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COMMUNICATIONS

SIMULTANEOUS HPLC DETERMINATION OF SOME DRUGS COMMONLY USED IN COLD MEDICATIONS: DEXTROMETHORPHAN, DIPHENHYDRAMINE, PHENYLEPHRINE, PHENYLPROPANOLAMINE AND PSEUDOEPHEDRINE

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ABSTRACT

In the present paper, a simple, direct, accurate and sensitive HPLC method applied over combinations of dextromethorphan, diphenhydramine, phenylephrine, phenylpropanolamine and pseudoephedrine is presented. The use of alumina particles bonded with polybutadiene as stationary phase allows the use of an alkaline mobile phase which provides an important improvement of the assay.

INTRODUCTION

Cold medications are one of the most extended formulations in the world. Several combinations of diphenhydramine, dextromethorphan, pseudoephedrine, phenylephrine and phenylpropanolamine are the most employed ones included in OTC cold medications in the present pharmaceutical market. The two former are an antitussive agent and an antihistaminic drug, respectively. The three later are sympathomimetic agents.

HPLC analytical methods applied over the determination of medications formulated with several drugs are very useful. They allow the quantification of each drug avoiding the interference between them and between their possible decomposition products. Nevertheless, according to the bibliographical revision performed, no HPLC analytical method applied over those medications containing combinations of these drugs has been found. On the other hand, HPLC analytical methods have been described for the determination of diphenhydramine [1], dextromethorphan [2, 3], pseudoephedrine [4], phenylephrine [5] and phenylpropanolamine [6].

The purpose of this study is to develop a simple, direct, accurate and sensitive HPLC method to be applied over combinations of diphenhydramine, dextromethorphan, pseudoephedrine, phenylephrine and phenylpropanolamine. The use of alumina particles bonded with polybutadiene as stationary phase allows the use of an alkaline mobile phase which provides an important improvement of the analytical method.

The proposed HPLC method provides an improvement in the analytical techniques used for the quantification of most of these kind of medications.

EXPERIMENTAL

Materials

Dextromethorphan,diphenhydramine,phenylephrine,phenylpropanolamine(Roig-Farma, E-Barcelona) and pseudoephedrine (Acofarma, Tarrasa, E-Barcelona). Methanol used was HPLC grade (Merck, D-Darmstadt). *Di*-ammonium hydrogenphosphate from Merck (D-Darmstadt). All the reagents were of guaranteed grade.

Methods

The HPLC system consisted of a constant-flow pump (Kontron Instruments, type 420), a Rheodyne type 7125 injector equipped with a 20 μL loop, a variable wavelength detector (Kontron Instruments, type 432) and an integrator (Konik Instruments, type DataJet 4600). The column used was packed with alumina particles bonded with polybutadiene (E. Merck, Aluspher RP select B, 5 μm particle size, 12.5 cm x 4 mm

ID). A flow rate of 1 mL / min for the mobile phase (methanol - water - *di*-ammonium hydrogenphosphate in a ratio of 75 : 25 : 0.1, v/v/w, pH = 8.5) was employed and the variable wavelength UV detector was set at 257 nm. Each peak area was automatically computed by the integrator. The elution was carried out in isocratic conditions at room temperature. The substances were dissolved in the mobile phase.

Quantitation. Calibration curves were determined for diphenhydramine, dextromethorphan, pseudoephedrine, phenylephrine and phenylpropanolamine in standard solutions.

Accuracy and precision. The accuracy and precision of the HPLC determination were evaluated from the recovery data for diphenhydramine, dextromethorphan, pseudoephedrine, phenylephrine and phenylpropanolamine from 10 standard solutions. The *intra*-day precision was evaluated from 20 injections of a standard solution with each one of the assayed substances.

RESULTS AND DISCUSSION

The calibration curves for the assayed substances were linear from 0.1 to 0.001 % (w/v) for diphenhydramine, from 0.1 to 0.001 % (w/v) for dextromethorphan, from 0.1 to 0.003 % (w/v) for pseudoephedrine, from 0.1 to 0.001 % (w/v) for phenylephrine and from 0.2 to 0.0125 % (w/v) for phenylpropanolamine. No interference from standard solutions was observed.

The accuracy of this method, as measured from the recovery data, was 97.13 % for diphenhydramine, 96.60 % for dextromethorphan, 98.70 % for pseudoephedrine, 95.47 % for phenylephrine and 96.42 % for phenylpropanolamine.

