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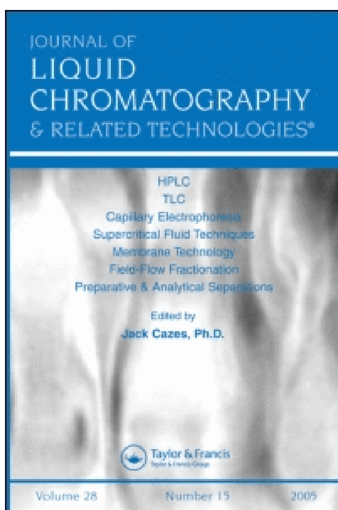

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E. M. Abdel-Moety[a]; O. A. Al-Deeb[a]; N. A. Khattab[a]
[a] Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

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DETERMINATION OF DEXTROMETHORPHAN HYDROBROMIDE IN BULK FORM AND DOSAGE FORMULATIONS BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

E. M. ABDEL-MOETY*, O. A. AL-DEEB, AND N. A. KHATTAB
Department of Pharmaceutical Chemistry
College of Pharmacy
King Saud University
P.O. Box 2457
Riyadh 11451, Saudi Arabia

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ABSTRACT

A simple LC-procedure for quantification of dextromethorphan in pure forms and pharmaceutical preparations (tablets, syrups, and drops) is described. The HPLC-separation of the active ingredient from the complex matrices of the dosage formulations is undertaken by dilution or extraction in the mobile phase [acetonitrile/acetate buffer (40 mM, pH 4.3) = 75:25, v/v] and elution on a reverse-phase μ-Bondapak™ C_{18} column (30 cm × 3.9 mm ϕ, 10 μm) isocratically (1.5 $ml.min^{-1}$) with UV-detection at 278 nm at ambient temperature. Good recovery testing of drug masses added to the dosage forms was obtained.

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INTRODUCTION

Dextromethorphan [(+)-3-methoxy-17-methyl-9α,13α-14α-morphinan] hydrobromide is a commonly prescribed antitussive in many cough-cold preparations. The drug has gained a wide acceptance as a non-addictive agent as it is almost devoid of analgesic activities. The utility of high performance liquid chromatography (HPLC) has made a dramatic impact in the analysis of organic compounds, especially the therapeutic agents in pure forms, biological specimens and dosage formulations. Various HPLC-methods have been described for the analysis of dextromethorphan, particularly in cough-cold syrups, employing ion-pairing or buffering.[1-12] Most of the described HPLC-procedures focussed on the improvement of the separation ability of dextromethorphan antitussive from other drug substances, rather than on the drug resolution from additives in various dosage formulations containing the drug. The application of several of these HPLC-procedures for quantification of the drug in pharmaceutical preparations was not always successful in separating the active ingredient enoughly each time. The drug separation occurs at excessive retention times with peak tailing in some cases.

The main task of the present study was to develop a rapid and sensitive method for accurate determination of dextromethorphan hydrobromide in the presence of the drug degradation products, various excipients, dye's, diluents, lubricants and/or sugar bases. The established HPLC-procedure was to be applied for the determination of the drug content in tablets, syrups and drops.

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EXPERIMENTAL

Instruments

Shimadzu LC-10 AD liquid chromatograph attached to SPD-10A tunable UV-detector, CTO-10A column oven controller, DGU-3A mechanical degasser, and C-R4A Chromatopac data unit, Shimadzu Corp., Analyt. Instrum. Div., Kyoto-Japan. Fixed loop injector (Rhydone, 20-μl) was utilized to carry the samples onto the column [Waters prepacked μ-Bondapak™ C_{18} column (10 μm, 30 cm × 3.9 mm ϕ), Waters Assoc., Milford-Mass., USA]. The mobile phase containing acetonitrile (HiPerSolv™ BDH Chemicals Ltd., Poole-UK) and 40 mM acetate buffer pH 4.3 (75:25, v/v) was prepared, filtered by aid of a suitable Millipore filter, then degassed using a Branson 1200 ultrasonic-bath. The separation was performed isocratically at a flow rate of 1.5 $ml.min^{-1}$ by setting the UV-detector at 278 nm at ambient temperature.

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Chemicals and Dosage Formulations

Reference dextromethorphan . HBr. [Lot. # 9211224, assigned content 100.1%] was kindly supplied by Saudi Pharm. Ind. & Med. Appl. Corp. (SPIMACO), Quassim-Saudi Arabia. The supplied material was utilized without further treatments.

