Pergamon

0731-7085(94)00091-3

Journal of Pharmaceutical & Biomedical Analysis, Vol. 12, No. 12, pp. 1601–1606, 1994
Elsevier Science Ltd
Printed in Great Britain
0731-7085/94 $7.00 + 0.00

Short Communication

Determination of pseudoephedrine hydrochloride in dosage forms by liquid chromatography*

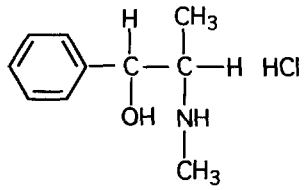
ALEKHA K. DASH

Department of Pharmaceutical Sciences, School of Pharmacy and Allied Health Professions, Creighton University, Omaha, NE 68178, USA

Keywords: *Pseudoephedrine HCl; reversed-phase liquid chromatography; microcapsules; tablets; capsules; pharmaceutical formulations.*

Introduction

Pseudoephedrine HCl (Fig. 1) is a potent bronchodilator and is used as a nasopharyngeal and otic decongestant. This drug is available alone or in combination with phenylephrine, phenylpropanolamine, acetoaminophen, ibuprofen and various antihistamines in decongestant formulations. Analytical methods available for the assay of this drug alone or in combination with other active ingredients include: spectrophotometric [1, 2]; GLC [3–7] and HPLC [6, 8–10]. Most of these methods either use multiple techniques or require complex sample extraction procedures prior to analysis. The objective of this investigation was to develop a simple and rapid LC method to analyse pseudoephedrine HCl in tablet, liquid, microcapsule and capsule dosage forms with a very simple sample preparation procedure.



Pseudoephedrine Hydrochloride

Figure 1
Structure of pseudoephedrine HCl.

The suitability of this method in the rapid separation and quantification of pseudoephedrine HCl in the presence of other active and inactive components in pharmaceutical formulations was also investigated.

Experimental

Materials

Pseudoephedrine HCl (Professional Compounding Centers of America, Houston, TX, USA), pseudoephedrine HCl reference standard (United States Pharmacopeial Convention, Rockville, MD, USA). pseudoephedrine HCl tablet (Target and Walgreens), capsules (Allent®, B.F. Ascher, KA, USA), liquid formulation (Pediacare®, McNeil, PA, USA), lidocaine (Sigma, St Louis, MO, USA), water (HPLC grade), methanol, monobasic potassium phosphate (Fisher Chemical, Fairlawn, NJ, USA) were used as supplied.

Chromatography

The LC system was comprised of a pump (model LC-600) programmed by a system controller (Model SCL-6B), an UV-Visible spectrophotometric detector (model SPD-6AV) and a recorder (model CR-501), all from Shimadzu (Tokyo, Japan). The separation was carried out on a 250 × 4.6 mm i.d. C-8 Spherisorb column (Phase Separations

*Presented in part at the Eighth Annual Meeting of the American Association of Pharmaceutical Scientists, Orlando, FL, 1993.

Inc., Norwalk, CT, USA). The mobile phase was a methanol–phosphate buffer (25 mM) (70:30, v/v, apparent pH 6.5) and the flow rate was 1.2 ml min^{-1}. The column effluent was monitored at 257 nm.

Solutions

Phosphate buffer (25 mM). Monobasic potassium phosphate (3.4 g) was dissolved in water (HPLC grade) and the volume made up to 1000 ml.

Mobile phase. Methanol (700 ml) was mixed with 300 ml of phosphate buffer. The solution was filtered through a prefilter and a 0.4 μm polycarbonate filter (Nucleopore, Pleasanton, CA, USA).

Standard solutions. Pseudoephedrine HCl standard solutions (16.0–250.0 μg ml^{-1}) were prepared in mobile phase. The stock standard solution was prepared by dissolving 81 mg of pseudoephedrine HCl in 100 ml mobile phase in a volumetric flask. Various standard solutions were then prepared from this stock solution after adequate dilution with the mobile phase.

Internal standard solution. Lidocaine solution (34.8 μg ml^{-1}) was prepared by dissolving 3.48 mg of lidocaine in 100 ml of methanol in a volumetric flask.

