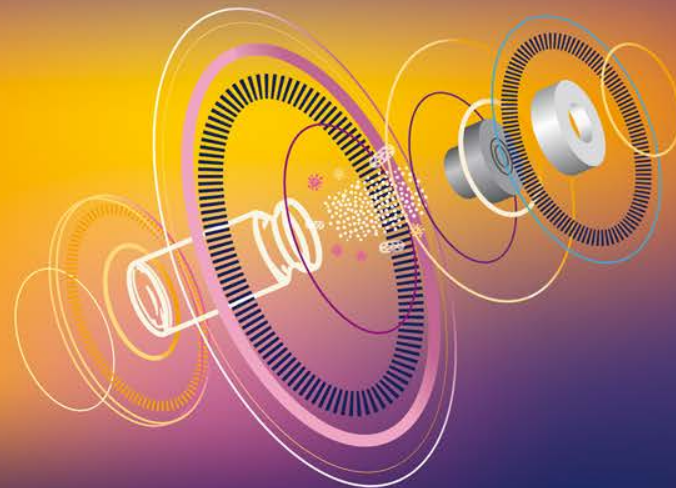


Silicone oil detection on rubber closure



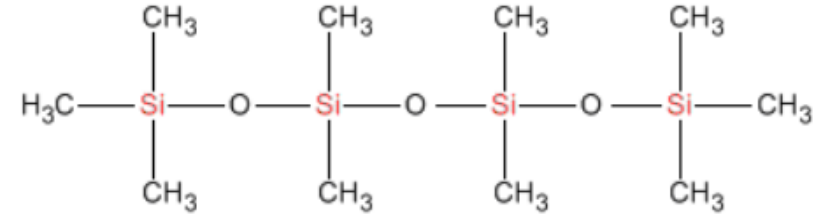
2020 PDA EUROPE

Parenteral Packaging

25-26 FEBRUARY 2020
BASEL | SWITZERLAND

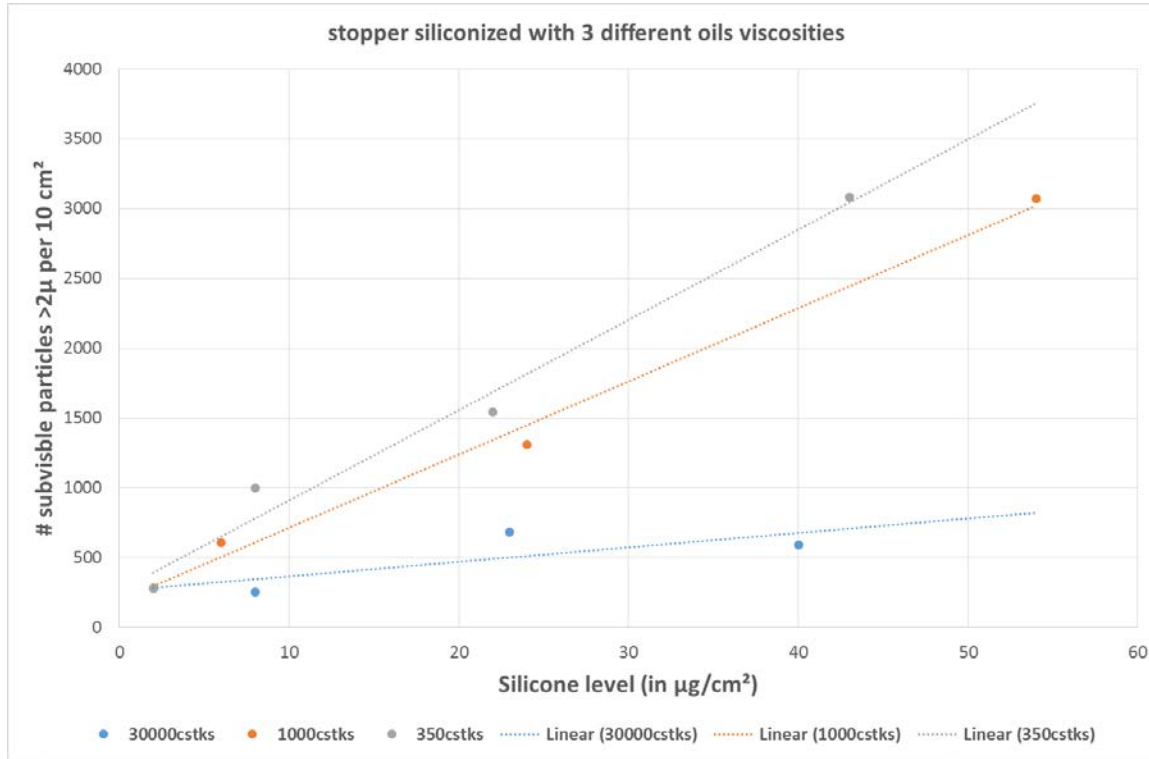
CONNECTING
PEOPLE
SCIENCE AND
REGULATION®

