Comparative Study between Dye Ingress Test and Deterministic Methods

Helium Mass Spectrometry, Optical Emission Spectroscopy, Mass Extraction

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Introduction

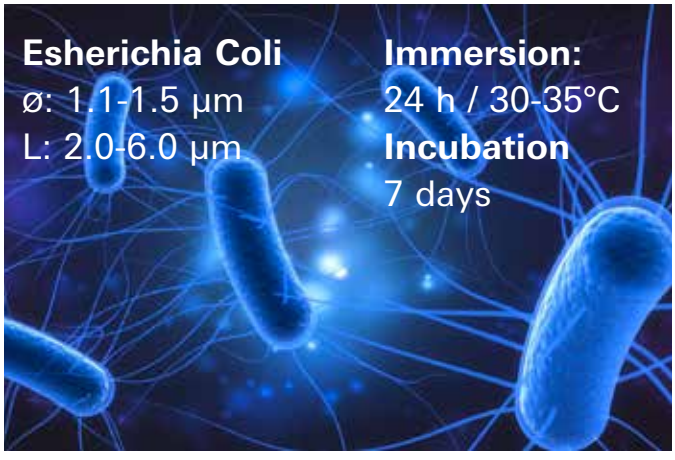
Abstract
Repeatable and proper Container Closure Integrity Testing of primary packaging's is essential to ensure quality and effectiveness of pharmaceutical products. Blue dye test and microbial ingress are mainly used for decades. Recently, guidelines provided by regulatory organizations like USP <1207> or Annex 1 request statistical analysis and push for use of deterministic and non-destructive methods.

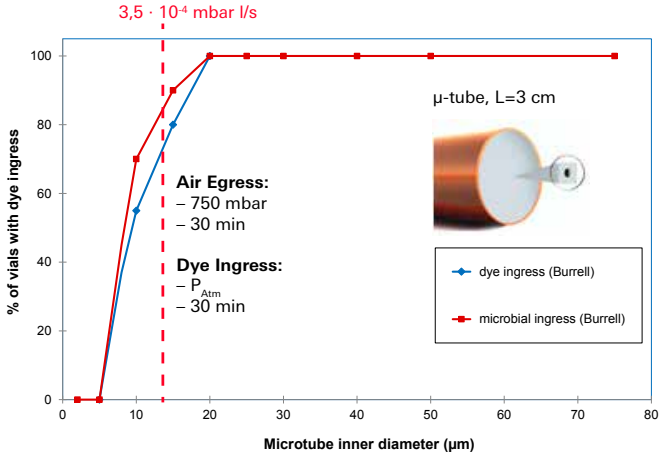
The following presents the results of a unique comparative study conducted on more than 500 glass vials that are prepared with leak artifacts (microtubes and glass micropipettes), which refers to Kirsch and Burrel's studies. Each sample has been tested with different technologies: Helium Leak test, Optical Emission Spectroscopy, Mass Extraction and Blue Dye test. Depending on the needs (R&D, Production, Quality) the results can help the reader to find a suitable deterministic test method to replace the blue dye test and follow the latest guidelines.

Comparative Study

In order to be able to refer to previous comparative studies between microbial ingress and helium leakage (Kirsch & All, see below) as well as dye ingress vs microbial ingress (Burrel & All, see below) we decide to use glass micropipettes and capillaries to prepare positive controls.

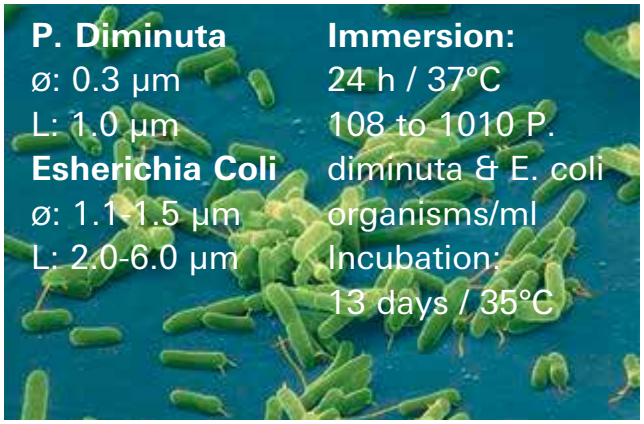
Dye Ingress Method – Correlation to Microbial Ingress
Burrell & All – PDA journal , Vol 54, No6,
November/December 2000