The precision, as measured from the standard deviation of the recovery data (tables 1 - 5) was ± 0.65 % for diphenhydramine, ± 1.08 % for dextromethorphan, ± 0.81 % for pseudoephedrine, ± 1.32 % for phenylephrine and ± 0.78 % for phenylpropanolamine.

The *intra*-day precision, as measured from the standard deviations of the peak areas (table 6) was 0.0929 ± 0.00190 for diphenhydramine, 0.3071 ± 0.00660 for

TABLE 1
Recovery data for the determination of diphenhydramine. (Each value represents the average of duplicate sample injection).

Solution	Theory (mg/100 mL)	Found (mg/100 mL)	Recovery (%)
1	63.3	61.6	97.23
2	62.5	61.1	97.76
3	62.8	61.0	97.13
4	62.9	61.8	98.17
5	62.8	61.4	97.69
6	53.8	52.5	97.49
7	48.4	48.2	99.48
8	69.2	67.7	97.83
9	62.0	60.7	97.90
10	62.4	61.0	97.76
Mean			97.84
SD			0.65

TABLE 2
Recovery data for the determination of dextromethorphan. (Each value represents the average of duplicate sample injection).

Solution	Theory (mg/100 mL)	Found (mg/100 mL)	Recovery (%)
1	111.6	109.4	98.03
2	98.5	95.1	96.60
3	104.1	103.3	99.23
4	96.3	95.8	99.48
5	104.4	103.0	98.66
6	101.0	100.2	99.25
7	90.9	90.3	99.39
8	106.5	103.8	97.42
9	86.9	84.9	97.70
10	97.8	94.8	96.93
Mean			98.27
SD			1.08

TABLE 3
Recovery data for the determination of pseudoephedrine. (Each value represents the average of duplicate sample injection).

Solution	Theory (mg/100 mL)	Found (mg/100 mL)	Recovery (%)
1	250.8	252.8	100.79
2	251.3	253.9	101.05
3	253.1	249.8	98.70
4	250.3	250.9	100.24
5	250.1	251.1	100.40
6	196.5	197.4	100.92
7	227.2	225.8	99.36
8	173.3	175.0	100.98
9	250.2	250.5	100.12
10	225.3	223.8	99.33
Mean			100.19
SD			0.81

TABLE 4
Recovery data for the determination of phenylephrine. (Each value represents the average of duplicate sample injection).

Solution	Theory (mg/100 mL)	Found (mg/100 mL)	Recovery (%)
1	52.5	51.3	98.18
2	50.8	48.5	95.47
3	51.7	49.6	96.03
4	48.8	48.3	98.97
5	50.0	48.7	97.30
6	59.4	58.6	98.57
7	46.3	46.2	99.78
8	57.0	55.5	97.37
9	60.0	59.2	98.58
10	58.8	57.3	97.45
Mean			97.77
SD			1.32

TABLE 5
Recovery data for the determination of phenylpropanolamine. (Each value represents the average of duplicate sample injection).

Solution	Theory (mg/100 mL)	Found (mg/100 mL)	Recovery (%)
1	250.8	244.2	97.39
2	251.1	248.7	99.02
3	251.2	242.2	96.42
4	250.4	246.4	98.40
5	249.9	245.0	98.04
6	209.9	205.9	98.07
7	212.5	210.4	99.01
8	174.8	170.7	97.65
9	240.8	237.3	98.55
10	215.9	212.0	98.19
Mean			98.07
SD			0.78

dextromethorphan, 0.2024 ± 0.00614 for pseudoephedrine, 0.4521 ± 0.00837 for phenylephrine and 0.2060 ± 0.00917 for phenylpropanolamine.

By using a neutral pH value of the mobile phase, the separation of the five used drugs was not adequate. Because of this, it is usual to utilize extreme pH values (7.0 - 7.5 and 2.0 - 2.5). These experimental pH conditions imply an important diminution in the average life of silica based columns. In this investigation, an alkaline mobile phase was used employing alumina particles bonded with polybutadiene as stationary phase. This new column allows the use of an alkaline mobile phase having a pH value of 12 units. The pH value used in this work was 8.5. Greater pH values were not employed in order to avoid the degradation of these drugs (phenylephrine is easily degradated by a oxidation process).

As it can be seen in table 6, none of the assayed standard solutions undergoes any degradation process in our experimental conditions.

TABLE 6
The *intra*-day precision (peak areas) for the determination of the indicated substances: diphenhydramine (D), dextromethorphan (Dex), pseudoephedrine (P), phenylephrine (Phe) and phenylpropanolamine (Php).

