LECTURE 5

Standardisation and analysis of tablets and capsules

Pharmacopoeial tests for solid oral dosage forms: uniformity, disintegration, dissolution, mechanical strength and assay



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. Types of tablets and capsules (Ph. Eur. 0478, 0016)
2. Uniformity of mass and content uniformity
3. Disintegration and dissolution
4. Mechanical properties: friability and resistance to crushing
5. Modified-release and gastro-resistant forms
6. Assay, impurities and a full specification

Many kinds of solid oral dosage forms

Uncoated tablets

Single- or multilayer; release not deliberately modified

Coated tablets

Sugar or film coating: taste masking, protection, identification

Gastro-resistant

Resist gastric fluid, release in the intestine

Modified-release

Prolonged, delayed or pulsatile release

Effervescent, soluble, dispersible

Dissolved or dispersed in water before use

Orodispersible, oral lyophilisates

Disperse in the mouth before swallowing

Hard capsules

Two-piece shells of gelatin or HPMC filled with powder, granules, pellets

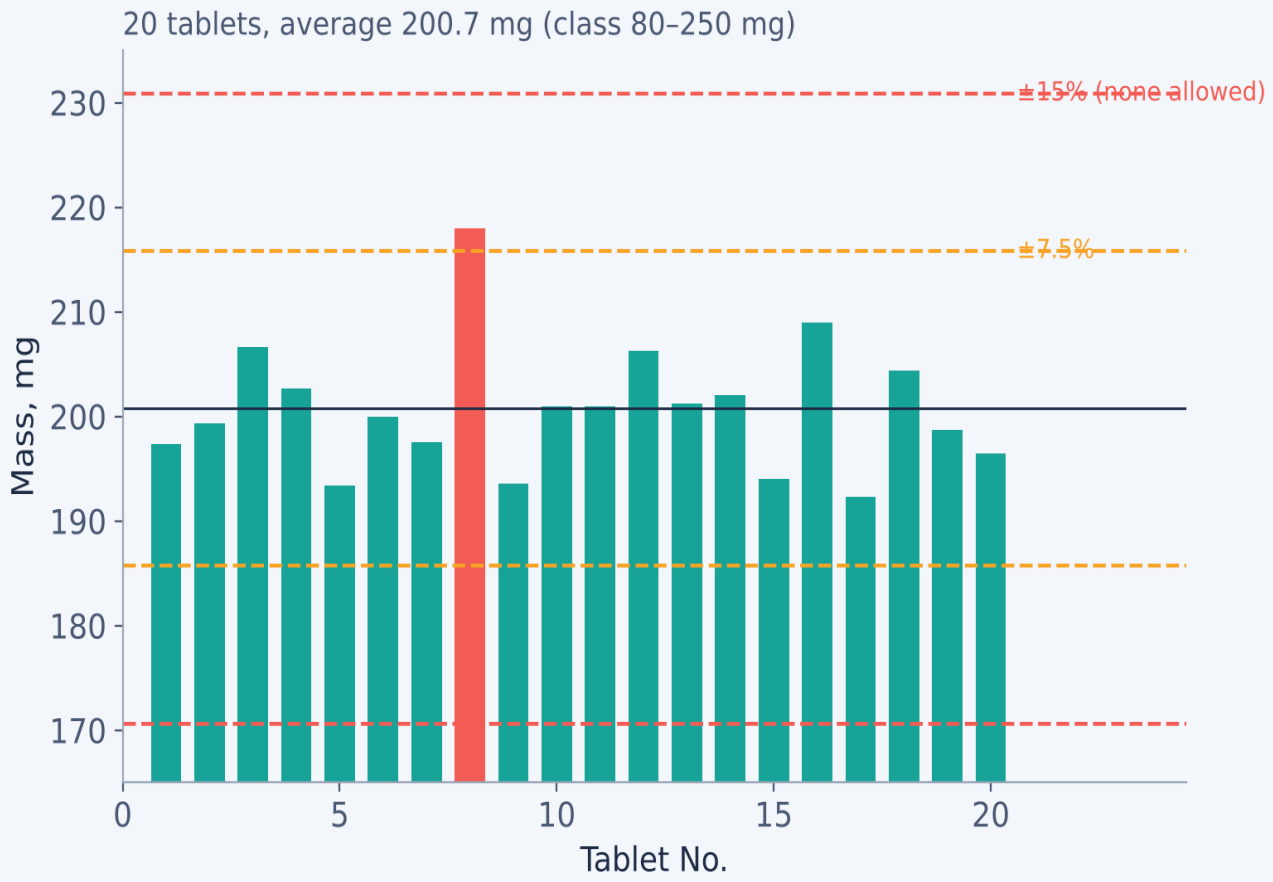
Soft capsules

One-piece shell with liquid or semi-solid content

Tests for tablets and capsules

Group	Test	Ph. Eur. chapter
Description	Appearance, shape, colour, markings, coating	—
Identity	IR, HPLC retention time, UV spectrum, TLC	2.2
Uniformity	Uniformity of dosage units (mass variation or content uniformity)	2.9.40 (2.9.5, 2.9.6)
Release	Disintegration; dissolution	2.9.1; 2.9.3
Mechanical	Friability (uncoated); resistance to crushing	2.9.7; 2.9.8
Purity	Related substances, water content, microbial quality	2.2.29, 2.5.12, 5.1.4
Assay	Content of active substance, usually 95.0–105.0% of label claim	2.2.29 / 2.2.25

