NOTE

Gas Chromatographic Determination of Benzyl Alcohol in Midazolam Injection

Dhanaji Patil†, Kiran Mangaonkar†, R.S. Lokhande*
and Swati Wabgaonkar
Department of Chemistry, University of Mumbai
Kalina, Mumbai-400 055, India

A simple, fast and accurate gas chromatographic method has been developed for the determination of benzyl alcohol content in midazolam injection. The analysis was carried out on Shimadzu 17A. The column used was 5% carbowax on Chromsorb HP (2 m, 3.6 mm *id*). The detector used was flame ionization detector. The validation of the proposed method was also carried out.

Key Words: Gas chromatography, Midazolam injection.

Midazolam injection is a sterile solution of midazolam in water for injections containing hydrochloric acid. Chemically midazolam is known as 8-chloro -6(2-fluorophenyl)-1-methyl-4H-imidazol (1, 5a)(1, 4) benzodiazepine. Several methods are reported in literature[2-4] for the determination of midazolam in blood plasma and in British Pharmacopia a simple titrimetric method is given for the determination of midazolam[1]. But there is no single method reported for the determination of benzyl alcohol in midazolam injection. Benzyl alcohol is used as stabilizer in midazolam injections. The per cent labelled claim of benzyl alcohol is 1.0% as a stabilizer. In this communication a new GC method for the determination of benzyl alcohol in midazolam injections has been reported.

Methanol HPLC grade supplied by E. Merck India Ltd. and water HPLC grade obtained from Elga purification system. Working reference standards of benzyl alcohol and phenol were used.

Chromatographic conditions

(1) Instrument: Shimadzu GC 17A,
(2) Column: 5% Carbowax on chromosorb hp (2 m × 3.6 mm),
(3) Detector: Flame ionization detector,
(4) Carrier gas: Nitrogen,
(5) Injector temperature: 250°C,
(6) Detector temperature: 270°C,

†Department of Chemistry, Ramnarain Ruia College Matunga, Mumbai-400019, India

(7) Oven temperature: 180°C (isothermal),

(8) Column flow: 50.0 mL/min,

(9) Detector sensitivity: $10^3 \times 256$,

(10) Injection volume: 1 µL,

(11) Retention time: benzyl alcohol about 4.2 min; phenol about 6.0 min.

Preparation of internal standard solution: 380 mg of phenol WS was accurately weighed in a 200 mL volumetric flask. 10 mL of methanol was added to dissolve the content and volume made up to 200 mL with water.

Preparation of Standard: 180 mg of benzyl alcohol WS was accurately weighed in a 100 mL volumetric flask. 20 mL of methanol was added to dissolve the content and volume made up to 100 mL with internal standard solution.

Preparation of Sample: 5.0 mL of sample was transferred from the ampoule to 25 mL volumetric flask and volume made with internal standard solution.

Procedure: 1.0 µL of standard and sample solution were injected into the gas chromatograph. From the peak area ratio of sample to standard, benzyl alcohol content was calculated. The study was carried out for three different formulations to check the precision of the method. The values obtained for three different formulations are given in the following Table

Sample area ratio	Standard area ratio	% Labellled benzyl alcohol content		
		Formulation-A	Formulation-B	Formulation-C
1.433	1.427	100.42	98.84	99.77
1.438	1.432	100.41	98.56	100.25
1.429	1.442	99.09	98.95	100.85
1.430	1.424	100.42	99.29	100.02
1.426	1.435	99.37	98.67	99.87
RSD for % labelled claim		00.65	00.28	00.43

Linearity

The plot of area ratio of benzyl alcohol *vs.* respective concentrations of benzyl alcohol are found linear in the range of 1.2–2.8 mg/mL with correlation 0.9993.

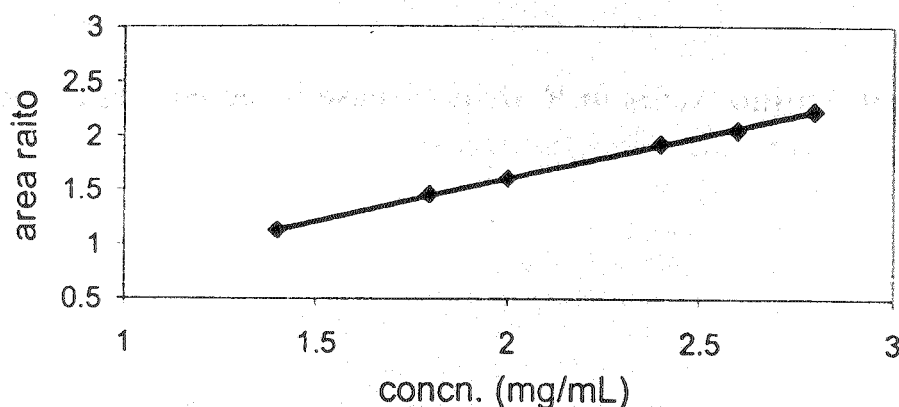| Concentration (mg/mL)	Area ratio
1.2	1.116
1.4	1.445
1.8	1.596
2.0	1.927
2.6	2.054
2.8	2.232

Fig. 1.   Linearity plot (y = 0.7908x + 0.0149, R^2 = 0.9993)

Recovery

To study the accuracy, reproducibility and the precision of the proposed method, recovery experiment was carried out by adding standard benzyl alcohol at three different levels in pre-analyzed sample. The study was carried out at 50, 100 and 200% above the concentration of benzyl alcohol present in the sample.

Sr. No.	Concentration of benzyl alcohol (%)	Area for benzyl alcohol present in the sample	Area for benzyl alcohol present in the sample + externally added benzyl alcohol	Recovery (%)
Level-1	1.5	25531	51699	100.72
Level-2	2.0	25531	129550	99.14
Level-3	3.0	25531	510661	98.98

The r^2 value was found 0.9993, which shows the response is linear for 1.2–2.8 mg/mL. High percentage of recovery shows that the method is free from interference of raw material and excipients used in formulations. The recovery values prove that the method is accurate and reproducible. The proposed method is simple, fast, accurate and precise; thus it can be used for the routine quality control analysis of benzyl alcohol content in midazolam injection.

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