Silicone oil



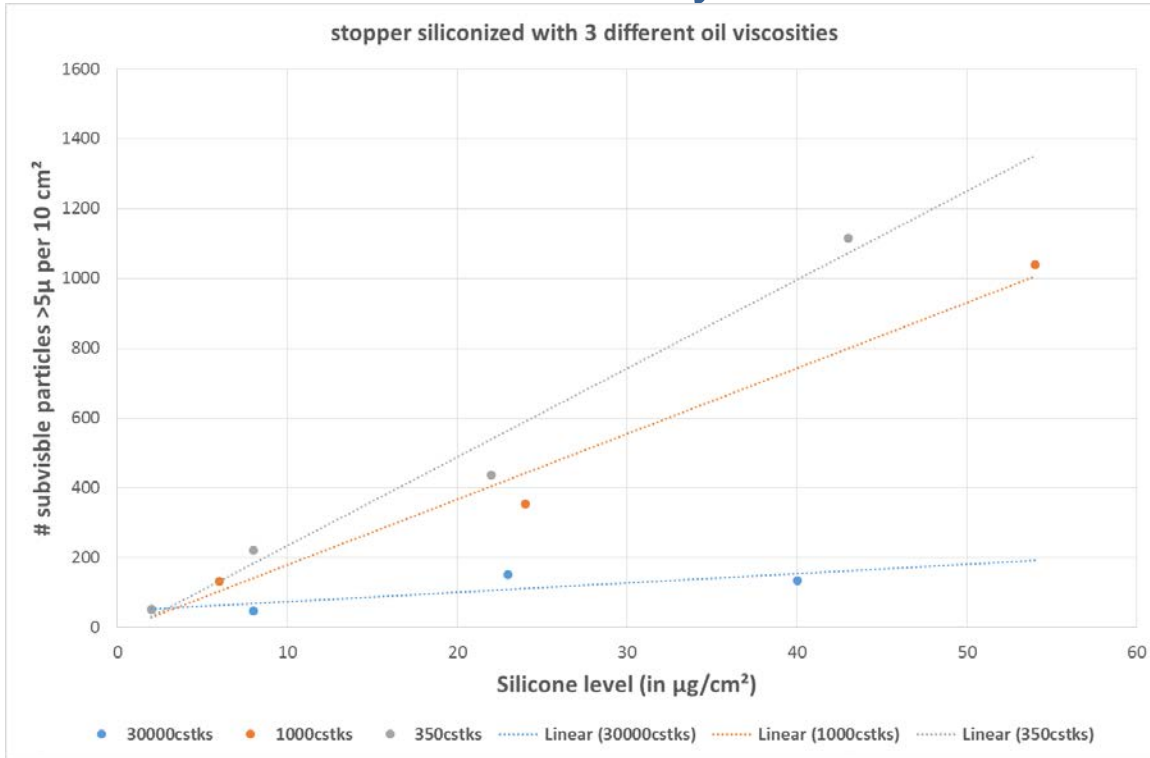
- Polydimethylsiloxane
- Very stable molecule, inert. Si-O bond has an energy of 119 kcal/mol or 498 kJ/mol in comparison to 90 kcal for C-C bond.
- Very low surface tension (= hydrophobic), around 21 nN/m.
- Viscosity range from 350 cSt to 30 000 cSt

