods that have been reported for the determination of amlodipine including, high-performance liquid chromatography. Many spectrophotometric methods have already been reported for the determination of phenothiazines. They are generally based on redox reaction, ion pair complex formation, binary complex formation, ternary complex formation, diazo-coupling, and oxidative coupling.

Charge transfer phenomena were introduced by Mulliken and widely discussed by Foster to define a new type of adducts. Hence, it is worthwhile to develop simpler and cost-effective methods for

simultaneous estimation of drugs for routine analysis of formulations. Spectrophotometric methods fulfil such requirements. HPLC, GC, and HPTLC methods which are widely used for pharmaceutical analysis are accurate and precise with good reproducibility, but the cost of analysis is quite high owing to expensive instrumentation, reagents and expertise.

Under the optimum conditions, Beer's law limit, molar absorptivity and Sandell's sensitivity were calculated. The limits of detection and quantification were also reported for both methods.

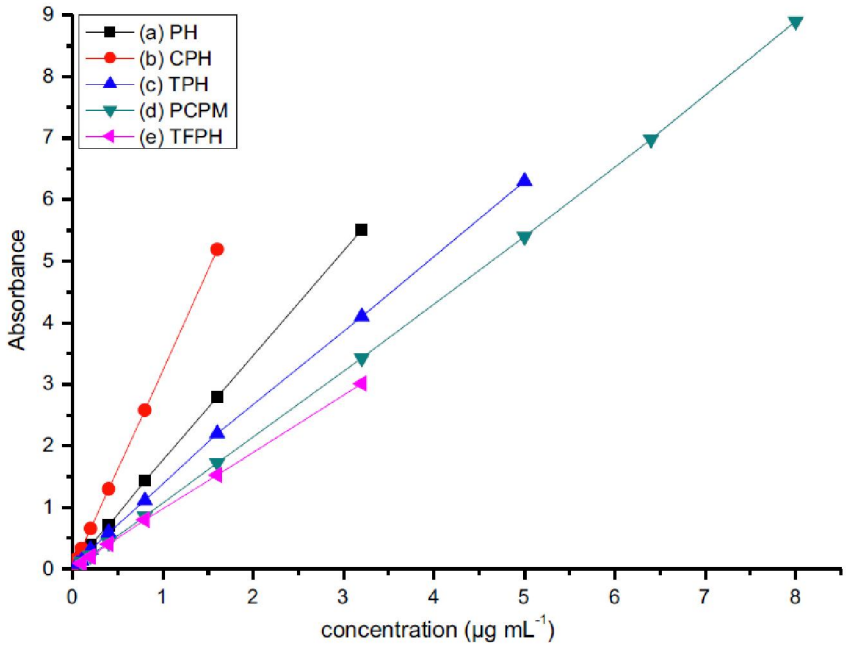

Fig. 1. Calibration graph for phenothiazine drugs

Statistical evaluation of the methods was examined by determining intra-day and inter-day precisions. The methods were successfully applied to the assay of drugs in their pharmaceutical formulations. No interference was observed from common additives and the validity of the methods was tested. Some of the spectrophotometric methods found in the literature are reasonably rapid and selective, but suffer from a number of disadvantages such as low sensitivity, narrow dynamic range, heating step, extraction step, poor stability of the colored species, and instrumental or procedural complications.

They are easily oxidized by different chemicals, and by electrochemical, photochemical, and enzymatic methods. Oxidation is interesting for the determination of the phenothiazines, because it improves the spectroscopic properties for UV–Visible and fluorescence detection. General approaches for the oxidation of the phenothiazines are based on either photochemical or chemical oxidation. The 2-substituted and 10-substituted phenothiazine derivatives exhibit many chemical properties, apart from interesting medicinal qualities. Phenothiazine and its derivatives are characterized by low ionization potentials.

The present investigation aims to develop a more sensitive and cost-effective method for the determination of phenothiazine in pure form and pharmaceutical formulations. The method employs potassium iodate as an oxidizing agent and leuco crystal violet (LCV) as a chromogenic reagent. The proposed methods have been demonstrated to be superior to the reported methods with respect to their speed, simplicity, sensitivity, and cost-effectiveness.

