LECTURE 8

Standardisation of ophthalmic, otic and nasal medicines and of medicines under pressure



Mucosal and inhaled dosage forms where sterility, physiological compatibility, particle size and the delivery device decide quality

Standardisation of Medicines and Raw Materials
Educational programme 6B10102 – Pharmacy · 4th year · Department of Fundamental Medicine, Al-Farabi Kazakh National University

OUTLINE

Lecture plan

1. Eye preparations (Ph. Eur. 1163)
2. Ear and nasal preparations (0652, 0676)
3. Related impurities: calculation methods
4. Pressurised preparations (0523): components and propellants
5. Container integrity and dose uniformity
6. Aerodynamic particle size of inhaled products

Requirements for eye preparations

Parameter	Requirement and rationale
Sterility	Mandatory for all eye preparations (2.6.1)
Preservative	Multidose containers need an effective preservative (5.1.3: bacteria ≥ 2 log at 6 h, ≥ 3 log at 24 h)
Container	Multidose eye drops normally ≤ 10 mL; in-use period after opening normally ≤ 4 weeks
pH and osmolality	Close to tears (pH ≈ 7.4; ≈ 0.9% NaCl equivalent) as far as stability allows
Particle size (suspensions)	Per 10 µg of solid: ≤ 20 particles > 25 µm, ≤ 2 particles > 50 µm, none > 90 µm
Clarity	Solutions practically clear and free from particles
Single-dose units	Preservative-free; uniformity and extractable volume

Ear and nasal preparations

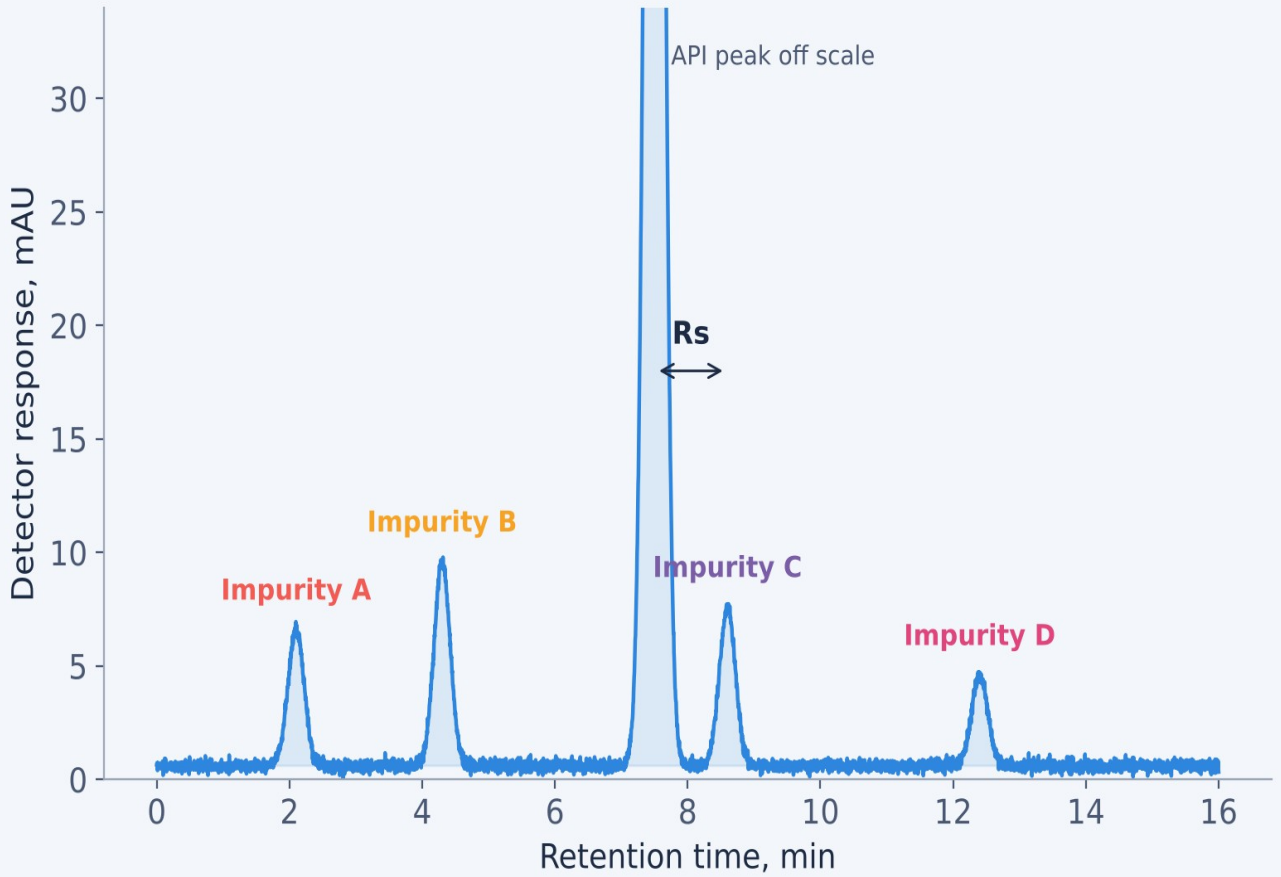
Ear preparations

- Drops, sprays, semi-solids, washes, tampons
- **Sterile and preservative-free** if for an injured ear or perforated eardrum
- Otherwise microbial quality of non-sterile products
- Often glycerol or propylene glycol vehicles
- Suspensions: particle size, redispersibility

