Journal of Chromatography, 355 (1986) 345–349
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

CHROM. 18 342

Note

High-performance liquid chromatographic determination of benzyl alcohol and its degradation product benzaldehyde in a pharmaceutical cream

D. GORMAND*, J. L. BRAZIER and F. COMET
L.E.A.C.M., Laboratoire d'Etudes Analytiques et Cinétiques du Médicament, Faculté de Pharmacie, 8 Avenue Rockefeller, 69373 Lyon Cedex 08 (France)
and
D. LECOMPTE
Laboratoires Lederle, 30–32 Boulevard Emile Zola, 69600 Oullins (France)
(Received November 15th, 1985)

Benzyl alcohol is commonly used in pharmaceutical formulations as an antiseptic, its usual concentration in creams and ointments being 1–2% (w/w).

Several methods have been developed for spectroscopic[1–4], thin-layer chromatographic[5,6], gas chromatographic (GC)[7] and high-performance liquid chromatographic (HPLC)[8–10] methods.

Menon and Norris[8] described an HPLC method for the determination of benzyl alcohol in the presence of hydroxyzine hydrochloride from an injection solution. Later, Rego and Nelson[9] described an HPLC method for its determination in the presence of hydrocortisone in pharmaceutical formulations. These two assays were not suitable for the determination of benzaldehyde. Floor *et al.*[10] proposed an HPLC method for the determination of Etoposide and its major potential impurities in the presence of benzyl alcohol and its main degradation product, benzaldehyde. This paper describes a reversed-phase HPLC assay for benzyl alcohol and benzaldehyde in a pharmaceutical cream.

EXPERIMENTAL

Reagents

All chemicals and solvents were of HPLC grade. Methanol, acetic acid, benzyl alcohol and benzaldehyde standards were obtained from Merck. Doubly distilled water was supplied by Lederle (Oullins, France). The pharmaceutical tested was a cream containing 1% (w/w) of benzyl alcohol.

Apparatus

An Altex Model 380 pump, a Waters Model 710B automatic injector, a Pye Unicam Model 4020 variable-wavelength spectrophotometer set at 260 nm and a Waters Assoc. Model 730 integrator data module were used.

HPLC was performed with Beckman Ultrasphere-octyl 5 μm column (150 ×

0021-9673/86/$03.50 © 1986 Elsevier Science Publishers B.V.

4.6 mm I.D.). The mobile phase was methanol–water (60:40) of pH 3.5 ± 0.05, adjusted with acetic acid, and was sonicated before use. The mobile phase was pumped through the column at a flow-rate of 1 ml/min. UV spectra of benzyl alcohol and benzaldehyde were recorded on a Pye Unicam 4021 spectrophotometer.

Sample preparation

An amount of sample of 2.5 g was introduced into a 50-ml volumetric flask and 30 ml of doubly distilled water were added. The cream was dispersed by gentle manual agitation, then further doubly distilled water was added to give a volume of 50 ml. The solution was filtered through a Whatman W 42 filter before injection. The final concentration of benzyl alcohol was about 500 μg/ml. A volume of 20 μl was injected into the column.

Preparation of standard solutions

A 250-mg amount of benzyl alcohol was accurately weighed into a 50-ml volumetric flask and diluted to volume with doubly bidistilled water. This standard solution was diluted with doubly distilled water to a final concentration of about 500 μg/ml.

A 30-mg amount of benzaldehyde was weighed in a 50-ml volumetric flask anmd diluted to volume with doubly distilled water. Dilution with doubly distilled water gave a final concentration of 1.5 μg/ml.

RESULTS

Spectral data

Fig. 1a and b show the UV spectra of benzyl alcohol and benzaldehyde in the mobile phase. The absorbance maxima are 257 nm ($\varepsilon = 1.748\ g^{-1}\ l\ cm^{-1}$) and 249 nm ($\varepsilon = 112.547\ g^{-1}\ l\ cm^{-1}$) for benzyl alcohol and benzaldehyde, respectively. At 260 nm the molar absorptivities are $\varepsilon_{alcohol} = 1.498\ g^{-1}\ l\ cm^{-1}$ and $\varepsilon_{aldehyde} = 66.535\ g^{-1}\ l\ cm^{-1}$. The molar absorptivity of benzaldehyde is higher owing to the conjugation of the benzene ring and the carbonyl group. The UV spectra of benzyl alcohol and benzaldehyde in the cream were found to be similar to those of the standard solutions (Fig. 2).

Chromatographic analysis

The retention times of benzyl alcohol and benzaldehyde were 4.5 min and 6.5 min, respectively. Blanks assayed following the same procedure did not show any interfering peaks at these retention times (Fig. 3).

Linearity

The linearity of the proposed method was checked by injecting authentic standards of benzyl alcohol and benzaldehyde.

Five standards of benzyl alcohol containing 125, 250, 500, 750 and 1000 μg/ml were injected five times each. Linear regression analysis of peak areas *versus* concentrations indicated good linearity:slope, 740.94; intercept, −0.86; $r = 0.9998$.