The proposed method has been successfully applied for determination of the drugs under investigation in pure and dosage forms. As an analgesic agent, it is almost as potent as morphine and has been widely used in the treatment of acute and chronic pain. Its main advantages over morphine are a ceiling effect of respiratory depression, low tolerance liability and a lack of significant withdrawal symptoms. It is available as an injection for intramuscular and intravenous administration.

Experimental

Apparatus

A Varian Carry 50 Bio UV spectrophotometer with 1-cm matched quartz cell was used for all absorbance measurements, and a Systronics type 331-pH meter was employed for the pH measurements.

Reagents and solutions

All chemicals used were of analytical reagent grade and double-distilled water was used throughout the experiment.

Standard drug solution

A standard solution of 1,000 lg mL-1 of phenothiazine derivatives was prepared by dissolving accurately weighed 100 mg of pure drug in distilled water, diluted to 100 mL. The stock solution was diluted stepwise to get working concentrations.

Potassium iodate solution: A 59 10-2-M aqueous solution was prepared in deionized water. Leuco crystal violet (LCV) [Eastman Kodak Co]: An amount of 250 mg of LCV was dissolved in 200 mL distilled water containing 3 mL 85 % phosphoric aci (Merck) and the volume was made up to 1 L with distilled water and stored in an amber-colored bottle away from sunlight.

Sodium hydroxide solution: A 0.1-M aqueous solution was prepared.

Hydrochloric acid solution: A 2-M aqueous solution was prepared.

Procedure

Preparation of calibration curve

Different aliquots of phenothiazine derivatives containing promethazine (0.05–4.0 lg mL-1), chlorpromazine (0.02–2.0 lg mL-1), triflupromazine (0.05–5.0 lg mL-1), trifluperazine (0.05–2.0 lg mL-1), and prochlorperazine (0.1–8.0 lg mL-1) were accurately measured and transferred into a series of 25-mL standard flasks and the volume was adjusted to 5.0 mL by adding distilled water. To each flask, 1 mL of 1 MHCl, 1 mL of LCV and 1 mL of potassiumiodate was added. The contents were mixed well and flasks were allowed to stand for 10 min with occasional shaking, then the pH of each mixture was adjusted with sodium hydroxide solution. The volume was diluted to the mark with water, mixed well, and the absorbance was measured at 598 nm against reagent blank.

Procedure for tablet

Twenty tablets were weighed and finely powdered. An accurately weighed portion of the powder equivalent to 50 mg of the phenothiazine salt was transferred into a 100-mL calibarated flask and diluted to volume with water. Using a mechanical stirrer, the powder was completely disintegrated and the solution was filtered. A suitable aliquot of this solution in the individual phenothiazine working range was treated as described in the recommended procedure.

Results and discussion

The proposed method is based on the oxidation of phenothiazine derivatives with KIO3 in acidic medium. Phenothiazine derivatives are reported to be oxidized to form sulfoxides. The process proceeds in two steps; the first is reversible electron abstraction from phenothiazine to the colored semiquinol cationic radical. The radical is stable for a certain period of time depending upon phenothiazine substitution, pH and buffer used. The second irreversible step leads to the generation of the colorless sulfoxide.

To optimize the detection system, the UV–Vis spectra of the phenothiazines were recorded; similar spectroscopic properties were observed for all analytes. The respective data are presented in Table 1. The phenothiazines and their corresponding sulfoxide are characterized by similar UV–Vis spectroscopic properties, with a slightly red shifted absorption maximum for the sulfoxide, e.g., at 340 nm for chlorpromazine. The radical cation exhibits an additional absorption maximum at 529 nm with small molar absorptivity.

In the proposed method, when KIO3 and the phenothiazines are mixed in solution, the formation of red color is observed, which is associated with the additional absorption band as described above. This color quickly fades away. As a result of the reaction between KIO3 and phenothiazines with sulfoxides, I2 is liberated. The liberated iodine is treated with LCV to form CV dye which gives an absorption maximum at 598 nm. The intensity of the color of the dye is directly proportional to the concentration of phenothiazines.

