

# Quantitative Determination of Residual Carbon Tetrachloride in a Drug Product by GC-ECD

Nahid Ameri • Carolyn Parsons • Saeed Hashemi

Irvine Pharmaceutical Services, Inc. • 10 Vanderbilt, Irvine, CA 92618



## Abstract

A method for the determination of residual carbon tetrachloride (a USP Class 1 Residual Solvent) in a drug product has been validated as a working concentration of 24 ng  $\text{CCl}_4/\text{mL}$  (4ppm) using gas chromatography and electron capture detection (ECD). USP <467> GC headspace analyses by flame ionization detection (GC-FID) involves minimal peak height and area of carbon tetrachloride, whereas electron capture detection is ideally suited for the analysis of this and other halide containing drug products.

## Methods

GC System: Agilent 6890N, Detector: Electron Capture, Column: Restek RTX-624 30m c 0.53mm x 3 $\mu\text{m}$ , Carrier: Helium @ 5mL/min., Inlet Temp.: 140°C, Detector Temp.: 300°C, Oven Profile: 40°C for 5 min., to 220°C @ 20°C/min., Run Time: 14 minutes. Injection volume: 1 $\mu\text{L}$ , Internal Standard: Trichloroethylene.

## Data

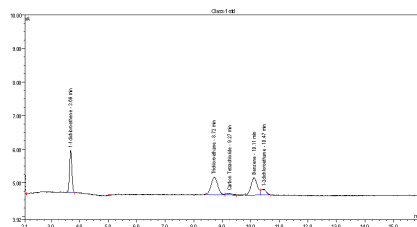


Figure 1: Chromatogram of Carbon Tetrachloride Detected by FID

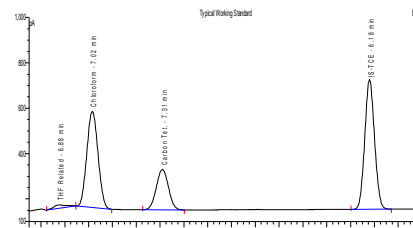


Figure 2: Chromatogram of Carbon Tetrachloride Detected by ECD

The pair of chromatograms above show the sensitivity comparison between Headspace FID and Liquid Injection ECD of comparable carbon tetrachloride concentrations.

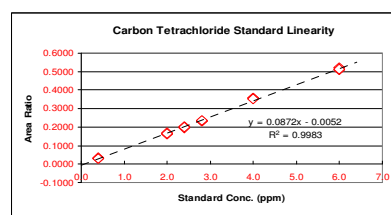


Figure 3: Carbon Tetrachloride Standard Linearity

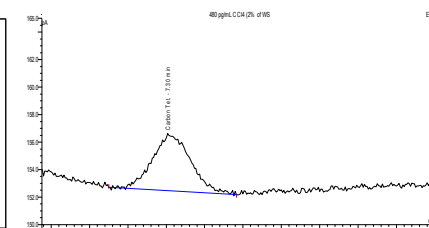


Figure 4: Chromatogram of LOD

The drug product was found to be soluble in dimethylformamide; however, to allow for solution homogeneity, the DMF solvent dielectric constant was lowered by diluting 50:50 with tetrahydrofuran. As radical species confound this  $\beta$ -emitting nickel 63 detector, extreme care was taken to prevent THF oxidation by conducting all solution handling under ice-bath conditions and solution preparations were allowed a cure time of 30 minutes.

## Results

This method is specific for carbon tetrachloride and standard linearity from 10% to 150% of the 4 ppm working limit has an  $R^2$  value > 0.998, based on area ratio vs. standard concentration (ppm). The bias is (-) 0.0052 or ~1.5%. Precision of the method is 0.8% RSD. Intermediate precision of 12 total spiked replicates is 1.7% RSD. A detection limit of 2% of the working limit was determined. At recovery levels below 50%, a matrix effect appears to boost the  $\beta$  capturing capability of carbon tetrachloride as it elutes through the electron cloud and leads to falsely elevated % recovery. Therefore, recovery is validated from 50% to 150% of the working limit (4ppm). The quantitation limit is set at 2 ppm.

## Conclusion

This method is robust, selective, reproducible, precise and quantitative.