The same procedure was applied to benzaldehyde using concentrations of 0.375, 0.75, 1.5, 2.25 and 3 μg/ml, and gave the following results:slope, 366.81; intercept, −14.69; $r = 0.9996$.

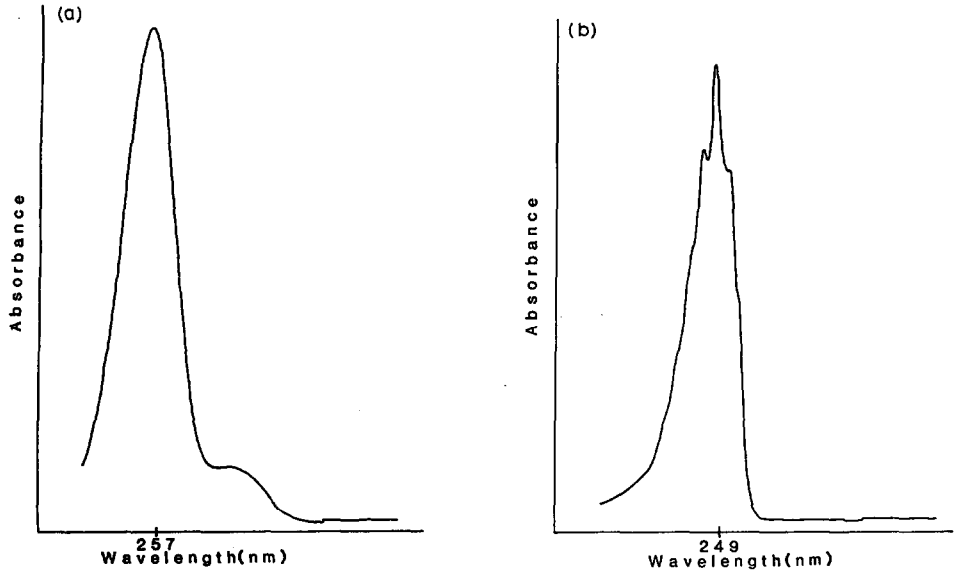

Fig. 1. UV spectra of (a) benzyl alcohol and (b) benzaldehyde standard solutions in the mobile phase (methanol–water, 60:40).

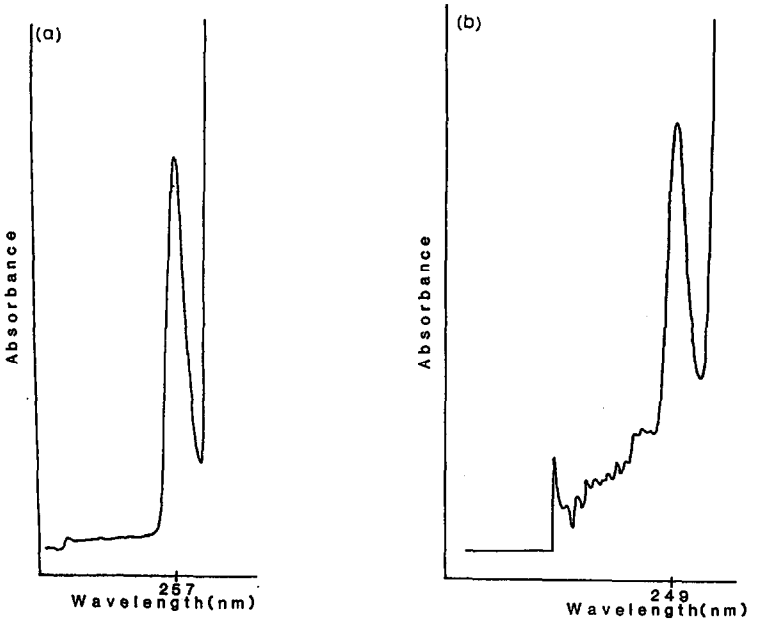

Fig. 2. UV spectra of (a) benzyl alcohol and (b) benzaldehyde in a pharmaceutical cream. Spectra recorded at the top of the chromatographic peak.