Sample preparation for LC

The internal standard solution (60 μl) was added to a borosilicate culture tube and evaporated to dryness at 40°C in an oven. Standard solution or sample to be analysed (500 μl) was spiked to the test tube and vortexed for 15 s. An aliquot (20 μl) was analysed by LC.

Calculation

The ratios of the peak area of pseudoephedrine HCl to that of the internal standard were calculated. The unknown pseudoephedrine HCl concentration was determined from the regression equation relating the peak-area ratio (PAR) of the standards to their nominal concentrations.

Analysis of pseudoephedrine HCl formulations

Tablet. Pseudoephedrine HCl tablets from generic sources (Target and Walgreens) were used in this study. The tablets were crushed in a glass mortar and quantitatively transferred into a volumetric flask. The volume was adjusted to 100 ml with the mobile phase. Approximately 1 ml of the above mixture was filtered through a 0.45-μm Nylon® filter (Micron Separations, Westborough, MA, USA) attached to a plastic syringe (Becton–Dickinson, Rutherford, NJ, USA). Pseudoephedrine HCl content in this solution was determined.

Capsule. Pseudoephedrine HCl capsule from a commercial source (Allent®, B.F. Ascher) was used in this study. The total capsule content was dissolved in 3 ml of methylene chloride, sonicated for 2 min and then the volume was adjusted to 100 ml with the mobile phase. Pseudoephedrine HCl content in this solution was determined after filtration through a 0.45-μm Nylon® filter.

Liquid formulation. A known weight of the liquid (Pediacare®, McNeil) was weighed in a 100-ml volumetric flask and diluted to volume with the mobile phase and pseudoephedrine HCl content was determined.

Microcapsules. Pseudoephedrine HCl microcapsules were prepared by coacervation induced by temperature change in a cyclohexane system. The microcapsules were washed carefully three times with water to remove the surface drug, if any, during preparation. Drug content in the microcapsules was then determined. A known amount of the microcapsules (10–12 mg) was mixed with 3 ml of methylene chloride and sonicated for 2 min. The volume was adjusted to 100 ml with the mobile phase. Pseudoephedrine HCl content in the solution was determined after filtration through a 0.45-μm Nylon® filter.

Stability of psdueoephedrine HCl in solution. The stability of psuedoephedrine HCl in the mobile phase at refrigerated temperature (≈4°C) over a period of 45 days was studied. Pseudoephedrine HCl samples were stored in a refrigerator in tightly closed volumetric flasks. At specific time intervals, the samples were analysed for the drug.

Results and Discussion

Assay characteristics

Specificity. Figure 2 shows representative chromatograms of pseudoephedrine HCl and

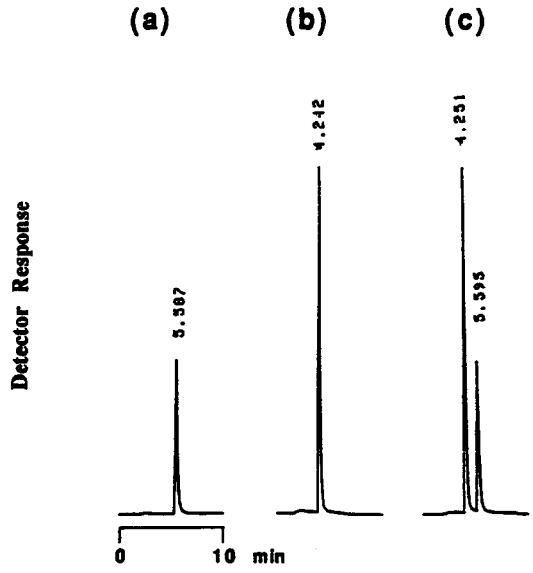


Figure 2
Representative chromatograms obtained following injection of: (a) lidocaine (34.8 mg l^{-1}); (b) pseudoephedrine HCl (227.9 mg mg l^{-1}); and (c) lidocaine (34.8 mg l^{-1}) and pseudoephedrine HCl (227.9 mg l^{-1}).

the internal standard in mobile phase. Figure 3 represents chromatograms of pseudoephedrine HCl obtained after injection of samples prepared from selected pharmaceutical formulations. None of these chromatograms show any interfering peaks.