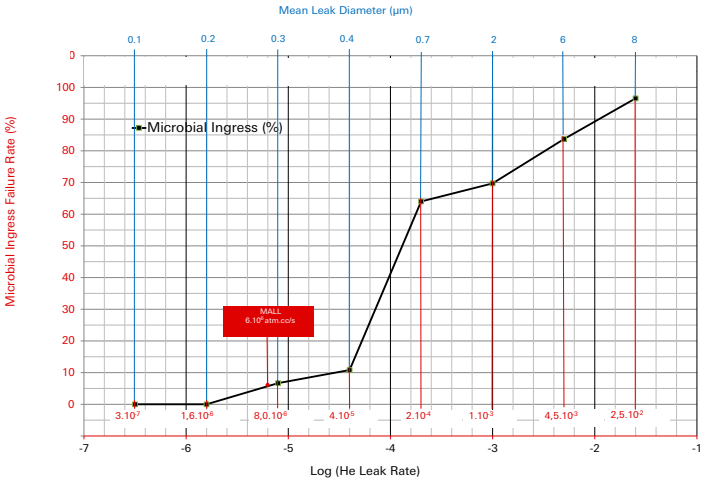




The dye ingress and microbial ingress methods have similar sensitivity to breached vials.
Dye Ingress sensitivity ~20 µm diameter for a µ-channel (3 cm long).

Helium Test Method – Correlation to Microbial Ingress Method
Kirsch, PDA J Pharm Sci & Technol, 51, 5,
September-October 1997 p. 195-202

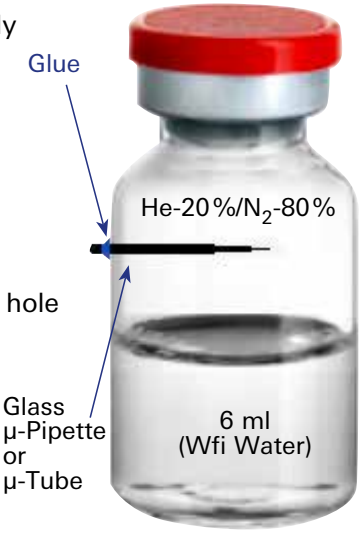




The MALL (Maximum Allowable Leak Limit) define is the USP <1207> corresponds to a Helium leakage of $6 \cdot 10^{-6}$ mbar·l/s for which the probability of microbial ingress failure rate was < 10%.

Sample Composition

- Standard ISO 20R Vials crimped manually
- Two types of defects have been used:
  - Glass Micropipettes
    (Ø 0.1 / 0.2 / 0.4 / 1 / 2 / 5 / 10 µm)
  - Capillaries, 3 cm long
    (Ø: 2 / 5 / 10 / 15 / 18 / 30 / 40 µm)
  - 30 samples prepared for each diameter
  - 30 negative controls with glue on the hole

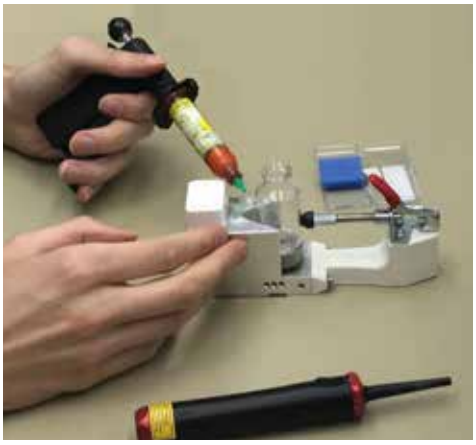


Vial Composition

- 6 mL WFI water
- Gas Headspace: He 20% / N_2 80%
- Gas mixture has been defined to allow measurement with the three deterministic test methods available:
  - 20% He (for He measurement)
  - 80% N_2 for O.E.S measurements (~ [N_2] in ambient air)
  - Mass Extraction measures the global leakage flow
  - The defect is connected to the gas headspace in order to have a better sensitivity for the blue dye test.

Sample Preparation

1. Drilling Holes 1,5 & 0,5 mm



2. Fixing capillaries and glass µ-pipettes with UV-glue

3. Filling with 6 ml of Wfi Water

4. Air evacuation
He: 20 % / N_2: 80 % filling

5. Installation of the rubber plug

6. Crimping, removing flip cap and labeling

Each vial has been manually prepared in a six step process that can be seen above.

