LOKT.06.034. Measurements and the Law

European guidelines and analysis method for controlling residual solvents in pharmaceutical product

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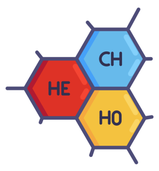
Introduction

What is residual solvent?

"Organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients or in the preparation of drug products"

Potential source of residual solvent



Synthesis/purification of API (Active Pharmaceutical Ingredient)

Excipient

Manufacturing process (Film coating, Polishing)

Why do we have to control residual solvent?

- Several medications require high doses or prolonged usage
- Chronic exposure of residual solvent can have adverse effects on health
- These solvents have the potential to contaminate the environment during production and household wastewater, leading to ecological repercussions

Related directive/guidelines

- EU Directive 2001/83/EC: Community code relating to medicinal products for human use

  "To apply for market authorization, the safety data should be provided"

- ICH Q3C - IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS
  - → Scope of application: Residual solvent in drug substance, Excipients and drug products
  - → Not applicable to solvent used as ingredient in the formulation
  - → Classification of solvent and acceptance limit
- European (and US) pharmacopoeia
  - → Controlled option
  - → Analytical procedure and analytical method validation

Class of residual solvent

Class	Definition	Example	Limit (ppm)
1	**The solvent should be avoided** • Unacceptable health hazard • Environmental hazard	Benzene	2
		Carbon tetrachloride	4
2	**The solvent should be limited** • Severe toxicity	Acetonitrile	410
		Methanol	3000
3	**Solvent with low toxic potential**	2-Propanol	5000
		Ethanol	

When should we analyse residual solvent?

- **Before market authorisation, to provide the safety data**
  - → 6 pilot batches
  - → 3 consecutive industrial batches
- **Batch production routine analysis**
  - → When solvent is used in the manufacturing process
  - → When the residual solvent content in the product is at risk of exceeding the acceptance limit
- **As part of annual product quality review**

How can we analyse the residual solvent?

Thermogravimetry

- **Instrument**: Hot air oven
- Use this method when only class 3 solvent is present

Put the test sample into a bottle, W_{sample}

↓

Dry sample at time and temperature specified in monograph

↓

Record the weight of dried bottle, W_{loss}

↓

Calculate the amount of residual solvent

$$\%\text{Residual solvent} = \frac{W_{loss}}{W_{sample}} \times 100$$

Gas Chromatography

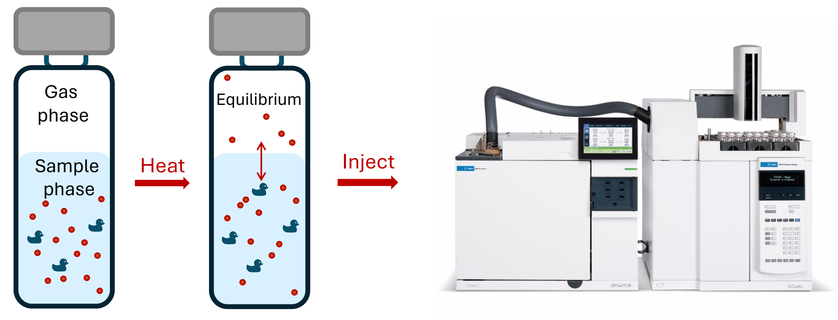
Instrument: Gas chromatography

Sample introduction

- Headspace sampler: The volatile compound diffuses to the gas phase

Detector

- Flame ionisation detector
- Mass-selective detector



Screening method

Use when don't know the solvent in the ingredient or formulation

Prepare a standard solution for screening and sample solution

↓

Perform an analysis

↓

The residual solvent peak in sample less than the corresponding standard?

No → Quantitative method

Yes ↓

Passes test, no further action

Quantitative method

Use when we want to measure exact amount of solvent

Prepare a standard solution for quantitation and sample solution

↓

Perform an analysis

↓

Calculate the amount and report

*Remark : EDQM/USP provide the standard mixture for screening and quantitative analysis

Conclusion

- Residual solvents are organic volatile chemicals from pharmaceutical ingredients or manufacturing processes that should be controlled for patient and environmental safety
- Should analysis and report the amount of residual solvent as part of safety data for the market authorization of the product
- The recommended analysis technique is Thermogravimetry and Head space-Gas chromatography

Reference

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Picture

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