Journal of Pharmaceutical and Biomedical Analysis 54 (2011) 1001–1006

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Detection of diethylene glycol adulteration in propylene glycol—Method validation through a multi-instrument collaborative study[☆]

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ARTICLE INFO

Article history:
Received 2 August 2010
Received in revised form 1 November 2010
Accepted 27 November 2010
Available online 8 December 2010

Keywords:
Near infrared transmission
Propylene glycol
Diethylene glycol
Partial least squares
Hand-held instruments

ABSTRACT

Four portable NIR instruments from the same manufacturer that were nominally identical were programmed with a PLS model for the detection of diethylene glycol (DEG) contamination in propylene glycol (PG)–water mixtures. The model was developed on one spectrometer and used on other units after a calibration transfer procedure that used piecewise direct standardization. Although quantitative results were produced, in practice the instrument interface was programmed to report in Pass/Fail mode. The Pass/Fail determinations were made within 10 s and were based on a threshold that passed a blank sample with 95% confidence. The detection limit was then established as the concentration at which a sample would fail with 95% confidence. For a 1% DEG threshold one false negative (Type II) and eight false positive (Type I) errors were found in over 500 samples measured. A representative test set produced standard errors of less than 2%. Since the range of diethylene glycol for economically motivated adulteration (EMA) is expected to be above 1%, the sensitivity of field calibrated portable NIR instruments is sufficient to rapidly screen out potentially problematic materials. Following method development, the instruments were shipped to different sites around the country for a collaborative study with a fixed protocol to be carried out by different analysts. NIR spectra of replicate sets of calibration transfer, system suitability and test samples were all processed with the same chemometric model on multiple instruments to determine the overall analytical precision of the method. The combined results collected for all participants were statistically analyzed to determine a limit of detection (2.0% DEG) and limit of quantitation (6.5%) that can be expected for a method distributed to multiple field laboratories.

1. Introduction

Propylene glycol (PG) is included in the FDA Inactive Ingredients Database [1] and is widely used in the pharmaceutical industry as an excipient [2]. It is a clear, colorless, viscous liquid with sweet taste. Recent findings of PG contamination with diethylene glycol (DEG) cause significant concern for the safety of consumers and pharmaceutical products [3–5]. With an increasing number of overseas suppliers of pharmaceutical raw materials, the best way to prevent economically motivated adulterated materials from entering the US market is to drastically increase the number of samples to inspect for quality control [6–8]. Therefore, it is important to develop rapid analytical methods that are suitable to identify toxic impurities and contaminants [9–13]. The USP [14] and other methods [15] of identifying diethylene glycol in propylene glycol use gas chromatography, which can only be done in the laboratory and are time consuming. Near infrared (NIR) absorbance spectroscopy coupled with chemometrics is a powerful tool in analytical chemistry to identify pure chemicals and components in mixtures [9]. Both propylene glycol and diethylene glycol have strong absorption bands in the NIR spectral region that can be used to create a quantitative chemometric model. Evidence from field surveillance suggested that economically motivated adulteration (EMA) would occur in the range of 5–15 wt% [7]. To intercept such adulterated materials we have suggested deploying portable spectrometers with chemometric models capable of detecting DEG as an impurity in propylene glycol–water mixtures down to the 1–2% level.

Typically, analytical instruments are used for one application at a time. Individual instruments are calibrated and validated for each particular task. This is not the case for field regulatory surveillance, as well as many PAT applications. Multiple copies of the same basic instruments are used by a variety of people in a range of environments. Even instruments of the same model may differ in wavelength calibration and photometric sensitivity. A means to standardize multiple instruments so that a model developed on

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[☆] The findings and conclusions in this article have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy.

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0731-7085/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.jpba.2010.11.042

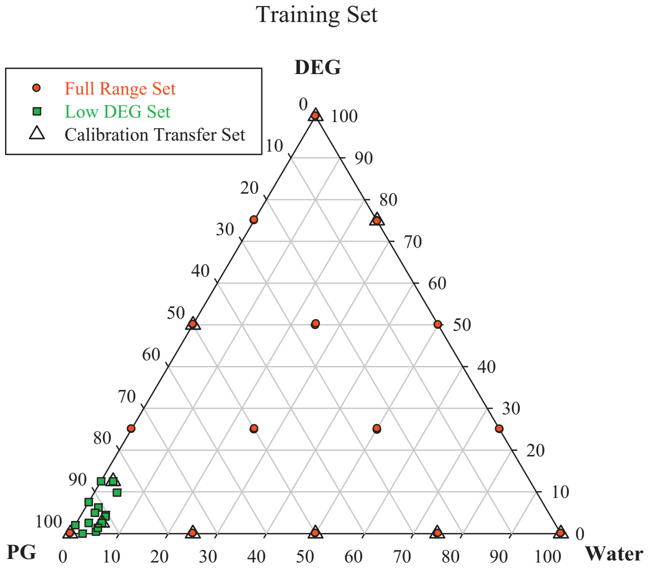

Fig. 1. Ternary diagram of training set sample compositions used in the PLS model.

one master instrument can be used on many similar secondary instruments is required. Though the specific problem at hand was the detection of diethylene glycol in propylene glycol, this work also evaluated the transfer of calibration models to multiple instruments using an optimized set of calibration transfer samples and piecewise direct standardization. Such a technique allows any instrument in the group to produce the same result as would be found on the master instrument.