Impact of silicone oil viscosity on sub-visible particles



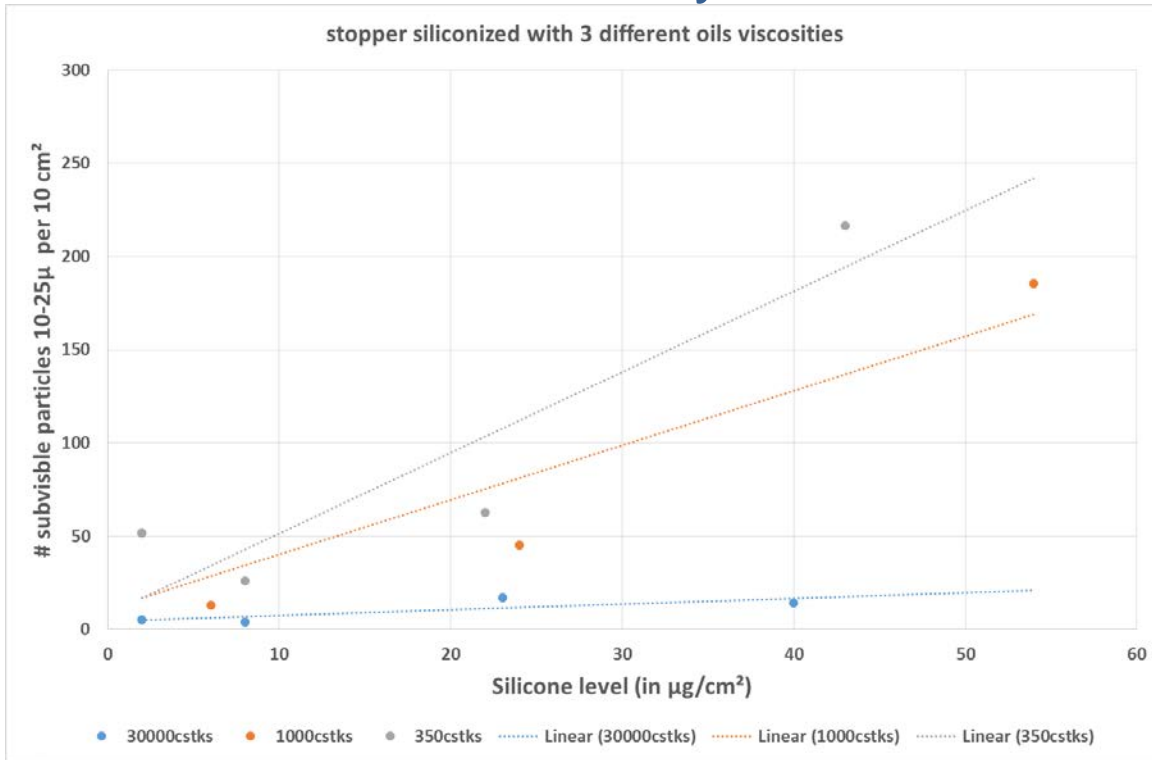
Particles $> 2\mu\text{m}$

Impact of silicone oil viscosity on sub-visible particles



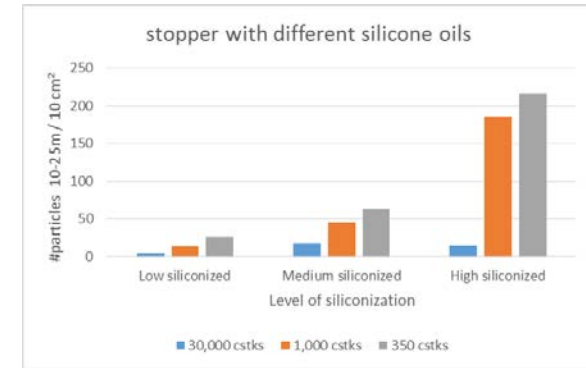
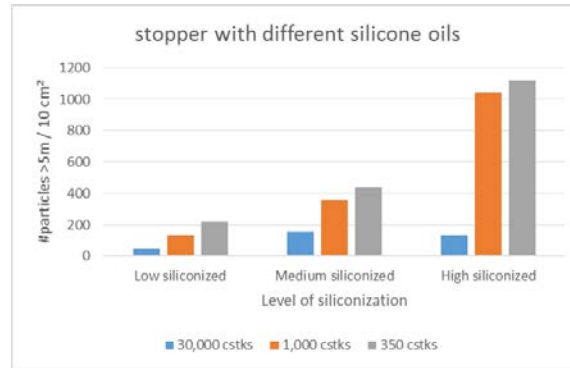
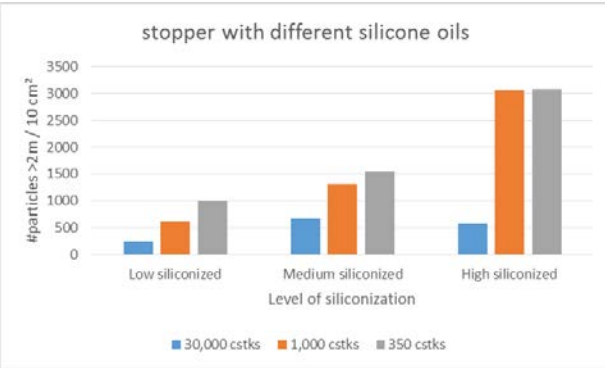
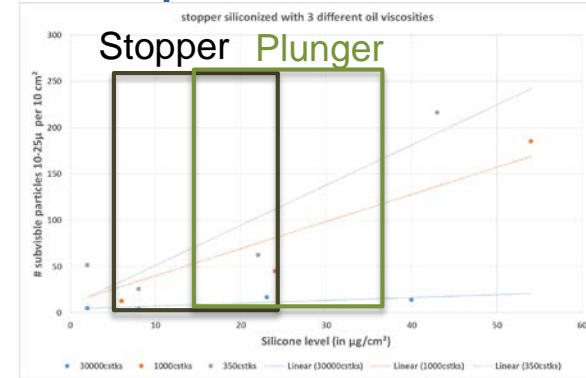
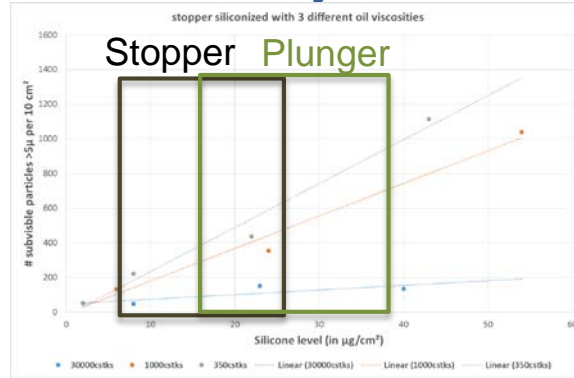
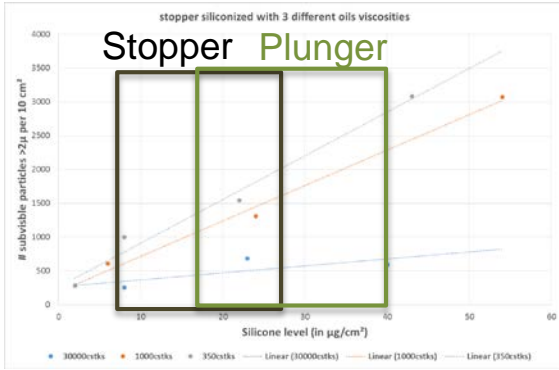
Particles > 5 μm

Impact of silicone oil viscosity on sub-visible particles



Particle 10-25 μm

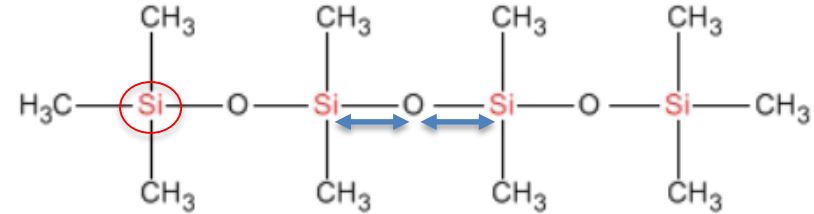
Impact of silicone oil viscosity on sub-visible particles



Functional effect

- Possible impact on break-loose force: plungers are typically more siliconized than stoppers.
- Impact of silicone oil leaching into solution on protein stability, due to protein denaturation after migration in hydrophobic silicon oil.

Outlines



- Quantification of silicone oil
 - By NMR¹
 - **By FT-IR**
 - On rubber
 - In solution
 - **By Atomic Absorption Spectroscopy (AAS)**