Pharmaceutical formulations. Various dosage preparations, tablets, syrups and drops, were collected randomly from local pharmacies.

- Tussilar™ tablets (sugar coated, BN 313274) and drops (BN 360283) are products of Kahira Pharm. & Chem. Ind. Co, Cairo-Egypt, each tablet or 1 ml drops contains 15 mg dextromethorphan.

- Romilar™ Expectorants, syrup (BN B6312 MFD0892) contains 15 mg of the drug in a teaspoonful, in addition to ammonium chloride and dexpanthenol, F. Hoffmann-La Roche Ltd, Basel-Switzerland.

Internal standard (IS). Labetalol, 2-hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]benzamide, Glaxo Gp. Res. Ltd., Greenford, Middlesex-UK, was used as internal standard (2 $mg.ml^{-1}$, in the mobile phase).

Analytical Techniques

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Standard solutions and graphs. The stock solution of dextromethorphan.HBr, 1 mg. ml^{-1} in the mobile phase, was diluted to 200 $\mu g.ml^{-1}$ as a working solution. To prepare the standard curve, serial dilutions containing 50-200 $\mu g.ml^{-1}$ of the drug in the mobile phase were prepared by diluting the working solution. Triplicate injections of each dilution were made and the curve, concentration *vs* detector response ($A_{278\ nm}$), was plotted. The slope consistency of the prepared standard graphs was checked at different days.

Drug analysis. In case of tablets, at least 20 tablets were weighed to get the average weight of a tablet. An aliquot of the powdered tablet, syrup or drops, claimed to contain 300 mg of the drug was transferred into a 100-ml calibrated flask. About 75 ml of the mobile phase were then added and extraction was performed mechanically for ~7 minutes before completing the volume with the mobile phase. From the filtered extract were diluted 1-ml portions separately in 20-ml volumetric flasks by the mobile phase to give a final concentration of 150 $\mu g.ml^{-1}$ after adding 2 ml of the internal standard. Replicate injections of each solution were made. To

determine the drug content refer either to the prepared calibration curve or compute the drug mass by sample/equivalent standard direct matching.

Recovery testing. To 1 ml of the drug extract in the mobile phase claimed to contain 1.5 mg dextromethorphan.HBr, an equal mass of the reference drug substance was added from the stock solution in the mobile phase, followed by 2 ml of the internal standard in the mobile phase in 20-ml volumetric flask. The volume was completed with the mobile phase, then mixed well to homogenize. Triplicate injections were made to calculate the average ratio response, due to the added masses *i.e.* the area of each added drug compared with that of the internal standard.

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RESULTS AND DISCUSSIONS

Different mobile phases and columns have been described for separation and determination of dextromethorphan usually admixed with other active drug substances. Recently, Thomas *et al.*[12] described a mixed/ion-pair liquid chromatographic method for quantification of the drug in admixtures with ascorbic acid, caffeine, chlorpheniramine maleate and paracetamol dispensed as sachets by utilizing a buffered aqueous acetonitrile mixture containing an ion-pairer. The separation was achieved on a Hypersil phenyl-2 column with multiwavelength UV-detection. The separation parameters for dextromethorphan were not the ideal. Preliminary investigations have been carried out to improve the peak asymmetry and reproducibility. Se·'eral mobile phase compositions have been tested to reach effective separation of the drug from the different formulations additives in the various pharmaceutical preparations containing it. Such C_{18}-columns have been widely used for separation of amines in many preparations.[7] Many microparticulate