Optimization of reaction variables

Effect of reagent concentrations

The goal of this investigation was to find a simple, reliable and accurate method for the determination of the drugs under study in routine work. For method A, the influence of iodate and LCV concentrations on the colored reaction has been checked. Optimization revealed that the 4.5 9 10-2–6 9 10-2 M of KIO3 gives the maximum and stable absorbance and that the intensity decreases with the increase in iodate concentration. Hence, 1 mL of 5 9 10-2 M KIO3 solution was used for the studies.

The concentration of LCV on its absorbance showed that maximum absorbance was found after the addition of 0.8 mL of LCV and it remained constant at higher concentrations; hence, 1 mL of LCV was used for further work.

Effect of time, temperature and pH

The reasonable reaction time was 10 min and delay up to 30 min had no effect on the absorbance, while the developed color remained stable for several days (Fig. 6).

The oxidation of phenothiazine derivatives with iodate was studied at the temperature range between 20 and 40 C. The rate of oxidation decreased slightly with increasing temperature. Therefore, working at room temperature, i.e. 25 C, was adopted.

The effect of various acids like HNO3, H2SO4, HCl, HClO4, etc. were checked and the best results were found in HCl medium. A pH 2–3 was required for liberation of I2 which gives a blue color with LCV at pH 4–4.5. After pH 5, the solution becomes turbid. Initial pH was maintained by 1 mL of 1 M HCl; later on, the pH was adjusted up to 4 by using 0.1 M NaOH solution.

Method validation

The absorbance versus concentration was plotted and a linear correlation was found. Beer's law range, the molar absorptivity and Sandell's sensitivity are given in Table 2. The limits of detection, limits of quantification, regression equation, and correlation coefficients values.

The accuracy and precession of the analytical method have been evaluated. For accuracy, the percentage relative error between the measured concentrations and the chosen concentration was calculated. The precision of the method was calculated in terms of intermediate precision (intra-day and inter-day). The SD and RSD values of intra-day and inter-day studies showed that precision was good.

Selectivity

To determine the selectivity of the proposed method, the analytical placebo was analyzed by the proposed methods. It was confirmed that the change in the absorbance with respect to the blank was caused only by the change in analyte concentration. To identify the interference by common tablet excipients, a synthetic mixture with the composition of phenothiazine derivatives (50 mg), talc (80 mg), starch (160 mg), calcium gluconate (80 mg), lactose (80 mg), sodium alginate (40 mg) and magnesium stearate (40 mg) was prepared and subjected to analysis by the proposed methods after solution preparation using the procedure described for tablets. The percentage recoveries suggesting no interference by the excipients in the assay of phenothiazine under the described optimum conditions.

Application to formulations

The proposed method was applied to the determination of phenothiazines in tablets and injections. The results in Table 4 show that the method is applicable for the determination of phenothiazines and that the excipients in the dosage forms do not interfere. A statistical comparison of the results by the proposed methods and a literature method showed that the results agree well with the claim and are also in agreement with the results obtained by the literature method. Statistical analysis of the results using Student's t test for accuracy and F test for precision revealed no significant difference between the proposed method and the literature method at 95 % confidence level with respect to accuracy and precision.

Conclusion

The aim of the present work was to suggest a simple, reliable and accurate extractive spectrophotometric method for the determination of some drugs. In conclusion, a simple, rapid, and cost-effective method for the determination of phenothiazine derivatives has been developed and validated. The proposed method is more sensitive than many existing methods, and is free from such experimental variables as heating or an extraction step. The stability of the color system is an advantage over the earlier methods. The method provides sensitivity comparable to that achieved by sophisticated and expensive techniques like HPLC. Thus, it can be used as an alternative for rapid and routine determination of bulk samples and tablets. Therefore, the validated methods could be useful for routine quality control assays of the studied drugs in the raw pharmaceutical materials and dosage forms.