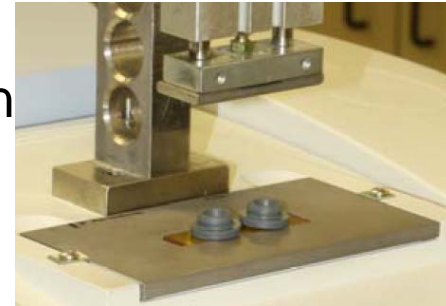
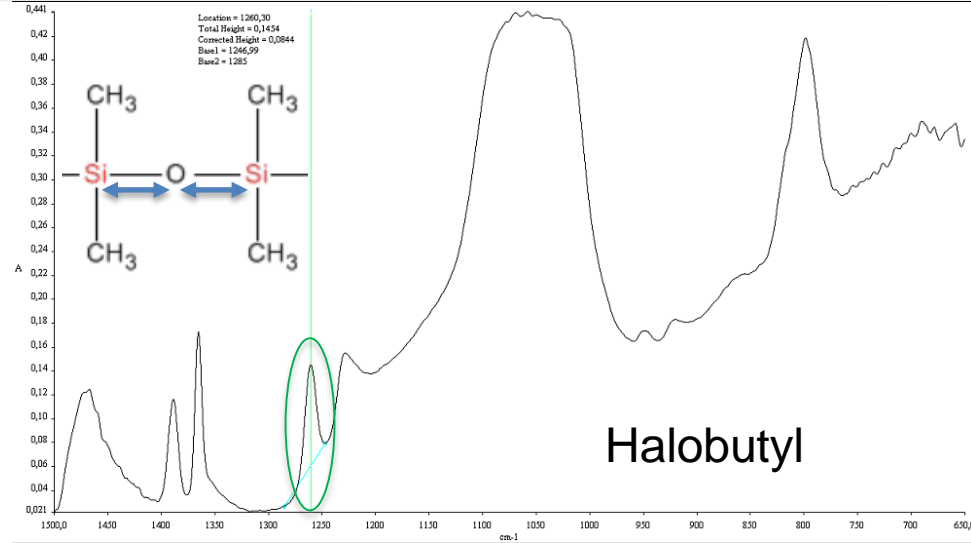
1: Determination of trace amounts of polydimethylsiloxane in extracts of chemicals by proton nuclear magnetic resonance spectroscopy, *Analyst*, 1990,115, 179-183

Quantification of silicone oil on rubber

On rubber

- Advantage:
 - Fast method
 - No use of solvents
- Disadvantage:
 - Rubber peaks can interfere with Si-O-Si vibration

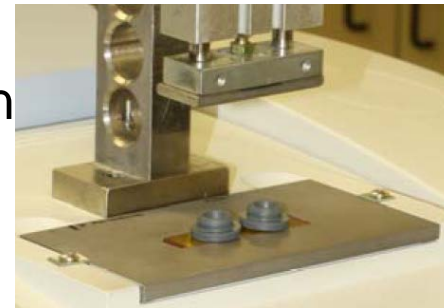
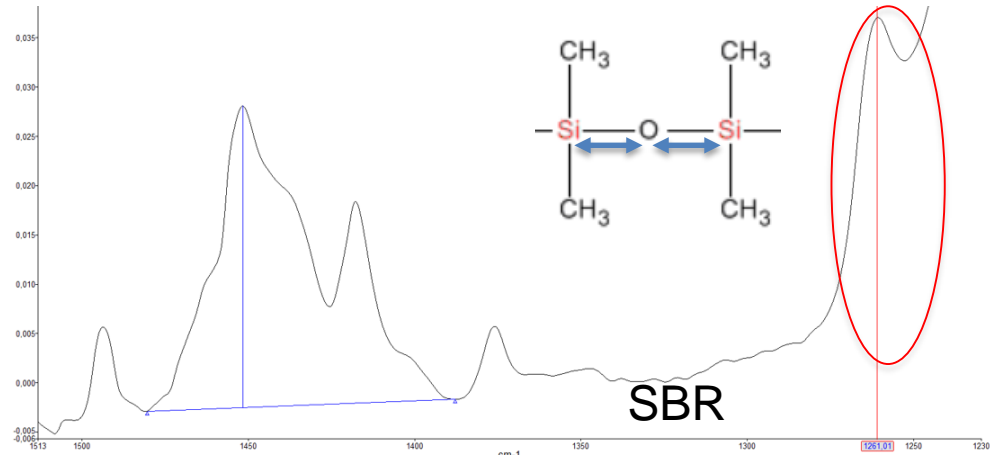
So determination of a Sila value per compound