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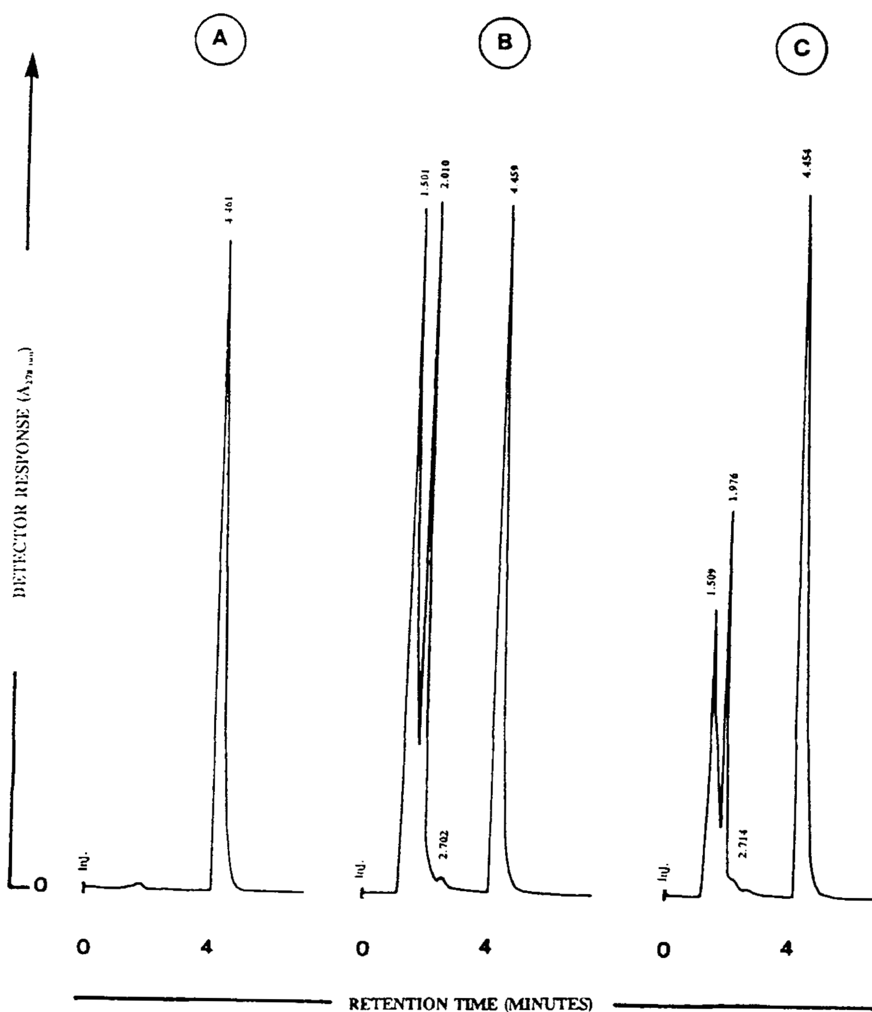

Fig. 1: HPLChromatographic separation of (A): pure dextromethorphan hydrobromide (150 $\mu g.ml^{-1}$), (B): same drug concentration from tablets extract, and (C): recovery testing of 75 μgml^{-1} drug added to the same amount from the tablets extract.

Table 1

Assay and recovery of dextromethorphan hydrobromide[x] in dosage formulations by adopting the proposed HPLC-procedure.

Formulation*	Assay+	Recovery+
Tablets	97.6±0.40(0.41,6)	100.9±0.29(0.28,4)
Syrup	101.2±0.13(0.12,4)	100.1±0.53(0.53,4)
Drops	108.9±0.18(0.16,6)	100.4±0.81(0.81,5)

[x]Purity 100.02±0.11% (n = 6).
+For more details, see experimental section.
+X±SD (CV, n), each run is the average of at least 3 experiments.

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reverse-phase columns with octadecylsilane (ODS, C_{18}) packings from different manufacturers had been tried. Good match between the reverse-phase micro-Bondapak™ column (10 μm, 30 cm × 3.9 mm ϕ) and a mobile phase containing acetonitrile and acetate buffer (40 mM, pH 4.3) = 75:25,v/v, was found to be more efficient for the separation and quantification of the antitussive agent and, hence, provide excellent elution of the active drug substance from excipients and other formulations additives. Typical HPLC-separation of pure dextromethorphan and the drug from the tablets extract in the mobile phase is shown in figure 1. The drug was consistently eluted (t_R = ~4.46 min.) at different days with excellent peak symmetry (factor = 1.01). Table 1 collects the results of analysis of a pure drug sample and the drug in tablets, syrups, and drops, in addition to the results of recoveries of added 50% drug mass. The precision of the method is clearly reflected as the obtained low deviations and variations.

Although the HPLC-assay is an external standard method, it was believed that the addition of an internal standard would slightly improve the precision of the assay procedure. Labetalol, a α- and β-adrenergic blocker, was found useful for such a purpose. The relative retention time (rel-t_R) of dextromethorphan to the internal standard is 1.67.

CONCLUSION

Excellent resolution of the antitussive agent dextromethorphan hydrobromide was obtained by the investigated HPLC-procedure. The applicability of the method for routine drug analysis revealed that the proposed procedure is simple, rapid and precise enough for the quantification of the named drug in several commercially available cough-cold tablets, syrups, and drops.

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