

Determination of Residual Solvents in Drugs by Ion Chromatography

Residual solvents in pharmaceutical products are to be determined in the process of the drug approval application. We have developed analytical methods by ion chromatography (IC) for determining ionic compounds and organic acids, which are not suitable analytes for the general gas chromatography (GC) method.

Test of residual solvents

The test should be performed to determine the organic solvents listed in the ICH guideline, and to confirm that the concentration of each solvent remained in pharmaceutical products is within the acceptable level.

ICH Q3C: IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS

The guideline recommends use of less toxic solvents, and describes 3 classes of solvents depending on their toxicity.

Class 1: Solvents to be avoided in the manufacture of pharmaceutical products.
(5 solvents, including benzene and carbon tetrachloride)

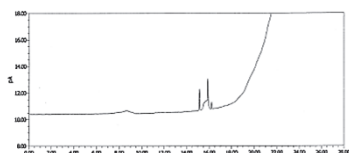
Class 2: Solvents to be limited in pharmaceutical products.
(26 solvents, including acetonitrile, chloroform, and methanol)

Class 3: Solvents to be limited by GMP or other quality-based requirements (less toxic).
(28 solvents, including acetic acid, ethanol, and formic acid)

Others: Solvents for which no adequate toxicological data was found. Manufacturers should supply justification for residual levels of these solvents in pharmaceutical products.
(10 solvents, including TFA and isopropyl ether)

Analysis method for residual solvents

Gas chromatography (GC) is generally used for analysis of residual solvents, but some solvents are not suitable.

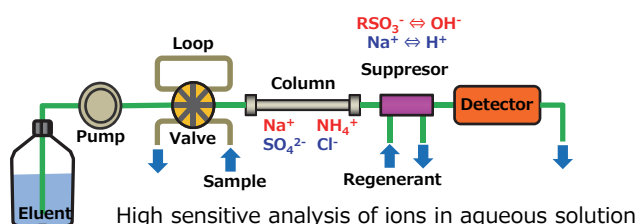


- High polarity
- Low volatility
- No C-H bond (FID detector)

Chromatogram of Formic acid (10 mg/mL), GC

Ion chromatography (IC)

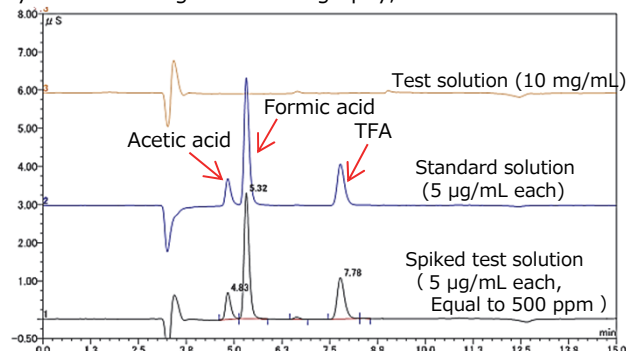
Analytes are separated based on their affinity to the ion exchange resin. Various ions in aqueous solutions can be detected with high sensitivity. An electrical conductivity meter or a mass spectrometer is usually used as the detector.



High sensitive analysis of ions in aqueous solution

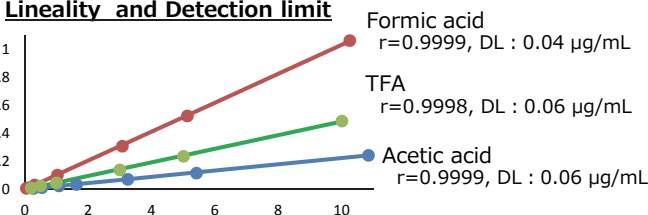
Analysis of TFA, Acetic acid, and Formic acid

An assay method for the simultaneous determination of TFA, acetic acid, and formic acid, which are difficult to be analyzed by conventional gas chromatography, has been established.



Chromatograms of TFA, Acetic acid, and Formic acid

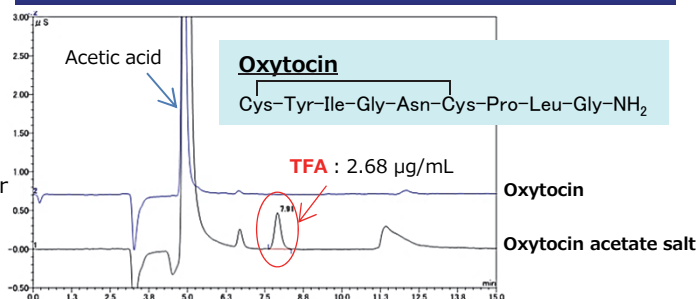
Linearity and Detection limit



Recovery

Additive conc.	0.25 µg/mL	1 µg/mL	5 µg/mL
Acetic acid	100.7	93.7	98.7
Formic acid	96.7	98.7	94.7
TFA	108.7	94.7	100.0

Residual TFA in Oxytocin acetate salt by IC



Chromatograms of Oxytocin and Oxytocin acetate salt

Typical Examples of Suitable Analytes for IC

Cation: Na^+ , NH_4^+ Anion: Cl^- , F^- , SO_4^{2-}
 Lower organic acid:
 Formic acid, Acetic acid, Oxalic acid, Citric acid
 Lower amine: Tetramethylammonium