DEVELOPMENT AND VALIDATION OF DOUBLE DIVISOR RATIO SPECTRA DERIVATIVE SPECTROPHOTOMETRY METHOD FOR TERNARY MIXTURE OF GUAFENESIN, DEXTROMETHORPHAN HBR, AND DIPHENHYDRAMINE HCL IN TABLET DOSAGE FORM

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ABSTRACT

Objective: This study aimed to develop spectrophotometry method by double divisor ratio spectra derivative to determine the levels of guaifenesin (GUA), dextromethorphan hydrobromide (DMP), and diphenhydramine hydrochloride (DPH) in tablet dosage form using ethanol as solvent.

Methods: 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 GUA, DMP, and DPH in tablet dosage form.

Results: The application of double divisor ratio spectra derivative spectrophotometry method for the determination of GUA, DMP, and DPH was performed on the first derivative at $\Delta \lambda$ (280.0 nm, 286.1 nm, and 260.2 nm, respectively). The selection of wavelengths based on wavelengths gives the best result. The mean % recoveries were found to be in 100.60%, 99.95%, and 101.74% for GUA, DMP, and DPH, respectively.

Conclusion: The method is successfully applied to analyze GUA, DMP, and DPH in pharmaceutical formulation with no interference from excipients as indicated by the recovery study. All validation parameters were within the acceptable range.

Keywords: Guaifenesin, Dextromethorphan HBR, Diphenhydramine HCL, Double divisor ratio spectra derivative spectrophotometry.

INTRODUCTION

Guaifenesin (GUA) is chemically known as (+)-3-(2-methoxy phenoxy)-propane-1,2-diol. It is empirical formula is $\text{C}_7\text{H}_{10}\text{O}_3$ which corresponds to molecular weight of 198.21. It has slight bitter aromatic taste. It is used to relieve the chest congestion. It controls the symptom but does not treat the cause of the symptom. It is an expectorant and thinning the mucus and clear the airways [1]. Dextromethorphan hydrobromide (DMP) is chemically known as [(+)-3-methoxy-17-methyl-9α,13α,14α-morphinan], used in the form of the base or as the monohydrated hydrobromide salt. DMP is a cough suppressant which is found in many over-the-counter cough and cold remedies [2]. Diphenhydramine hydrochloride (DPH) is an antihistamine medication having the compound name 2-(diphenylmethoxy)-N,N-dimethylethylamine hydrochloride and has formula $\text{C}_{19}\text{H}_{21}\text{NO}\cdot\text{HCl}$. DPH is used to treat sneezing, runny nose, watery eyes, hives, skin rash, itching, and other cold or allergy symptoms [3].

GUA was determined individually and with other compounds by spectrophotometry [1,4-6], reversed-phase high-performance liquid chromatography (RP-HPLC) [7,8] and HPLC [9-11] methods. DMP was determined individually and with other compounds by spectrophotometry [12-14], potentiometric [12], RP-HPLC [7], and HPLC [11] methods. DPH was determined individually and with other compounds by conductometry [15], spectrophotometry [16], and HPLC [11].

Double divisor ratio spectra derivative spectrophotometry method for simultaneous estimation is a simple, accurate, and cost-effectiveness [17]. According to the best of our knowledge, there is no published double divisor ratio spectra derivative spectrophotometry method for simultaneous estimation GUA, DMP, and DPH in their combination.

METHODS

Reagents and chemicals
All material and reagents were analytical grade. The raw standard of GUA was purchased from Zhejiang Halzhou Pharmaceutical, Linhai City, China. DMP and DPH were purchased from Beijing Taiyang Pharmaceutical Industry. Commercially available tablets were obtained from a local pharmacy.

Instruments and apparatus
The spectrophotometric measurements were carried out on a Shimadzu - ultraviolet (UV) 1800 spectrophotometer, matched quartz cells 1 cm and UV probe 2.42 software was used for all spectral measurements. Boeco analytical balance and Branson 1510 ultrasonicator was also used.

Preparation of standard solution
Accurately weighed 50 mg of GUA, DMP, and DPH standard was separately transferred into 100 mL volumetric flask and dissolved in ethanol to give solutions containing 500 µg/mL GUA, DMP, and DPH.