In this work we used a multi-site, multi-instrument collaborative study to analyze the variations inherent in four "identical" near infrared spectrometers. Our objective is to develop an intermediate measure of the precision that accounts for different users, secondary instruments and locations. The spectrometers were used to quantitatively measure the composition of a ternary mixture (PG–DEG–water) using a chemometric model (PLS) developed on one master instrument. Water was included because USP grade PG allows variable water content and the DEG calibration model must therefore be insensitive to water composition. Detection and quantitation limits were determined for the entire group of secondary instruments and compared to the results typical for any single instrument.

2. Materials and methods

2.1. Materials

USP grade propylene glycol and reagent grade DEG were purchased from Fisher Scientific (Fair Lawn, NJ, USA). The water contents of as-received PG and DEG were determined by Karl–Fischer titration to be 0.03% and 0.05%, respectively. Disposable dual pathlength plastic CVD-UV cuvettes (Plastibrand®, Ocean Optics, Dunedin, FL, USA) were sealed with polyethylene caps and Parafilm 'M'®. The sample pathlength was 0.5 cm.

2.2. Design of experiment

JMP 5.1 software [16] was used to generate an optimum ternary array of training samples, see Fig. 1. The training set had 29 samples chosen in such a way that the first fifteen samples encompassed the full ternary range while the remaining fourteen simulated more realistic adulterated propylene glycol (over 85% propylene glycol–water mixtures with up to 15% diethylene glycol). Thirty-nine test samples were made up to cover the same overall range (Fig. 2a), again with emphasis on lower levels of adulteration (see Fig. 2b). All samples were made in bulk by weight (nominally 50 g total weight basis). Karl–Fischer water determinations for PG and DEG were taken into account in the formulation. All were mixed for 30 min on a Turbula® orbital mixer.

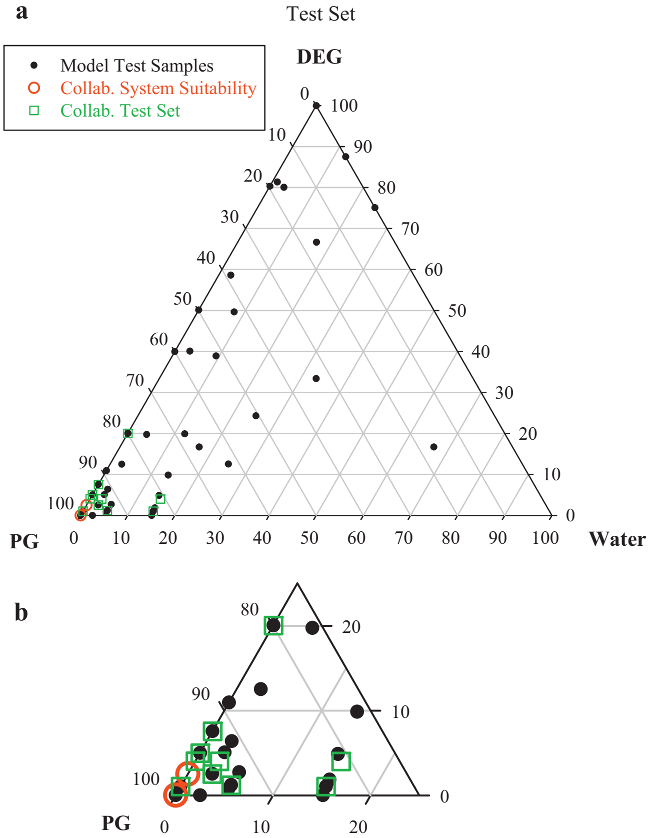

Fig. 2. (a) PLS model test set. (b) Close-up of low DEG, low water region of system suitability (circles) and test samples (squares) used in the collaborative study.

2.3. Near infrared spectra

NIR transmission measurements were made on a B&W Tek, Inc., *i-Spec* BWS025 that uses a 5 W incandescent source and a cooled 256 element InGaAs CCD array detector in the range 1100–2200 nm. The sample cuvettes were placed in a fiber-optic coupled sample holder. Spectra were measured using an integration time of about 5 ms. 300 spectra were co-added before calculating optical density. An empty cell was scanned initially as a reference. The overall time required to analyze one sample was less than 2 s.

Four portable NIR spectrometers of the same model (referred to as NIR01, NIR02, NIR03 and NIR04) were characterized in-house and one was selected based on stability, reproducibility and low noise to be a 'Master' instrument on which the chemometric model was constructed and to which the others were mathematically matched using a 'calibration transfer' method. All instrument operation, subsequent chemometric calculations and report generation were handled by Visual BASIC for Applications (VBA) program running in Excel and Word.

A printed and illustrated step-by-step protocol, along with a video and the sample set was distributed to four collaborating FDA field laboratories (referred to as 1, 2, 3 and 4). The sample set was measured at least three times (twice on battery and once on AC