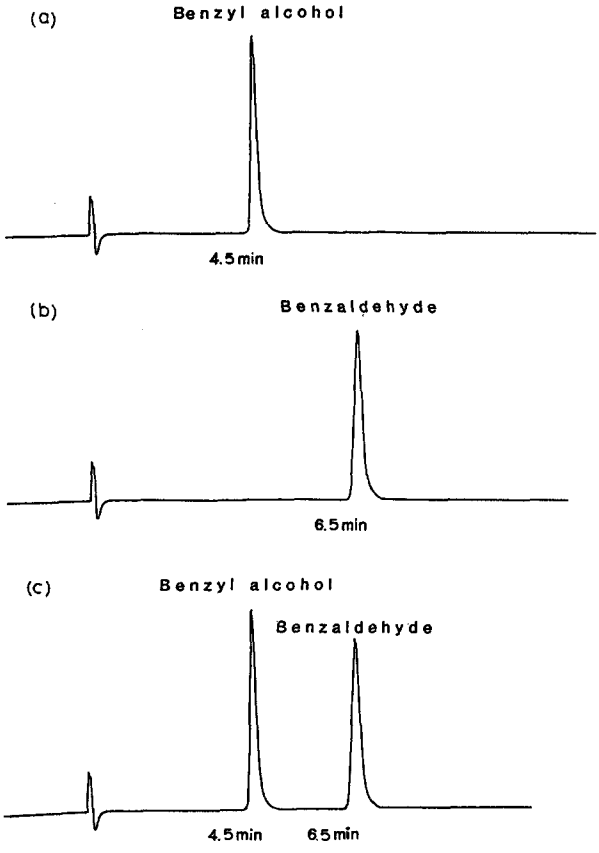

Fig. 3. Chromatograms of (a) standard solution of benzyl alcohol, (b) standard of benzaldehyde and (c) a pharmaceutical cream.

The linearity of the method was tested with the cream. Five sample weights corresponding to 25, 50, 100, 150 and 200% of the theoretical sample weight (2.5 g) were assayed using the same procedure, each sample being injected five times. The linearity was also good and the correlation coefficients were 0.999 and 0.997 for benzyl alcohol and benzaldehyde, respectively.

Precision

The repeatability of the assay determined from the coefficients of variation from nine injections of solutions containing 500 μg/ml of benzyl alcohol and 1.5 μg/ml of benzaldehyde was 0.30 and 1.22%, respectively.

The reproducibility of the method was determined over three days by injecting a solution containing 500 μg/ml of benzyl alcohol and 1.5 μg/ml of benzaldehyde five times each day. A variance analysis was performed on the results. Using the *F*-test, the tabulated value for F (12.2) was 3.89 whereas the calculated F values were 0.45 and 0.50 for benzyl alcohol and benzaldehyde, respectively. These results indicated no significant differences between the various injections. The reproducibility of the method is good.

Accuracy

The accuracy of the method was determined on solutions containing theoretical concentrations of benzyl alcohol of 125, 250, 500, 750 and 1000 μg/ml and of benzaldehyde of 0.375, 0.75, 1.5, 2.25 and 3 μg/ml. Each result calculated from calibration graphs was compared with the expected value. The inaccuracy is given by the equation $I = (\Delta x/x) \cdot 100$ and the accuracy is $A = 100 - I$. The mean accuracies were 99.07 and 98.42% for benzyl alcohol and benzaldehyde, respectively.

Recovery of benzyl alcohol from cream

To study the recovery of benzyl alcohol from the formulation, a cream containing all inactive and active components except benzyl alcohol was prepared then, an exact amount of benzyl alcohol was added and mixed thoroughly. Ten samples of this cream were treated according to the analytical procedure and each was injected five times into the column. The amount of benzyl alcohol added was 1.032% (w/w) and the amount found was being 1.052% (w/w). There was no significant difference between these two values.

Limits of detection

The limits of detection defined by a signal-to-noise ratio of 2, of benzyl alcohol and benzaldehyde were determined using standard solutions and were found to be 12.6 and 0.33 ng, respectively, with an injection volume of 20 μl. The molar absorptivity of benzaldehyde at 260 nm is nearly 40 times higher than that of benzyl alcohol, which permits the simultaneous determination of the two compounds in a pharmaceutical preparation with the same tuning sensitivity of the detector.

CONCLUSION

The HPLC method described here is linear, precise, accurate and sensitive. Moreover, it is fast and easy to carry out. Its analytical performance makes it suitable for the industrial quality control of pharmaceutical creams containing benzyl alcohol and its degradation product benzaldehyde.

REFERENCES

1 V. V. Kobyakov, A. M. Ovsepyan and V. P. Panov, *Khim. Farm. Zh.*, 16 (1982) 371.
2 A. F. Fell, *J. Pharm. Pharmacol.*, 30 (1978) 63.
3 P. P. Shorygin, V. A. Petukhov, A. Kh. Khomenko and E. A. Churnyshev, *Zh. Fiz. Khim.*, 42 (1968) 1057.
4 T. Pedersen, *Dan. Kemi*, 48 (1967) 413.
5 F. J. van de Vaart, A. Hulshoff and A. W. M. Indemans, *Pharm. Weekbl., Sci. Ed.*, 5 (1983) 109.
6 J. Churáček, M. Kušková, H. Pechová and Říha, *J. Chromatogr.*, 49 (1970) 511.
7 A. Habboush and A. Al-Rubaie, *J. Chromatogr.*, 157 (1978) 409.
8 G. N. Menon and B. J. Norris, *J. Pharm. Sci.*, 70 (1981) 697.
9 A. Rego and B. Nelson, *J. Pharm. Sci.*, 71 (1982) 1219.
10 B. J. Floor, A. E. Klein, N. Muhammad and D. Ross, *J. Pharm. Sci.*, 74 (1985) 197.