Retention time reproducibility. The reproducibility of the retention time of pseudoephedrine HCl and lidocaine was determined from 30 consecutive injections during an analysis of a series of pseudoephedrine HCl samples. The relative standard deviation (RSD%) was found to be 0.54 and 0.35% for pseudoephedrine HCl and lidocaine, respectively.

Linearity. The standard curves were linear over the concentration range of 16.0–250 μg ml^{-1}. The equation of the standard curve relating the peak area ratio (P) to the pseudoephedrine HCl concentration (C in μg ml^{-1}) in this range was: $P = 0.013C - 0.017$, $r^2 > 0.999$.

Precision. Within-day precision was determined by analysis of four different standard curves on the same day, and all analyses were carried out using the same column. Between-day precision was determined by the analysis of the same solutions on 7 different days during a period of 45 days. During this time period, the stock solution was refrigerated (≈4°C) and solutions for the standard curves were prepared fresh each day from the stock solution. The variability in the peak area ratio at each concentration was used to determine the precision of the assay procedure (Table 1). Within-day and between-day RSD values ranged from 0.4 to 2.6% and 1.5 to 3.9% respectively.

Accuracy. Three quality control samples and the standard solutions were refrigerated for 1 month. The quality control samples were prepared from the USP reference standard (Lot: H-3). These samples were analysed several times during this period and the accuracy of the assay was determined by comparing the

Table 1
Within-day and between-day analytical precision of the assay

	Within-day*		Between-day†	
Conc. (mg l^{-1})	Peak area ratio‡	RSD (%)	Peak area ratio§	RSD (%)
0.00	0.000	—	0.000	—
16.2	0.203 ± 0.005	2.6	0.209 ± 0.008	3.9
40.5	0.495 ± 0.002	0.5	0.488 ± 0.009	2.0
64.8	0.782 ± 0.013	1.7	0.804 ± 0.014	1.8
113.4	1.41 ± 0.008	0.6	1.44 ± 0.037	2.6
194.4	2.52 ± 0.009	0.4	2.57 ± 0.046	1.8
243	3.08 ± 0.028	0.9	3.11 ± 0.046	1.5
Slope	0.012 ± 0.00008	0.6	0.013 ± 0.0002	1.4

* Analysed on the same day.
† Analysed on seven different days within a period of 45 days.
‡ Mean ± SD; $n = 4$.
§ Mean ± SD; $n = 7$.

