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Note

Simultaneous determination of phenylephrine hydrochloride, chlorpheniramine maleate and sodium benzoate by reversed-phase, paired-ion and competing-base high-performance liquid chromatography

DAVID EMLYN HUGHES
Norwich Eaton Pharmaceuticals, Inc., P.O. Box 191, Norwich, NY 13815 (U.S.A.)
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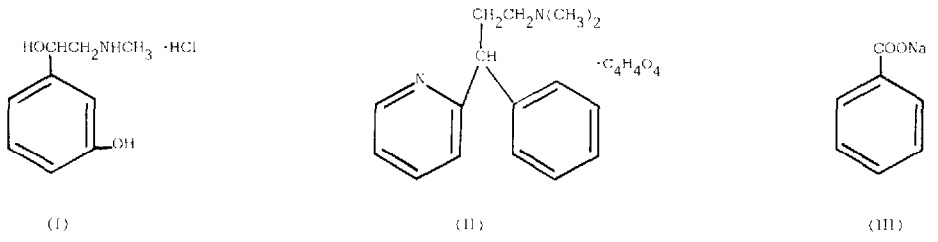
Formulations for cold symptons frequently contain several active drugs. Analysis of such a formulation presents no difficulties if a separate assay is performed for each species of interest. It is often useful, however, to determine all species in a single chromatographic assay providing that the assay does not require particularly difficult or exotic sample handling. A simultaneous determination is feasible when the species are homologues or of the same functional class. If the components are of widely differing polarities, their simultaneous determination is less likely.

Reversed-phase liquid chromatographic systems are useful for the analysis of cold preparations[1–4] provided that the moieties are of similar chromatographic polarity. Hence, if the very polar phenylephrine hydrochloride (I, Fig. 1) is to be retained, a predominantly aqueous mobile phase is required. Chlorpheniramine maleate (II) represents the opposite case in which the low polarity of the molecule dictates strong retention on a reversed-phase system. Sodium benzoate (III) represents a molecule of apparently intermediate polarity. Polar binary aqueous mobile phases may retain phenylephrine hydrochloride, but then chlorpheniramine maleate will not elute. If the polarity is decreased, chlorpheniramine maleate will elute but phenylephrine hydrochloride will not be retained.

This paper describes how a doubly modified mobile phase (ion-paired and competing-base) allows the simultaneous determination of a polar and non-polar species.



(I) (II) (III)

Fig. 1. Structures of phenylephrine hydrochloride (I), chlorpheniramine maleate (II) and sodium benzoate (III).

EXPERIMENTAL

Instrumentation

A high-performance liquid chromatograph (ALC/GPC-204; Waters Assoc., Milford, MA, U.S.A.) with an injector (Model 7125; Rainin Instrument Co., Woburn, MA, U.S.A.) with a 20-μl loop, Model 6000 reciprocating pump (Waters Assoc.) and a Model 440 absorbance detector at 254 nm (Waters Assoc.) were used. The mobile phase was passed through a μBondapak CN 30 cm × 4 mm (Part No. 84042, Waters Assoc.) column at the rate of 1.3 ml/min.

Reagents, materials and mobile phase

Phenylephrine hydrochloride, chlorpheniramine maleate and sodium benzoate were supplied by Alba (Tenafly, NJ, U.S.A.). The mobile phase was methanol–water (15:85) which contained approximately 5 ml each of PIC B-7 (Cat. No. 85103, Waters Assoc.) and Radial-Pak D-4 (Cat. No. 85466, Waters Assoc.). The mobile phase was filtered through a 0.5-μm Millipore filter and degassed under vacuum prior to use.

Sample and standard preparation

The standard solution was prepared by accurately weighing *ca.* 100 mg of phenylephrine hydrochloride and sodium benzoate and *ca.* 40 mg of chlorpheniramine maleate into a 100-ml volumetric flask. The salts were diluted to volume with water. Of this solution, 10.0 ml was then diluted to 100 ml with water.

For the sample, 10.0 ml of a syrup containing *ca.* 1 mg/ml of phenylephrine hydrochloride and sodium benzoate and 0.4 mg/ml of chlorpheniramine maleate was pipetted and diluted to 100 ml with water.

Sample analysis

The amount of the three species present in the syrup, expressed in mg/ml syrup, was calculated from

$$\text{mg species/ml} = \frac{\text{peak height sample}}{\text{peak height standard}} \times (\text{mg standard}) \times 0.01$$

A placebo containing water, sucrose, citric acid, coloring and flavoring was prepared and spiked with standards for the recovery samples.

RESULTS AND DISCUSSION

Unmodified mobile phases were not able to retain phenylephrine hydrochloride. Addition of pentanesulphonic acid (PIC B-5) resulted in some retention and heptanesulphonic acid (PIC B-7) in satisfactory retention. The chlorpheniramine maleate would not elute even when the methanolic content was increased to 25%; and at this composition, the phenylephrine hydrochloride was no longer retained. The dibutylamine (D-4) was then added as a competing-base to decrease the efficiency of chlorpheniramine maleate retention by the column. When the methanol content was adjusted to 15%, the separation (Fig. 2) was found to be satisfactory. Hence, the ion-paired phenylephrine hydrochloride was retained and the dibutylamine effectively competed with chlorpheniramine maleate at the nitrile sites, allowing chlorpheniramine maleate to be eluted.

