

VALIDATION OF A GAS CHROMATOGRAPHIC METHOD FOR DETERMINATION OF ETHANOL IN LIQUID PREPARATIONS INTENDED FOR CHILDREN

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ABSTRACT

In 1984, the American Academy of Pediatrics recommended limiting alcohol content to no more than 5% and restricting the volume of products containing alcohol to non-lethal quantities. In 1993, a committee representing the Food and Drug Administration and the Nonprescription Drug Manufacturers Association agreed to develop voluntary limits for the alcohol content of liquid dosage preparations. The committee concluded that all over-the-counter products designed for children less than six years of age should be alcohol-free. Products labeled for children 6-12 years of age should contain no more than 5% alcohol. Products for children over 12 years and adults should be limited to 10% alcohol content. In certain products requiring higher alcohol contents to achieve solubility, warning labels would instruct parents to contact a physician prior to giving these products to children. To date, limited documentation of such interaction exists because of a lack of scientific studies on this subject. Hence attempt was made to evaluate quantity as well as quality aspects in terms of contamination from menthol, camphor and propylene glycol.

Keywords: Gas Chromatography, Validation, Alcohol, Pediatric Formulations

INTRODUCTION

Ethanol is commonly used as a solvent in the manufacturing of oral liquid dosage formulations. Two concerns exist with the use of ethanol in products designed for the pediatric market, acute intoxication with accidental overdose and chronic toxicity associated with routine use for chronic medical conditions. It is desirable that no ethanol be included in medicinal products intended for use in children.

However, if ethanol is required to solubilize the active ingredients, the Committee on Drugs has made the following specific recommendations to the FDA: (1) Over-the-counter (OTC) liquid preparations should be limited to a maximum of 5% v/v ethanol. (2) Physician supervision is suggested for children less than age 6 years using OTC preparations containing alcohol. (3) The amount of ethanol contained in any medicinal preparation should not be able to produce a blood concentration greater than 25 mg/100 ml after a single recommended dose. (4) Appropriate intervals between medication doses should be prescribed to prevent the accumulation of blood alcohol. (5) The packaged volume of ethanol-containing products should be kept to a reasonable minimum to prevent potential lethal ingestions. (6) Safety closures should be recommended for medications with greater than 5% ethanol content.

These levels represent only guidelines, however, and are not enforced by the FDA. To date, limited documentation of such interaction exists because of a lack of scientific studies on this subject. Though it is desirable that no ethanol be included in medicinal products intended for use in children, the preparations selected contains upto 10% of alcohol as per label claim. Review of literature reveals that some pharmaceutical manufacturers replace ethanol as a solvent by propylene glycol, thus problem of intoxication remains same. Hence attempt was made to evaluate quantity as well as quality aspects in terms of contamination from menthol, camphor and propylene glycol¹⁻⁴.

MATERIAL AND METHODS

All the work described in this paper was carried out on a Chemito GC 7610 with a flame ionization detector 861. The column used was 8 feet x 1/8- inch carbowax 20 M (HP), 80-100 mesh.

Operating conditions

1. FID H₂/air: 30/300ml/min.
2. Column: Carbowax 20M (HP)
3. Column temperature: ~80°C

4. N₂ carrier: ~30ml/min.
5. Injector temperature: 180°C
6. Detector temperature: 180°C

Solvents

Ethanol, HPLC grade (99.98%), E. Merck

Water, HPLC grade, E. Merck

Methods

Standard ethanol solution

Solutions were prepared with HPLC grade ethanol (99.98%) and HPLC grade water to contain 1, 2, 3, 4, 5, and 6 percent. V/v of ethanol.

Sample preparation

50 ml of sample was pipette out and transferred to 250ml round bottom flask and was attached to distillation assembly. The assembly was heated and approximately 40-45ml of distillate was collected in 100ml volumetric flask.

Internal standard method

Highest precision obtained with internal standard method. 3ml of n-propanol was added as an internal standard to the sample solution and to the standard solution. Then volume was made upto 100ml.

Qualitative analysis

Two micro-liters portion of sample solution and the standard solution was injected and chromatograms were obtained. Retention time (R_t) was recorded as the analytical parameter.

Quantitative analysis

Quantitation was performed by constructing calibration graphs, which are prepared by plotting the peak area ratio ethanol to internal standard against ethanol content (Figure 1).

Analysis of standard ethanol

A range of standard was prepared containing six different concentration of ethanol. 2 micro-liter portion of each was injected and chromatograms were obtained. The graph of concentration verses area was found to be linear with, Y= 0.2563 & R²= 0.9969.

Analysis of sample by Gas Chromatography- 2 micro-liter portion of each sample solution was injected and chromatograms were obtained. The concentration was determined from standard working curve. The values obtained were multiplied by 2 to get % v/v.