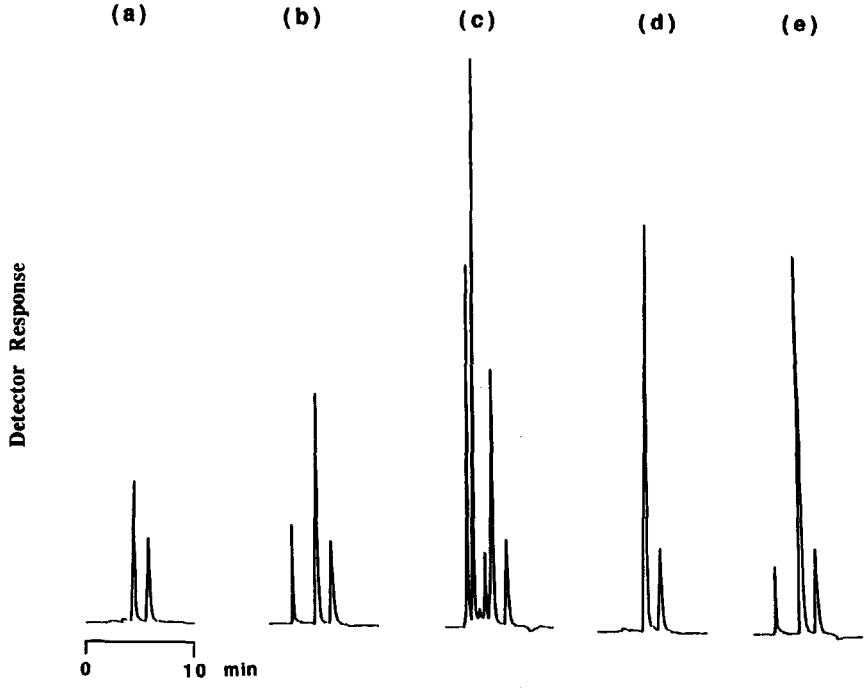


Figure 3
Representative chromatograms obtained following injection of samples prepared from different formulations containing pseudoephedrine HCl: (a) ethylcellulose microcapsules; (b) Allent® capsules; (c) Pediacare® liquid; (d) tablet (Walgreen); and (e) tablet (Target).

measured concentration to its nominal value (Table 2). The RSD was less than 4.1%.

Sensitivity. The sensitivity criteria were determined from seven different standard curves using the lowest limit of reliable assay measurement criteria as described by Oppenheimer *et al.* [11]. The critical level is the assay response above which an observed response is reliably recognized as detectable. This was 2.85 ± 0.42 μg ml^{-1} (mean ± SD). The detection level is the actual net response which may *a priori* be expected to lead to detection. This was 5.71 ± 0.83 μg ml^{-1}. The determination level, the concentration at which the measurement precision will be satisfactory for quantitative determination, was 14.7 ± 2.19 μg ml^{-1} for a level of precision of 10% RSD.

Applications of the method

Analysis of marketed formulations. Pseudoephedrine HCl content in different commercially available pharmaceutical formulations was determined. The measured concentrations were compared with the nominal (label claim) concentration (Table 3). The USP limits for pseudoephedrine HCl potency are: 98–100.5% for reference standard; 93–107% for tablets and creams; and 90–110% for pseudoephedrine HCl syrups [1]. Our results show that the potency of all products analysed fall

Table 2
Accuracy in the analysis of pseudoephedrine HCl in quality control samples, measured over a period of 45 days

Nominal conc. (mg l^{-1})	Measured conc.* (mg l^{-1})	Accuracy†	RSD (%)
24.3	23.9 ± 0.970	98.30	4.07
48.6	48.6 ± 1.38	100.1	2.86
97.2	101.4 ± 1.75	104.3	1.73

*Mean ± SD; $n = 7$.
†Accuracy = (measured conc./nominal conc.) × 100.

Table 3
Determination of pseudoephedrine HCl in various pharmaceutical formulations

Product type	Nominal conc. ($mg\ l^{-1}$)	Measured conc.* ($mg\ l^{-1}$)	Mean† (% nominal)	RSD (%)
Tablet‡	30.0	28.6 ± 0.59	95.3 ± 1.96	2.05
Tablet§	60.0	59.2 ± 0.47	98.6 ± 0.77	0.78
Allent® capsules	117.5 ± 4.3	116.5 ± 1.83	99.7 ± 1.40	1.41
Microcapsules	5.04 ± 0.19	4.94 ± 0.21	97.9 ± 2.59	2.64
Pediacare® liquid	9.40	10.1 ± 0.14	107.2 ± 1.52	1.42

*Mean ± SD; $n = 3$.
†The USP limits for pseudoephedrine HCl potency are: 93–107% for tablets and 90–110% for syrup.
‡Generic (Target).
§Generic (Walgreens).

within the range set by the USP. The analysis of pseudoephedrine HCl in the commercial products required a sample filtration step through a 0.45-μm Nylon® syringe filter prior to injection into the LC system. The loss of drug, if any, during this process was then evaluated. Standard solutions were injected into LC system prior to and after filtration through 0.45-μm Nylon® filters. The absolute peak areas of the standard solutions were compared. The results indicate that the filtration step does not have any influence on the absolute peak area of the drug.

Pseudoephedrine HCl content in microcapsule. Pseudoephedrine HCl content in three batches of ethylcellulose microcapsules containing different drug to polymer ratios were analysed. The measured drug content and the RSD for each microcapsule are shown in Table 3. The measured concentrations were compared to their nominal values and the RSD was found to be below 3%.

