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Short Communication

Analysis of gas-chromatographic method for the determination of ethanol in an 18-F-fluorodeoxyglucose (FDG-18) solution

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A gas chromatographic method for determination of ethanol in an fluorodeoxyglucose (FDG)-18 solution was developed. The pre-validation tests were made to test some parameters. Three samples in the concentration of 400, 4000 and 7200 ppm, respectively were analyzed using the novel methodology. The results of the technique were not good. Although the method seems to be capable to identify ethanol in solution, the pre-validation demonstrated a problem in the technique. The linearity results showed an R^2 of 0.66. Further tests must be made to implement this technique in a daily routine.

Key words: Validation, chemical analysis, quality control.

INTRODUCTION

The quality control of radiopharmaceuticals used in positron emission tomography has gained increased attention due to the widespread use of various probes in clinical studies. These radio probes, because of their short half-lives, must be produced as needed and subjected to several quality control testings at most production facilities before clinical application (Nakao et al., 2009). Determination of ethanol is one of these parameters. Since ethanol is a sub product of the reaction to produce 18-F-fluorodeoxyglucose (FDG-18), its concentration is directly related to the concentration of the FDG-18 produced. Moreover, the concentration of ethanol has a maximum value of 0.5% dehydrate ethanol in FDG-18 solutions (Hung, 2002; Yu, 2006). The intravenous LD_{50} value in rats for dehydrated alcohol is 1,440 mg/kg (Oxford, 2009). The oral LD_{50} value in rats for dehydrated alcohol is 7,060 mg/kg (Oxford, 2009). One may wonder why acetonitrile has the lowest acceptance threshold (that is, 0.04%) of the 3 residual solvents (ecetonitrile, dehydrate ethanol and ether), when dehydrated alcohol has a lower intravenous LD_{50} value and ether has the lowest oral LD_{50}. According to the "Guidance for Industry Q3C Impurities, Residual Solvents" issued by the FDA, residual solvents are grouped into 3 classes (that is, classes 1, 2, and 3) (FDA, 2009). The classification of residual solvents involves a risk assessment not only of their potential toxicity to humans but also of any possible deleterious effects they may have on the environment (Hung, 2002). Based on the "Q3C: Tables and List", acetonitrile is categorized as a class 2 solvent, whereas both dehydrated alcohol and ether are categorized as class 3 solvents. Class 1 comprises of solvents known to be human carcinogens, strongly suspected to be human carcinogens, or hazardous to the environment. Their use must be avoided in the manufacturing of drug substances, excipients, and drug products. Class 2 solvents have inherent toxicity, and their use in pharmaceutical products must be limited (USP, 2004). Class 3 solvents are those with a lower

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Abbreviations: FDG-18, Fluorodeoxyglucose 18; **RSD,** relative standard deviation; **FID,** flame ionization detector; **RSD,** relative standard deviation.