Blue Dye Test Conditions & Setup

Method Parameters	USP 31 <381> PH.Eur. 3.2.9	ISO 8362-5 Annex C	Modified ISO	Pfeiffer Vacuum
Dye solution	1% aq. Methylene Blue			
Vacuum	– 27 kPa	– 25 kPa	– 37 kPa	– 37 kPa
Immersion time at vacuum	10 min	30 min	30 min	60 min
Time P_{Atm}	10 min	30 min	30 min	30 min
Detection	Visual inspection			

Blue Dye Ingress Standard Test Conditions

Dye solution:

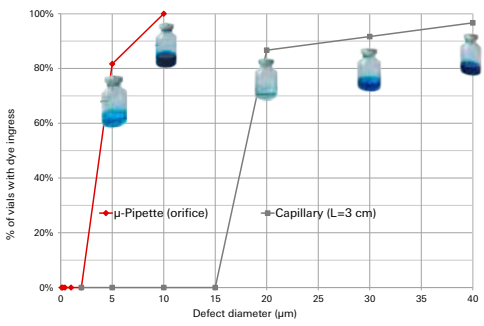
- 1% FD&C Red No. 40
- 0.25% sodium dodecyl sulfate (SDS)
- De-Ionized water

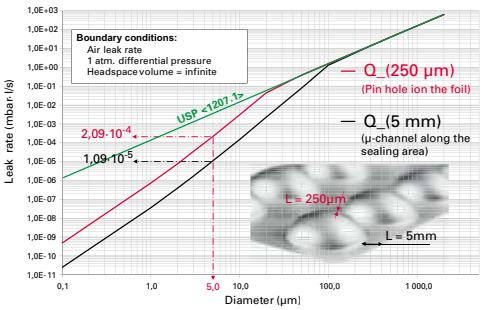
Blue Dye recipe has been set up to get a detection limit measured by Burrel & all using 3 mL water filled vials.
Due to the bigger headspace and consequently bigger dilution volume of the used 6 mL vials, the immersion time at vaccum has been set to 60 min.

Impact of the Defect Geometry

- The detection limit will depend on the defect geometry
- Considering the diameter of the defect all methods (blue dye and others) will be more sensitive for sharp edge orifice
- It is important to consider the right leak artifact as close as possible to your real production defect

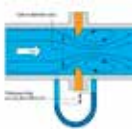
Blue Dye recipe:
-37 kPa / 60 min – Patm / 30 min



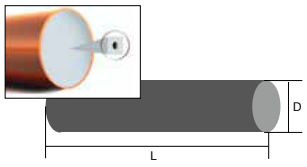


Gasflow will be measured by Helium O.E.S. and Mass Extraction

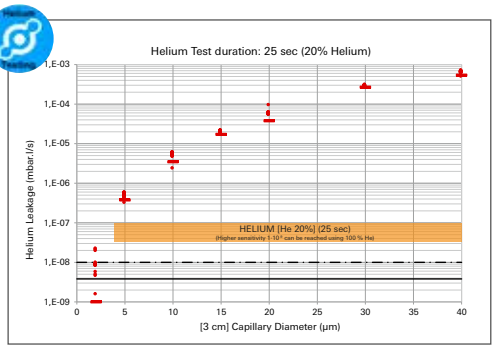
Sharp Edge orifice (d_0)
USP <1207> reference

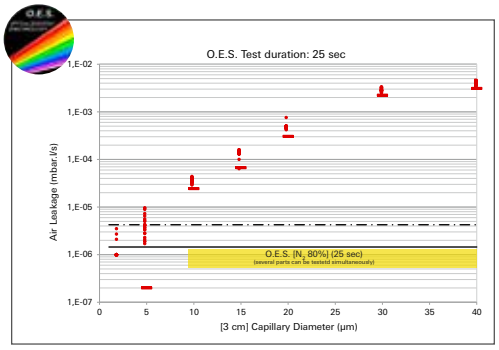


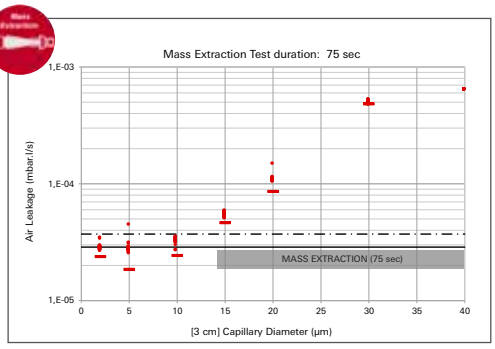
Capillary (D, L)