On rubber

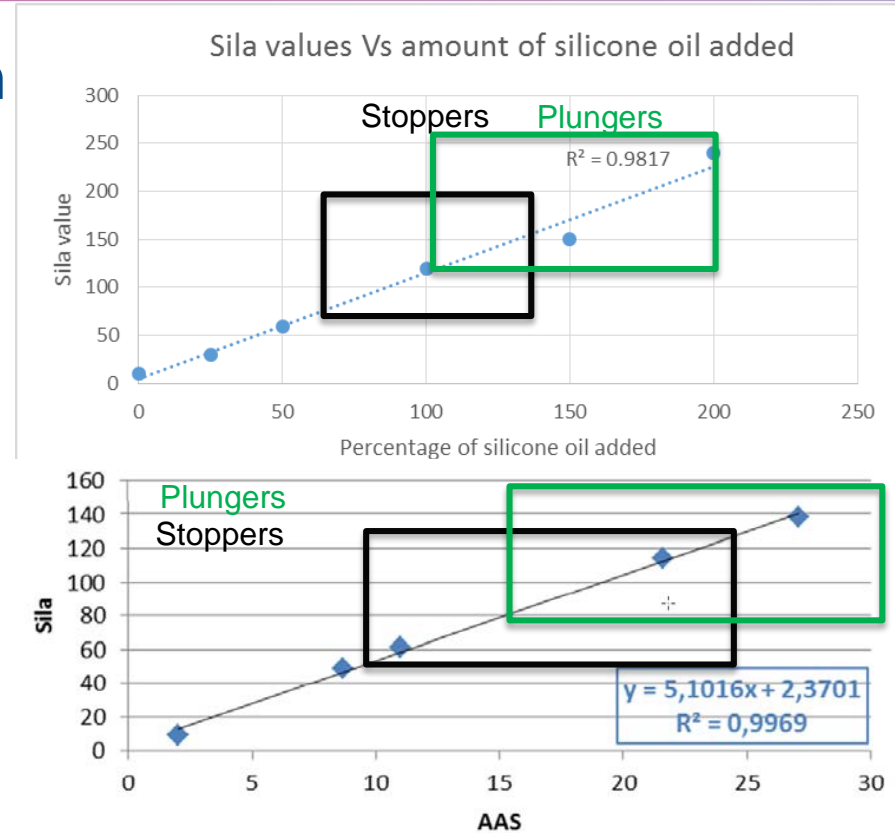
- Advantage:
 - Fast method
 - No use of solvents
- Disadvantage:
 - Rubber peaks can interfere with Si-O-Si vibration

So determination of a Sila value per compound



Quantification and correlation with AAS

- Sila value correlates with increasing amount of silicone oil
- Quick method that correlates with AAS
- Quantification of traces of silicone oil is challenging



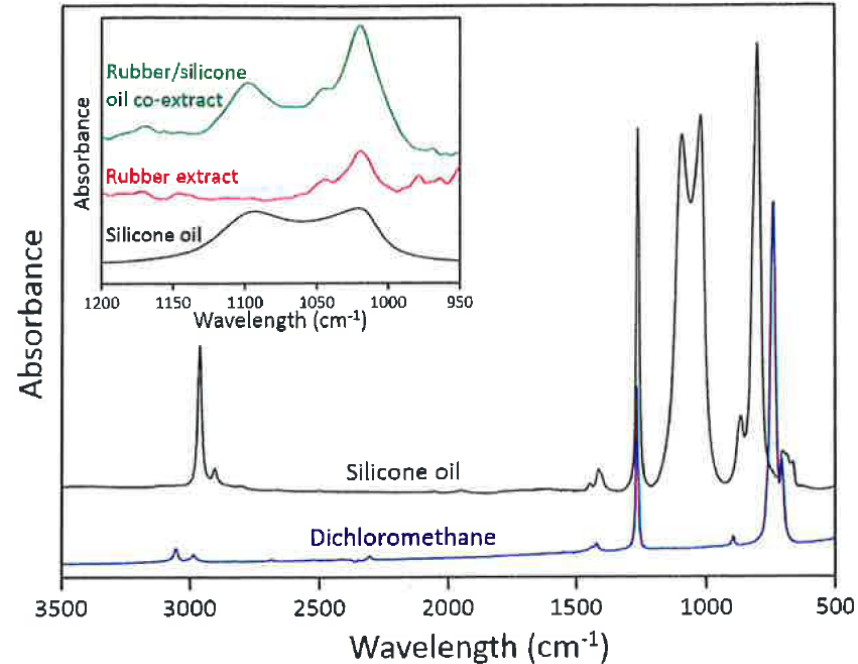
Quantification of silicone oil in solution

General procedure

- Extraction of silicone oil from the rubber (with DCM or MIBK)
- Measurement of silicone oil amount into the solution by FT-IR (with DCM) or AAS (with MIBK)
- Advantages:
 - Little influence of the compound underneath
 - Possibility to have calibration curve with stock solution