References:

1. Alarfaj et al., 2015. N.A. Alarfaj, S.A. Altamimi, L.Z. Almarshady. Asian J. Chem., 21 (1) (2015), pp. 217–226.
2. Baviskar et al., 2014. D.T. Baviskar, S.C. Jagdale, N.O. Girase, A.Y. Deshpande, D.K. Jain. Asian J. Chem., 21 (1) (2014), pp. 206–210.
3. Choudhary et al., 2015. B. Choudhary, A. Goyal, S.L. Khokra. Asian J. Chem., 22 (1) (2015), pp. 562–568.
4. Gangwal and Sharma, 1996. S. Gangwal, A.K. Sharma. Indian J. Pharm. Sci., 58 (1996), p. 216
5. K. Nesmeˇra´k, V. C ˇ erveny´ , J. Hranı´cˇek, P. Rychlovsky´, Microchem. J. 106, 226–232 (2013).
6. K. Upadhyay, A. Asthana, N. Tiwari, S.B. Mathew, Res. Chem. Intermed 39(8), 3553–3563 (2013).
7. N. Tiwari, A. Asthana, K. Upadhyay, Res. Chem. Intermed. 39(8), 3867–3875 (2013).
8. M. Rizk, E.A. Taha, S. Mowaka, Y.M. Abdallah. Kinetic fluorimetric determination of Mesna (sodium-2-mercaptoethanesulfonate) in drug products through oxidation with cerium (IV). Eur J Chem, 4 (3) (2013), pp. 220–225.
9. M.D. Arun, M.P. Sunil, L.G. Kailash, A.J. Gey. Development and validation of spectrophotometric methods for the simultaneous estimation of miconazole nitrate and mitronidazole in bulk powder form. Int. Res. J. Pharm., 5 (2014), pp. 597–603.
10. M. Rizk, E.A. Taha, S. Mowaka, Y.M. Abdallah. Validated stability-indicating HPLC method for

the determination of mesna in presence of its degradation products. J Chromatogr Sci, 53 (5) (2015), pp. 742–748.
11. I. Salama, M.S. Gomaa. Comparative determination of miconazole, nystatin, hydrocortisone and neomycin by HPTLC/HPLC-DAD. Eur. J. Chem., 4 (2013), pp. 29–34.
12. P.K. Pagare, C.S. Satpute, V.M. Jadhav, V. Kadam. Forced degradation studies and validated stability-indicating HPTLC method for determination of miconazole nitrate in soft lozenges. Pharm. Lett., 4 (2012), pp. 1793–1804.
13. R. El Sheikh, N.S. Esmail, A.A. Gouda, W. Abdel Basset. Extractive spectrophotometric determination of some α-adrenergic-antagonists in pure forms and in pharmaceutical formulations. Chem. Ind. Chem. Eng. Q., 18 (2012), pp. 179–191.
14. R. El-Sheikh, M. Zaky, A.A. Gouda, S.A. Aboal Ezz. Extractive spectrophotometric determination of vardenafil HCl and yohimbine HCl in pure and pharmaceutical dosage forms. J. Chil. Chem. Soc., 59 (2014), pp. 2248–2255.
15. S.R. Kadam, M.V. Janjale, S.B. Akole, S.S. Bhosale. Application of mixed hydrotropic solubilization technique for simultaneous spectrophotometric estimation of metronidazole and miconazole nitrate from different pharmaceutical dosage forms. Int. J. Pharm. Biol. Arch., 3 (2012), pp. 383–390.
16. S. Asghar, S. Sheikh, S. Ahmad. Simultaneous determination and validation of miconazole nitrate with the antimicrobial preservatives using RP-HPLC method: for benzoic acid, sodium propyl hydroxyl benzoate and sodium methyl hydroxy benzoate in pharmaceutical cream. Int. J. Pharm. Res. Sch., 3 (2014), pp. 106–113.
17. Vinay et al., 2011. K.B. Vinay, H.D. Revanasiddappa, O.Z. Devi, P.J. Ramesh, K. Basavaiah. Rapid titrimetric and spectrophotometric determination of ofoxacin in pharmaceuticals using N-bromosuccinimide. Braz. J. Pharm. Sci., 47 (2011), pp. 251–260.
18. Zenita and Basavaiah, 2011. O. Zenita, K. Basavaiah. Utility of N-bromosuccinimide for the titrimetric and spectrophotometric determination of famotidine in pharmaceutical formulations. Int. J. Anal. Chem. (2011).

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