Nasal preparations

- Drops, sprays (metered and non-metered), powders, washes
- Need not be sterile; microbial limits apply
- pH ≈ 5.5–6.5 and near isotonic to protect cilia
- **Metered sprays:** uniformity of delivered dose, number of deliveries
- **Droplet size:** fraction < 10 µm limited (lung deposition)

Three ways to calculate impurities by HPLC



Formulas

- **External standard (CRS):** X = (Ai/Ast) × (Cst × P / Ct) × 100
- **Diluted test solution:** X = (Ai × F / Aref) × D
- **Normalisation:** X = Ai × F / ΣA × 100
- **F** = correction factor; D = dilution of reference, %
- **Disregard limit** applied after correction; placebo peaks excluded

The device is part of the dosage form

Canister

Aluminium, often coated; withstands internal pressure

Metering valve

Meters 25–100 µL; elastomer seals: leaks and leachables

Actuator

Orifice controls plume and droplet size; product-specific

Formulation

Drug + propellant ± ethanol, surfactant; solution or suspension

pMDI

Pressurised metered-dose inhaler: the most demanding form

Sprays

Cutaneous and nasal sprays: delivery rate, spray pattern

Foams

Cutaneous, rectal, vaginal: relative density, expansion

Safety

“Pressurised container. Do not pierce or burn. Protect from > 50 °C”

From CFCs to low-GWP propellants

Propellant	Status	Boiling point	GWP (100 yr)
CFC-12	Phased out (Montreal Protocol)	−30 °C	10 900
HFA-134a (norflurane)	Current standard	−26 °C	1 430
HFA-227ea (apaflurane)	Current standard	−16 °C	3 220
HFA-152a	Next generation	−24 °C	124
HFO-1234ze(E)	Next generation	−19 °C	< 1

GWP values: IPCC AR4 (HFO-1234ze: AR5). Each change of propellant means a new formulation and full re-testing

Weighing tests catch many failures

Leak rate

mg per year
$(W_1 - W_2) \times 365 \times 24 / T$;
storage ≥ 3 days at 25 °C

Shot weight

Mass per actuation
checks valve metering

Net content

Full minus empty can
fill per container

Actuations

≥ labelled number
fire to exhaustion and count

- **Example:** $W_1 - W_2$ = 5.2 mg in 72 h → 5.2 × 365 × 24 / 72 = 632.7 mg/year; training limit 500 mg/year → does not comply
- **Priming:** discard the first actuations as stated on the label before any test

The same dose from the first to the last actuation

Sampling

- 10 doses per inhaler
- 3 at the beginning, 4 in the middle, 3 at the end of the labelled number
- Dose collection apparatus, 28.3 L/min
- Each dose assayed (HPLC)

Acceptance

- **Stage 1:** ≥ 9 of 10 doses within 75–125% of the average, all within 65–135%
- **Stage 2** (if 2–3 outside 75–125%): 2 more inhalers; ≤ 3 of 30 outside 75–125%, none outside 65–135%
- Check the current edition for the reference value

Example: doses 88–127 µg, average 101.0 µg; dose 127 µg = 125.7% → 9 of 10 within 75–125% → complies at stage 1

How much of the dose reaches the lungs?

> 5 µm

Deposited in mouth and throat, then swallowed

1–5 µm

Reach the airways and lungs: the fine particle dose

< 1 µm

Partly exhaled

Apparatus

Twin impinger (A), multi-stage liquid impinger (C), Andersen impactor (D), Next Generation Impactor (E)

Results

FPD (mass < 5 µm), FPF (% of dose), MMAD and GSD

Use

Release, stability, comparability of generic inhalers

Key take-aways

1. **Eye preparations** are always sterile; multidose ≤ 10 mL, in-use ≤ 4 weeks; suspension particle limits 25/50/90 µm
2. **Ear preparations** for an injured ear must be sterile and preservative-free; nasal ones need not be sterile
3. **Impurities** are calculated by external standard, diluted test solution or normalisation
4. **Pressurised preparations:** container, valve and actuator are part of the dosage form
5. **Inhalers:** leak rate, delivered dose uniformity and aerodynamic particle size decide performance

SELF-CHECK

Control questions and literature

Questions

1. Why must all eye preparations be sterile?
2. State the particle size limits for eye suspensions.
3. When must ear preparations be sterile and preservative-free?
4. Write the formula for impurities by the diluted test solution method.
5. Name the components of a pMDI and their role in quality.
6. Calculate the leak rate: loss 3.6 mg over 96 h.
7. Describe stage 1 of the delivered dose uniformity test.
8. Why is aerodynamic particle size more important than total dose?

Sources

- Ph. Eur. 1163, 0652, 0676, 0523, 0671
- Ph. Eur. 2.9.18 Aerodynamic assessment of fine particles
- Ph. Eur. 5.1.3 Efficacy of antimicrobial preservation
- ICH Q3B(R2)
- State Pharmacopoeia RK