Selection of analytical wavelength
The solutions of GUA, DMP, and DPH were prepared in diluent by appropriate dilution and spectrum was recorded. The absorption spectra of the solutions prepared at different concentrations of GUA (6–36 µg/mL), DMP (9–25 µg/mL), and DPH (9–25 µg/mL) were scanned in the range of 200–400 nm. The double divisor value in various concentrations is calculated to selected wavelength range analysis.

Assay of tablet formulation by double divisor ratio spectra derivative spectrophotometry method
Content of 20 tablets was weighed accurately. A powder quantity equivalent to 75 mg GUA, 5 mg DMP, and 7.5 mg DPH was accurately weighed and transferred into volumetric flask of 100 mL capacity. 30 mL

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of ethanol was transferred into this volumetric flask and sonicated for 10 min. The flask was shaken and volume was made up to the mark with diluent. The above solution was filtered through Whatman filter paper (0.45 µ). The solution was made up to the mark with diluent to give a solution containing 18 µg/mL of GUA, 12 µg/mL of DMP, and 18 µg/mL of DPH. The resulting solution was analyzed by proposed method. The quantitation was carried out by keeping these values to the straight line equation of calibration curve.

Method validation
The method was validated based on linearity, accuracy, precision, limit of detection (LOD), and limit of quantification (LOQ). It was validated according to the International Conference on Harmonization Guidelines.

RESULTS AND DISCUSSION
Selection of analytical wavelength
Selection of analytical wavelength is carried out by dividing absorption spectra of solutions at different concentrations using the sum of the absorption spectra of solutions of DMP+DPH (25 µg/mL each in diluents), DPH+GUA (18 µg/mL each in diluents), and GUA+DMP (12 µg/mL each in diluents), respectively, for the determination of GUA, DMP, and DPH as double divisor to get the ratio spectra and their first derivatives were plotted with delta lambda 2 nm and scaling factor 1.0. The divided and derivatized spectra’s (Figs. 1-3) showed maximum and minimum wavelengths. The wavelengths 280.0 nm, 286.1 nm, and 260.2 nm were selected for analysis of GUA, DMP, and DPH, respectively.

Method validation
The low values of percent relative standard deviation are indicative of the precision and reproducibility of the method. The resulting mixtures were assayed according to the above-stated procedure, and the results were calculated as the percentage of analyst recovered. LOD and LOQ values were indicated that the method shows high sensitivity. The good recovery values assure the high accuracy of the proposed method. Validation parameters for this method are shown in Table 1.

Based on Table 1, this research has good result validation method for simultaneous GUA, DMP, and DPH in their combine tablet dosage form.

Application of the method in commercial tablet
The proposed method was applied for the determination of GUA, DMP, and DPH in their combined commercial tablet and the results are shown in Table 2.

The results of analysis of pharmaceutical dosage form by the proposed method are in good agreement with label claim of the drug. According to this result, the proposed method is potential to use in routine drug analysis, especially drugs with contained the combination of several drugs. It is easy to work, especially for routine analysis and no require long conditioning tools.

CONCLUSION
The proposed method provides a simple, accurate, and precise quantitative analysis for the estimation of GUA, DMP, and DPH as a ternary mixture. The proposed method is simple as there is no need for solvent extraction and direct as it estimates each component independent of the other, and also the method is rapid, low cost, and

| Parameters | GUA | DMP | DPH |
|------------|-----|-----|-----|
| Accuracy (%) | 100.6 | 99.95 | 101.74 |
| Precision | 0.6422 | 0.6750 | 0.0254 |
| RSD (%) | 1.5817 | 1.1671 | 1.1071 |
| LOD | 4.7932 | 5.0630 | 3.3550 |

GUA: Guaifenesin, DPH: Diphenhydramine hydrochloride, RSD: Relative standard deviation, LOD: Limit of detection, LOQ: Limit of quantification, DMP: Dextromethorphan hydrobromide
harmless to the environment. Hence, it could be applied in quality control laboratories.

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CONFLICT OF INTEREST
We declare that there is no conflict of interest.