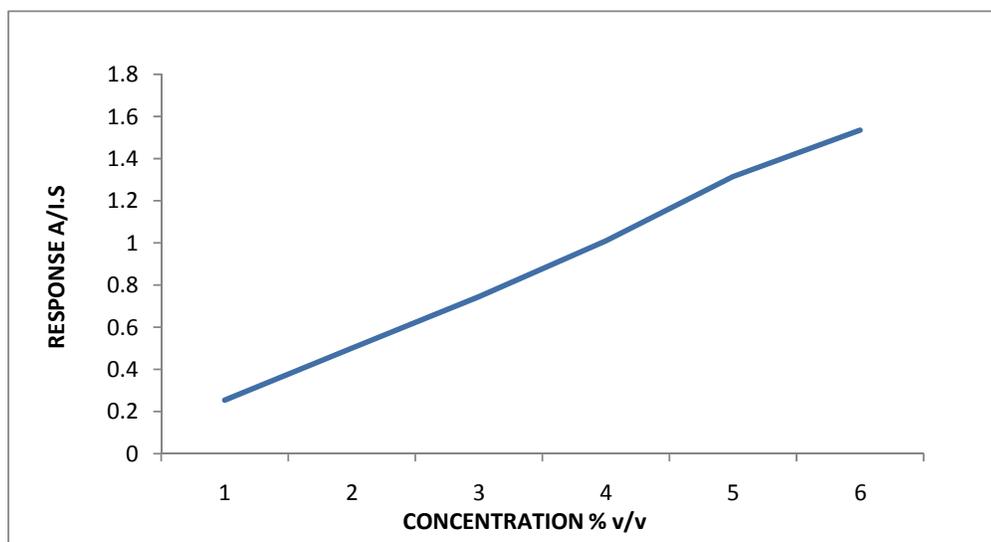


Fig. 1: Standard curve of ethanol by gas chromatography

Table 1: Analyses of samples

Sample	Label claim	Percent content	Variation
S1,[A,B,C]	4%V/V	4.56-4.72	12.5%-17.5%V/V
S2,[A,B,C]	5%V/V	5.0-5.72	14.0%V/V
S3,[A,B,C]	5%V/V	5.1-5.38	2.0-8.0%V/V
S4,[A,B,C]	9%V/V	9.52-10.5	5.5-14.4%V/V
S5,[A,B,C]	9.5%V/V	10.88-11.86	5.26-14.73%V/V

S1 to S5- Sample code. [A,B,C]—Three different batches of each sample

Study of validation parameters

Validation is documented evidence, which provides a high degree of assurance for specific method. It is completed to insure that an analytical method is accurate, reproducible and rugged over the

specific range that analyst is analyzed to provide an assurance of reliability and for FDA compliance. Method validation is the process of providing assurance that an analytical method is acceptable for its intended purpose.

Table 2: Study of validation parameter⁵

Validation Parameters	Results
System Suitability	Mean=3.03% S.D.=0.0407 R.S.D.=1.34%
Linearity	Y=0.2563X R ² =0.9969
Recovery Study	% recovery=103.5%
Precision for- system	Mean=3.03% S.D.=0.0407 R.S.D.=1.34%
Ruggedness- by Analyst	Mean=2.67% S.D.=0.035 R.S.D.=1.31%
Ruggedness- on Days	Mean=2.05% S.D.=0.026 R.S.D.=1.13%

RESULTS AND DISCUSSION

During qualitative evaluation, retention time, the analytical parameter recorded found to be same for both, standard ethanol and the alcohol in the various formulations. This indicates that the alcohol present is ethanol. The results obtained by quantitative evaluation do not comply with label claim for alcohol contents. Considerable variation was found,

Preparation S1 having label claim of 4% v/v shows batch to batch variation upto 12.5%-17.5% Preparation S2 having label claim of 5%v/v shows batch to batch variation upto 14%. Preparation S3 having label claim of 5% shows batch to batch variation upto 2%-8%. Preparation S4 having label claim of 9% shows batch to batch variation upto 5.55%-14.44%. Preparation S5 having label claim of 9.5% shows batch to batch variation upto 5.26%-14.73%.

CONCLUSION

Pediatricians and other health care providers should be aware of the widespread presence of alcohol in liquid medications and its potential to toxicity. Alcohol-containing medicines may affect the disposition of other drugs, cause undesirable drug interactions, or induce disulfiram (Antabuse)-like reactions. Since CNS toxicity occurs when the concentration of ethanol in the blood is 25 mg/100 mL, a single dose of alcohol-containing medication must not be able to produce this level of ethanol. Although fatal blood ethanol concentrations are widely quoted, such information does not take into consideration the effects of chronic administration, effects of simultaneous treatment with other medications, possible development of hypoglycemia, and reported fatalities with lower blood concentrations. Finally, continued efforts should be made to have alcohol removed from liquid preparations for children. In those

instances in which alcohol is a necessary solvent, preparations should be packaged in small volumes with safety closures.

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