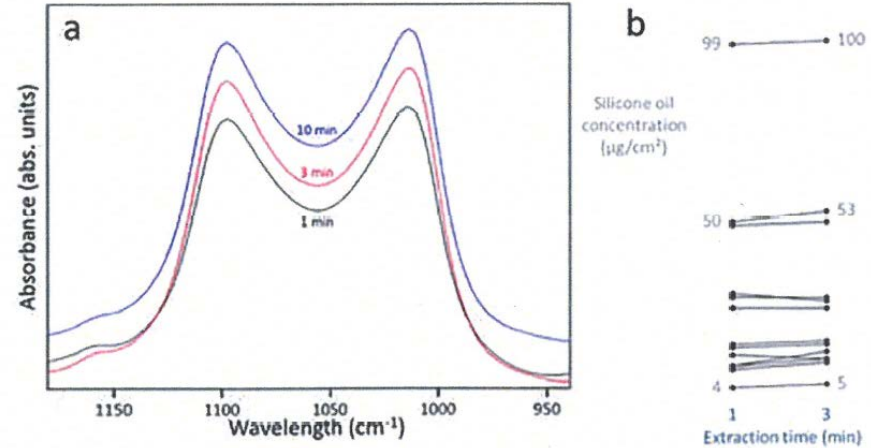
Detection wavelength

- Selection of a solvent that do not have much vibration in IR: DCM
- Selection of a wavelength that do not display interference of possible rubber extractables: 1095 cm^{-1}



Procedure

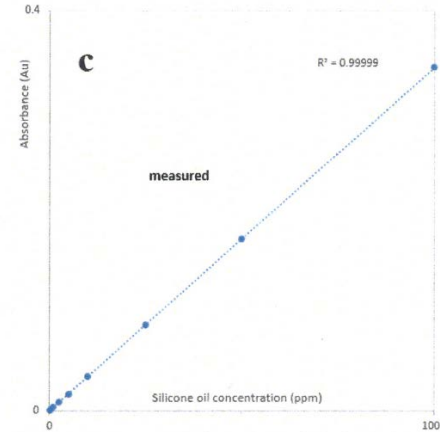
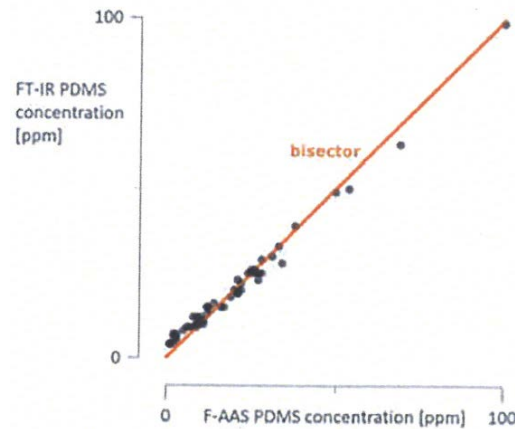
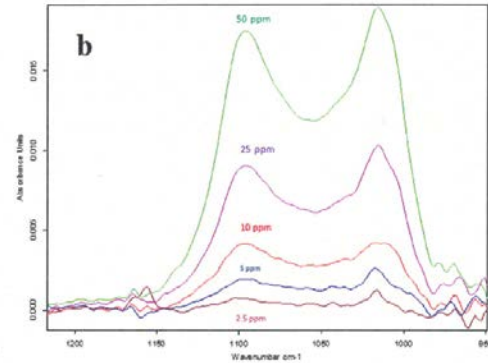
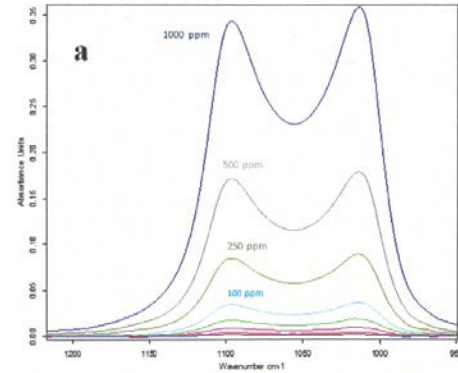
- An extraction time of 3 minutes is advised.
- Longer extraction time could lead to extraction of chemicals from the rubber.