REFERENCES
1. Rao BK, Kumari JI, Nageswara RM, Babu CR. A new and sensitive UV spectrophotometric method for the determination of guaifenesin in dosage forms. Int J Pharm Pharm Res 2015;3:139-48.
2. Drozd J. Comparison of classic and derivative UV spectrophotometric methods for determination of dextromethorphan hydrobromide. Acta Fac Pharm Univ Comenianae 2012;59:22-9.
3. Ul Hassan SA. Method development of diphenhydramine HCl (C17H21NO. HCl) on spectrophotometer. IOSR J Appl Chem 2015;8:59-62.
4. Pushpalatha E, Tejaswini P, Najboonbi M, Vineesha S, Madhanna MD, Kumar TA, et al. Development of UV spectroscopic method for the determination of guaifenesin in bulk and formulation. Int J Pharm Res Anal 2015;5:90-5.
5. Bhattacharyya I, Bhattacharyya SP, Kyal C, Choudhury P, Dhakal B, Ghosh SK. Estimation and validation of stability indicating UV spectrophotometric method for the determination of guaifenesin in presence of its degradant products. Int J Pharm Pharm Sci 2013;5 Suppl 1:262-8.
6. Prabhu PP, Das P, Krishna NM, Subrahmanyam EV. Spectrophotometric method for development of guaifenesin in pharmaceutical dosage form. Int J Pharm Chem Biol Sci 2013;3:881-6.
7. Raghava RT, Kumar NA, Kumar SR, Reddy AM, Rao NS, Rao IV. Development and validation of a stability-indicating RP-HPLC method for the simultaneous estimation of guaifenesin and dextromethorphan impurities in pharmaceutical formulations. Corp Chromatogr 2013. Article ID: 315145, 12 pages.
8. Senthilraja M, Giriraj P. Reverse phase HPLC method for the simultaneous estimation of terbutaline sulphate, bromhexine HCl and guaifenesin in cough syrup. Asian J Pharm Clin Res 2011;4:13-5.
9. Ansari M, Kazemipour M, Shahrriar M. Simultaneous quantitation of theophylline and guaifenesin in syrup by HPLC, derivative and derivative ratio spectrophotometry for quality control purposes. Iran J Pharmacol Ther 2006;5:67-72.
10. Ahmed NR, Lottfi SN. High performance liquid chromatographic method for the determination of guaifenesin in pharmaceutical syrups and in environmental samples. Baghdad Sci J 2012;10:1014-21.
11. Çağlar H, Büyükutucel E. HPLC method development and validation simultaneous determination of active ingredients in cough and cold pharmaceuticals. Int J Pharm Pharm Sci 2014;6:421-8.
12. Elmosallamy MA, Amin AS. New potentiometric and spectrophotometric methods for the determination dextromethorphan in pharmaceutical preparations. Anal Sci 2014;30:419-25.
13. Krunali T, Vijya P, Rohit M, Meshram DB. UV spectrophotometric method for estimation of dextromethorphan in bulk and syrup formulation by area under curve method. Int J Pharm Chem Sci 2013;2:1961-4.
14. Vijayalakshmi R, Bhargavi S, Dhanaraju MD. Simultaneous UV spectrophotometric determination of cetirizine and dextromethorphan in tablet dosage form. E J Chem 2010;7:314-8.
15. Al Bratty M, Hashem H, Noureldeen A, Manoharan G, Towhari F. Conductometric determination of the antihistaminic diphenhydramine hydrochloride using silver nitrate as a titrant. Int J Pharm Pharm Sci 2015;7:72-6.
16. Ali NW, Abdelkawy M, Abdelhamid NS. Simultaneous determination of paracetamol and diphenhydramine HCl mixture in the presence of their degradation products. IOSR J Pharm Biol Sci 2013;6:44-52.
17. Gohel RV, Parmar SJ, Patel BA. Development and validation of double divisor-ratio spectra derivative spectrophotometric method for simultaneous estimation of olmesartan medoxomil, amlopidine besylate and hydrochlorothiazide in tablet dosage Form. Int J Pharm Tech Res 2014;6:1518-25.