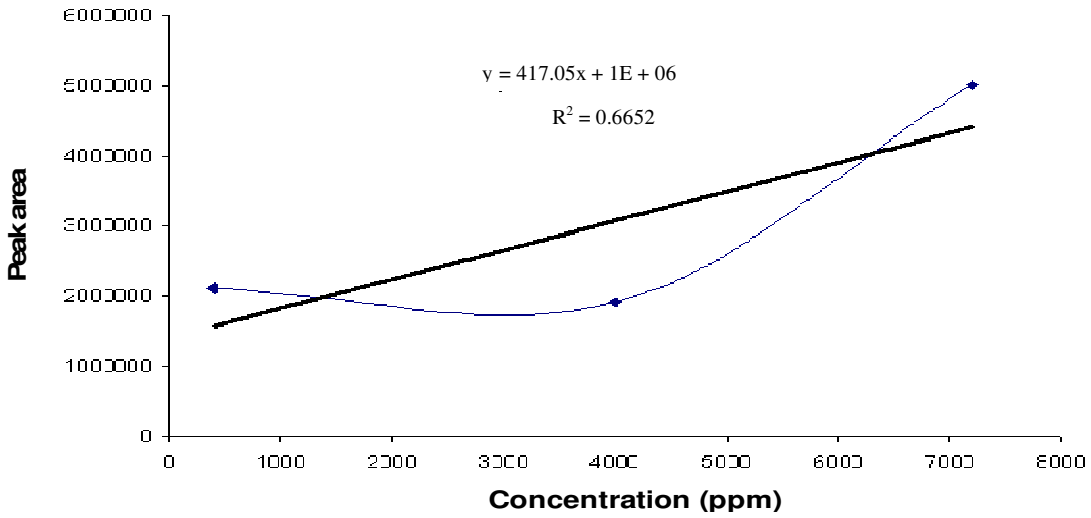

Figure 1. Graph of the linearity of the curve for determination of ethanol in FDG-18 injectable solution (area X concentration).

potential for toxicity and thus pose a lower risk to human health (FDA, 2009; USP, 2004). Therefore, the acceptance percentage limit for acetonitrile is lower than that of dehydrated alcohol or ether (Hung, 2002). In order to quantify ethanol in radiopharmaceuticals, this method was developed and pre-validated.

MATERIALS AND METHODS

Gas chromatography

The analysis of ethanol was carried out on a Shimadzu 17 AF3 gas chromatograph using a capillary column DB - 1701 J and W Scientific (14 % cyanopropyl - Phenyl) metylpolysiloxane and a flame ionization detector (FID). The quantification of the solvent was made using external standardization. Once both chromatographic and experimental conditions were established, the method was validated.

Standard solution

An “in time” solution was prepared by diluting 0.99 mL of ethanol in 100 mL of water in a 100 mL volumetric flask. The final concentration was a standard solution of 8000 ppm (parts per million).

Validation

Three parameters were evaluated initially; linearity, accuracy and system suitability test.

Linearity

The linearity of the method was assessed by analyzing 3 different concentrations of standard solution containing ethanol (400, 4000 and 7200 ppm). Before injection of the solutions, the column was equilibrated for at least 30 min with the mobile phase flowing through the system. Each measurement was carried out in two replicates of 10 µL injections for standard solution to verify the reproducibility of the detector response for each concentration level. The calibration curves were plotted as peak areas of ethanol versus concentrations of the standard solution using linear regression analysis.

System suitability test

Relative standard deviation (RSD) values for the area tailing factor and retention time were the chromatographic parameters selected for the system suitability test.

Accuracy

To confirm the accuracy of the proposed method, a total of 9 determinations were performed using 3 concentrations levels covering the specific range.

RESULTS AND DISCUSSION

The aim of this study is to quantify ethanol in FDG-18 solutions since there are no official methods for this determination. An optimum mobile phase consisting of helium was used. The retention time was 4.4 min. The linearity of the method was studied from 400 to 7200 ppm. No linear response was observed over the examined concentration, with correlation coefficient (r^2) = 0.6652. The representative linear equation for ethanol was:

$$y = 417.05x + 1E+06$$

Where, x is the concentration in ppm and y is the peak area (Figure 1).

The repeatability of the method was calculated as the

Table 1. Data obtained from the determination of ethanol using the novel methodology.

Concentration (ppm)	Values in area	Average	RSD
400	3731095	4201350	2319904
400	450255		
4000	4828848	5274116	4828848
4000	472071		
7200	4698618	9713554	4698618
7200	5331254		

Table 2. Recovery of ethanol from the samples with known concentrations.

Standard samples		
Added (ppm)	**Found (ppm)**	**Recovered (%)**
400	7676.18	5.21
4000	10248.45	39.03
7200	20893.31	34.46

Each value is a mean of 2 replicate analyses.

RSD of the assays for ethanol in the same concentration range. Also, the RSD value was higher as shown in Table 1. The accuracy was evaluated using 3 different standard solutions containing ethanol at 400, 4000 and 7200 ppm, respectively. Recovery data is reported in Table 2. The values obtained were within 5.21 -39.34% not satisfying the acceptance criteria for this study (98-102%).

Conclusion

The method, pre validated for determination of ethanol in FDG-18 solution was shown to be non accurate and linear. More studies, specially related to the robustness of the equipment must be done to be conclusive about the use of this methodology in a daily routine.

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