Quantification

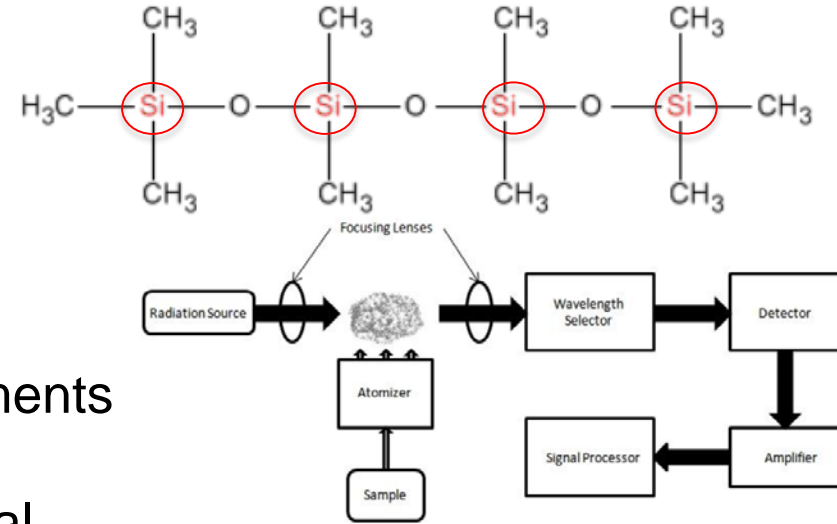
- Excellent correlation between silicone oil concentration in stock solution and absorbance detected by FT-IR.
- Excellent correlation between FT-IR and AAS.

$$\text{Degree of siliconization} \left(\frac{\mu\text{g}}{\text{cm}^2} \right) = \frac{C_{\text{extract}} \left(\frac{\mu\text{g}}{\text{ml}} \right) \times V_{\text{DCM}} (\text{ml})}{A_{\text{rubber stoppers}} (\text{cm}^2)}$$



AAS

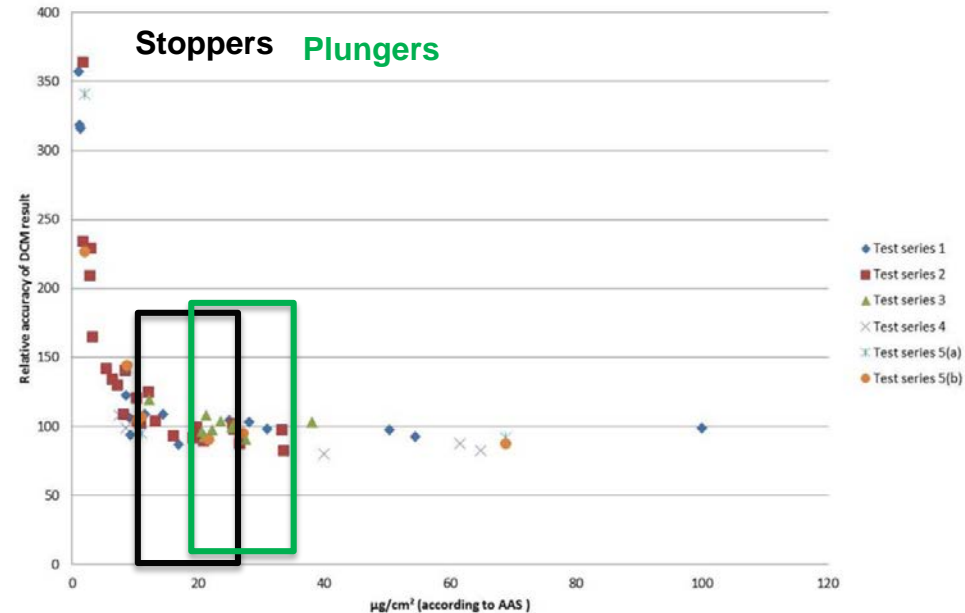
- Works by burning solution (MIBK)
- Detect the absorption typical of elements
- Quantitative method to detect several elements, including silicone.



Comparative accuracy

- Good accuracy of the FT-IR method for the normal range of siliconization.
- Detection of traces of silicone should be performed with AAS.

'Relative accuracy' of DCM/FTIR result compared with MIBK/AAS result:
= 100 * (DCM result/AAS result)



Conclusion

- Measurement on products:
 - Fast but possible influence from the compound underneath
- Measurements on solution after extraction
 - More tedious but quantitative results can be easily obtained by FT-IR or AAS

Thanks to:
Dr Anita Thijs



2020 PDA EUROPE

Parenteral Packaging

CONNECTING
PEOPLE
SCIENCE
AND
REGULATION®