Injection	D	Dex	P	Phe	Php
1	0.0924	0.3110	0.1960	0.4507	0.2106
2	0.0948	0.3131	0.2088	0.4389	0.2125
3	0.0926	0.3016	0.2048	0.4542	0.2111
4	0.0932	0.2983	0.2051	0.4533	0.1994
5	0.0924	0.3031	0.2069	0.4390	0.2098
6	0.0934	0.3023	0.1964	0.4535	0.2119
7	0.0939	0.3158	0.2016	0.4544	0.2039
8	0.0923	0.3023	0.2076	0.4544	0.2105
9	0.0931	0.2992	0.2079	0.4443	0.1866
10	0.0928	0.3120	0.2092	0.4568	0.2078
11	0.0915	0.3058	0.2047	0.4536	0.2075
12	0.0923	0.3054	0.2004	0.4574	0.2063
13	0.0915	0.3043	0.1938	0.4555	0.1863
14	0.0929	0.3020	0.1994	0.4564	0.2083
15	0.0944	0.3142	0.2081	0.4690	0.2144
16	0.0934	0.3011	0.2023	0.4629	0.2040
17	0.0918	0.3189	0.2004	0.4534	0.2119
18	0.0982	0.2979	0.2054	0.4346	0.2138
19	0.0924	0.3150	0.2046	0.4565	0.1912
20	0.0877	0.3105	0.1846	0.4426	0.2210
Mean	0.0929	0.3071	0.2024	0.4521	0.2060
SD	0.0019	0.0066	0.0061	0.0084	0.0092

The selectivity of the method can be appreciated in figure 1. As it can be seen, the peaks corresponding to phenylephrine (D) and phenylpropanolamine (E) are relatively close. This circumstance is due to the used mobile phase composition, having a 25 % of water. By increasing the proportion of water from 25 % to 30 %, a separation between these peaks is obtained, but a more important diminution in the capacity factors of

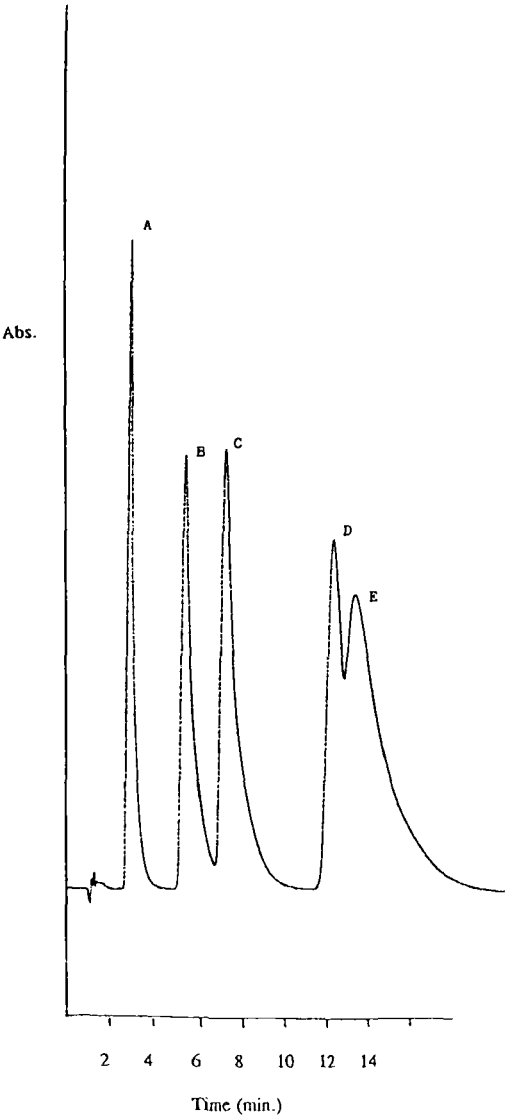

FIGURE 1

HPLC separation of diphenhydramine (A), dextromethorphan (B), pseudoephedrine (C), phenylephrine (D) and phenylpropanolamine (E)

phenylephrine (D), pseudoephedrine (C) and dextromethorphan (B) is produced. The result is a poor resolution for pseudoephedrine and dextromethorphan. So, the mobile

TABLE 7
Capacity factors for the assayed substances.

Substance	k'
Diphenhydramine	1.722
Dextromethorphan	4.278
Pseudoephedrine	6.185
Phenylephrine	11.278
Phenylpropanolamine	12.289

phase methanol - water - *di*-ammonium hydrogenphosphate in a ratio of 75 : 25 : 0.1, v/v/w was selected. The obtained capacity factors are showed in table 7.

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