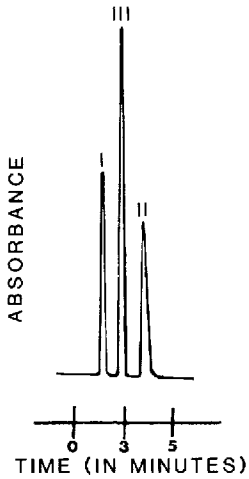


Fig. 2. Chromatogram of phenylephrine hydrochloride (I), chlorpheniramine maleate (II) and sodium benzoate (III).

Method performance

Standards of phenylephrine hydrochloride (0.40–2.0 μg), chlorpheniramine maleate (0.64–1.6 μg) and sodium benzoate (0.6–0.4 μg) were chromatographed and the linearity of standards was found to be acceptable. The correlation coefficient was at least 0.9997 in all three cases.

The recovery from placebo averaged 99.8% for phenylephrine hydrochloride and 102% for chlorpheniramine maleate and sodium benzoate (Table I). The precision was better than 2% in all cases (Table II).

TABLE I

ACCURACY OF ASSAY FOR PHENYLEPHRINE HYDROCHLORIDE, CHLORPHENIRAMINE MALEATE AND SODIUM BENZOATE

Phenylephrine hydrochloride			*Chlorpheniramine maleate*			*Sodium benzoate*		
Added (mg)	*Found (mg)*	*Recovery (%)*	*Added (mg)*	*Found (mg)*	*Recovery (%)*	*Added (mg)*	*Found (mg)*	*Recovery (%)*
8.0	7.94	99.2	3.20	3.18	99.4	8.0	8.10	101
8.0	8.0	100	3.20	3.18	99.4	8.0	8.10	101
8.0	8.0	99.8	3.20	3.18	99.4	8.0	8.14	102
10.0	9.61	96.1	4.00	4.04	101	10.1	10.1	101
10.0	9.61	96.1	4.00	4.00	100	10.0	10.0	100
10.0	9.43	94.3	4.00	4.00	100	10.0	10.1	101
12.0	12.5	104	4.80	5.04	105	12.0	12.4	103
12.0	12.5	104	4.80	5.14	107	12.0	12.3	102
12.0	12.6	105*	4.80	5.09	106**	12.0	12.4	103***

* $\bar{x}$ = 99.8%.
** $\bar{x}$ = 101.8%.
*** $\bar{x}$ = 101.6%.

TABLE II

PRECISION OF ASSAY FOR PHENYLEPHRINE HYDROCHLORIDE, CHLORPHENIRAMINE MALEATE AND SODIUM BENZOATE

Volume of sample (ml)	*Phenylephrine hydrochloride (mg/ml)*	*Chlorpheniramine maleate (mg/ml)*	*Sodium benzoate (mg/ml)*
8.0	1.01	0.411	1.01
8.0	1.01	0.400	0.981
8.0	1.01	0.416	1.00
10.0	1.03	0.419	1.02
10.0	1.03	0.420	1.01
10.0	1.02	0.414	1.01
12.0	1.03	0.426	1.03
12.0	1.02	0.421	1.01
12.0	1.03*	0.424**	1.02***

* $\bar{x}$ = 1.02 mg/ml, S.D. = $7.6 \cdot 10^{-3}$ mg/ml, R.S.D. (1σ) = 0.75%.
** $\bar{x}$ = 0.417 mg/ml, S.D. = $7.9 \cdot 10^{-3}$ mg/ml, R.S.D. (1σ) = 1.9%.
*** $\bar{x}$ = 1.01 mg/ml, S.D. = $1.2 \cdot 10^{-3}$ mg/ml, R.S.D. (1σ) = 1.2%.

Selectivity

A sample without the preservative sodium benzoate was allowed to age for 1 month. Although additional peaks appeared on the chromatogram, phenylephrine hydrochloride and chlorpheniramine maleate determinations were consistent with the initial assay. A sample which was stressed for 5 days at 40°C with the preservative showed no additional peaks. The assay is not interfered with by several other amines, notably atropine sulfate, pyrilamine maleate, phenytoloxamine citrate and methscopolamine nitrate. Atropine sulfate and phenytoloxamine citrate are sufficiently separated on the chromatogram that they can be determined in the presence of phenylephrine hydrochloride and chlorpheniramine maleate.

In summary, the method is sufficiently accurate and precise to determine phenylephrine hydrochloride, chlorpheniramine maleate and sodium benzoate in cold formulations. The use of a doubly-modified mobile phase allows the simultaneous determination of drugs of different polarity.

REFERENCES

1 T. R. Koziol, J. T. Jacob and R. G. Achari, *J. Pharm. Sci.*, 68 (1979) 1135.
2 N. Muhammad and J. A. Bodmar, *J. Liquid Chromatogr.*, 3 (1980) 113.
3 A. G. Ghanekar and V. Das Gupta, *J. Pharm. Sci.*, 67 (1978) 1247.
4 R. G. Achari and E. E. Theimer, *J. Chromatogr. Sci.*, 15 (1977) 320.