Stability of pseudoephedrine HCl. Pseudoephedrine HCl has been reported to be very stable both in bulk or in pharmaceutical formulations [12]. Tablet and syrup formulations stored at 15–30°C for 5 years showed no appreciable decomposition [13]. Since most of the standard and stock solutions used in this assay were stored at 4°C over a period of at least 45 days, we were interested to determine the stability of this compound in the mobile phase at 4°C over a period of 45 days. No appreciable degradation of the drug was detected within 45 days. Furthermore, no degradation products were also detected in the chromatograms. The slopes of the standard curves obtained from standard solutions stored under similar conditions over a 45 day period were consistent. This result indicates that the compound is stable in the mobile phase over a period of at least 45 days. However, the peak area of the internal standard (lidocaine) decreased after 1 month. This is probably due to the degradation of the internal standard in methanol. This study further concludes that the internal standard solutions should not be used 1 month after its date of preparation.

Analysis of pseudoephedrine HCl in presence of other components. This method was also used to determine pseudoephedrine HCl in formulations with other active ingredients. The presence of phenylephrine HCl, brompheniramine maleate and tripolidine HCl did not interfere with this assay method. However, a high concentration of ibuprofen, phenylpropanolamine and acetaminophen in a formulation interfere with the quantitation of pseudoephedrine HCl.

Conclusion

A simple, sensitive and reproducible method was developed for the analysis of pseudoephedrine HCl in different pharmaceutical formulations. The method did not require any complex extraction procedure prior to the LC analysis and used a less expensive mobile phase system. This method was successfully used to determine the pseudoephedrine HCl content in an ethylcellulose microcapsule formulation. Other active drugs (phenylephrine HCl, brompheniramine maleate and tripolidine HCl) in combination with pseudoephedrine HCl neither coelute with the drug nor interfere with its assay. The limitation of this method was that the method was not suitable for the assay of pseudoephedrine HCl in the presence of acetaminophen, phenylpropanolamine and

ibuprofen. The stability studies indicated that the drug was stable in the mobile phase at 4°C over a period of at least 45 days.

Acknowledgements — Financial support was provided by the Health Future Foundation, Omaha, Nebraska.

References

[1] *The United States Pharmacopeia*, 12th edn, pp. 1388–1390. The United States Pharmacopeial Convention, Rockville, MD (1990).
[2] L. Chafetz, *J. Pharm. Sci.* **60**, 291–294 (1971).
[3] E. Brochmann-Hanssen and A.B. Svendsen, *J. Pharm. Sci.* **51**, 938–941 (1962).
[4] K. Yamasaki, K. Fujita, M. Sakamoto, K. Okada, M. Yoshida and O. Tanaka, *Chem. Pharm. Bull.* **22**, 2898–2902 (1974).
[5] A.H. Beckett and B. Testa, *J. Pharm. Pharmacol.* **25**, 382–386 (1972).
[6] E.V. Rao, G.R. Rao, S. Raghuveer and P. Khadgapati, *Analyst* **112**, 871–874 (1987).
[7] E.T. Lin, D.C. Brater and L.Z. Benet, *J. Chromatogr.* **140**, 275–279 (1977).
[8] I.L. Honigberg, J.T. Stewart and A.P. Smith, *J. Pharm. Sci.* **63**, 766–769 (1971).
[9] T.L. Spriek, *J. Pharm. Sci.* **64**, 591–593 (1974).
[10] K. Sagara, T. Oshima and T. Misaki, *Chem. Pharm. Bull.* **31**, 2359–2365 (1983).
[11] L. Oppenheimer, T.P. Capizzi, R.M. Weppelman and M. Mehta, *Anal. Chem.* **55**, 638–643 (1983).
[12] S.A. Benezra and J.W. McRae, in *Analytical Profiles of Drug Substances*, Vol. 8 (K. Florey, Ed.), pp. 489–507. Academic Press, New York (1979).
[13] R.H. Manski and T.B. Johnson, *J. Amer. Chem. Soc.* **51**, 1096–1919 (1929).

[Received for review 10 March 1994; revised manuscript received 16 June 1994]