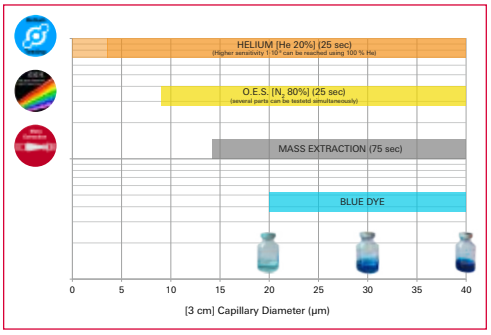
Results Capillaries



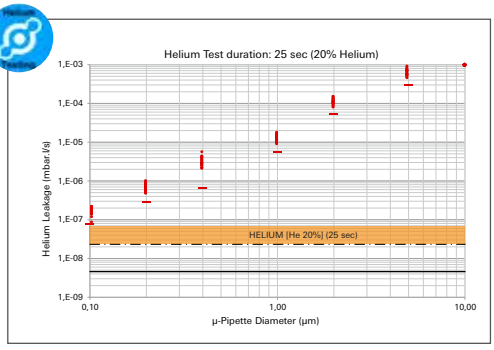


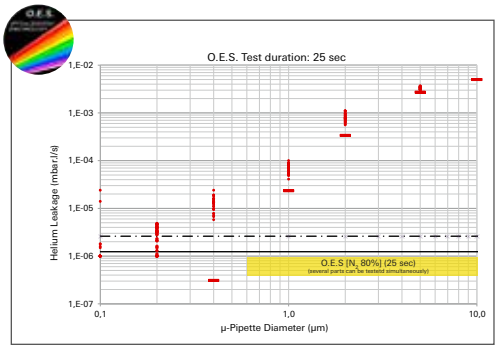


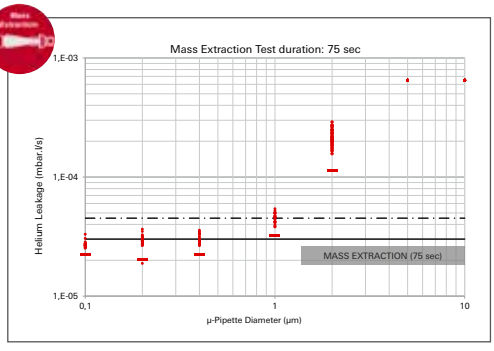
Summary – Capillaries



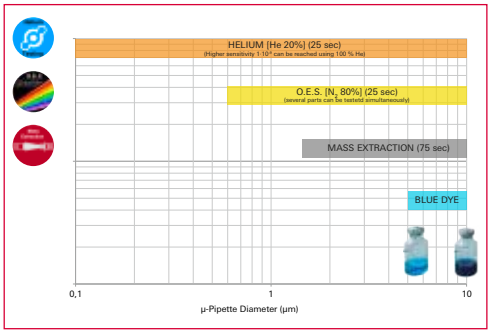
Results Capillaries







Summary – µ-pipettes (orifice)



Summary and Conclusion

	Deterministic	Non-destructive	Objective	Traceable	Sensitive	Easy to set-up	High speed test	Automated
Ideal CCIT Method								
Blue dye	⌄⌄	⌄	⌄	⌄	⌄	⌃⌃	—	⌄⌄
Helium Testing	⌃	⌄⌄	⌃	⌃	⌃⌃	⌄⌄	⌃⌃	⌄⌄
Mass Extraction	⌃	⌃	⌃	⌃	—	⌃⌃	—	⌃
O.E.S.	⌃⌃	⌃	⌃	⌃	⌃	⌃⌃	⌃⌃	⌃

Impact of the Defect Geometry

- Moving from a dye ingress test to a deterministic method could be done by considering the application:
  - Validation & Qualification
  - IPC in Production
  - Commercial shelf-life stability assessment
- and the desired test result:
  - Go/No-Go relative measurement (i.e. Mass Extraction)
  - Calibrated quantitative measurement (i.e. O.E.S. or He)
- Assessing the sensitivity of your dye ingress test is the prerequisite to upgrade to a deterministic method
- A feasibility study on the specific samples is necessary to find a applicable deterministic CCIT method

Sources:
Burrell & All – PDA journal, Vol 54, 6, November/December 2000
Kirsch & All, PDA journal, Vol 51, 5, September/October 1997

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