Twenty tablets, one average, two limits



Permitted deviation

- **Tablets ≤ 80 mg:** ± 10%
- **Tablets 80–250 mg:** ± 7.5%
- **Tablets > 250 mg:** ± 5%
- **Capsules < 300 mg:** ± 10%; ≥ 300 mg: ± 7.5%
- **Requirement:** not more than 2 of 20 units outside the deviation, none outside twice the deviation
- **Here:** 1 tablet outside ± 7.5% → complies

Acceptance value: one number for accuracy and spread

$$AV = |M - \bar{X}| + k \cdot s$$

Acceptance value
$\bar{X}$ mean content, s standard deviation, M reference value (98.5–101.5% rule)

10 units

Stage 1: k = 2.4
complies if AV ≤ L1 = 15.0

+20 units

Stage 2: k = 2.0
AV of 30 ≤ 15.0; no unit outside 0.75 M–1.25 M (L2 = 25.0)

- **Applies when** dose < 25 mg or < 25% of the unit mass (otherwise mass variation may be used)
- **Example:** $\bar{X}$ = 99.0%, s = 2.5% → M = 99.0, AV = 0 + 2.4 × 2.5 = 6.0 ≤ 15.0 → complies

Disintegration time limits

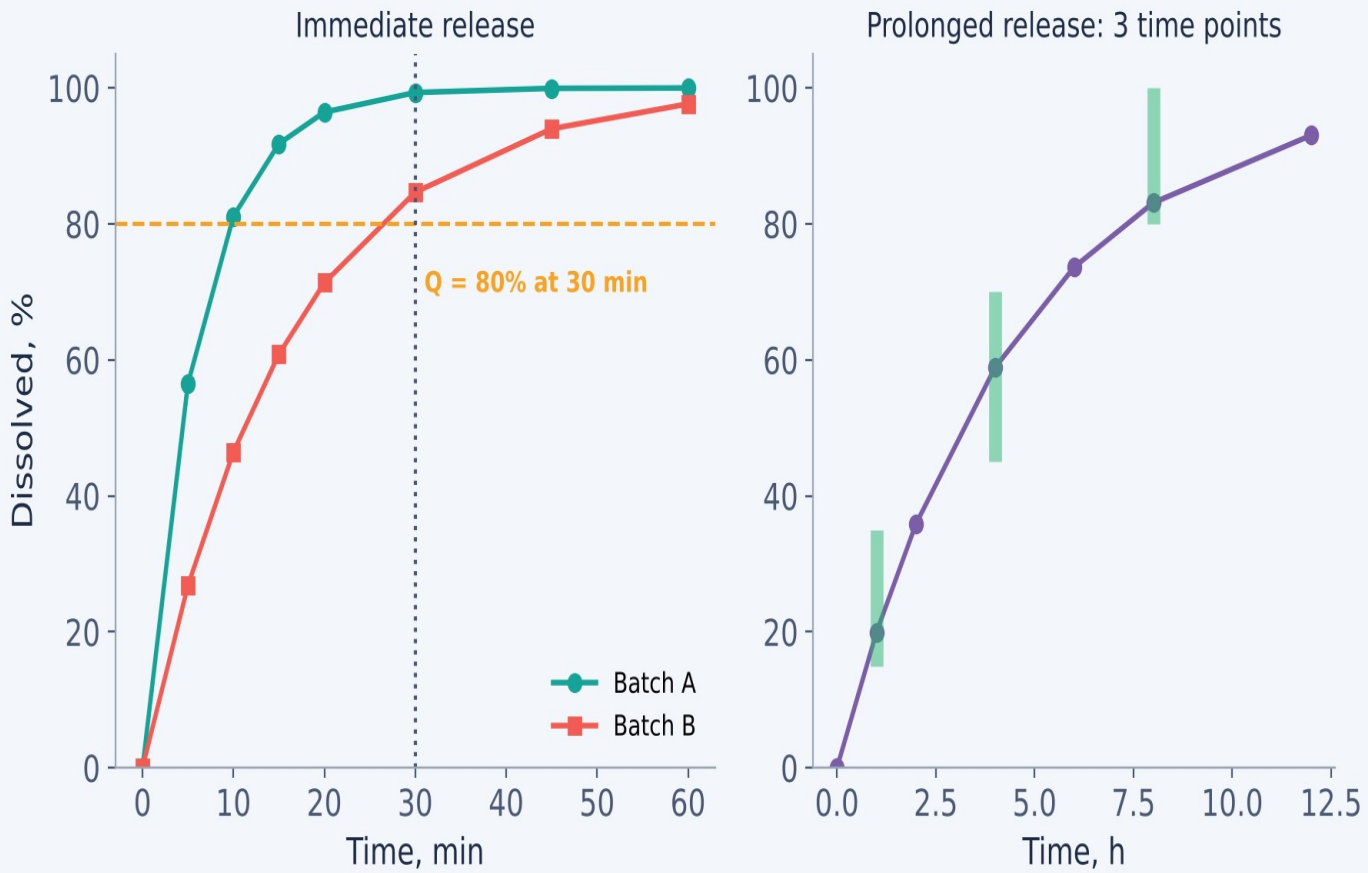
Dosage form	Medium	Time limit
Uncoated tablets	Water, 37 °C	≤ 15 min
Film-coated tablets	Water, 37 °C	≤ 30 min
Sugar-coated tablets	Water (0.1 M HCl if needed)	≤ 60 min
Hard and soft capsules	Water (or 0.1 M HCl)	≤ 30 min
Effervescent tablets	200 mL water, 15–25 °C	≤ 5 min
Orodispersible tablets	Water	≤ 3 min
Gastro-resistant tablets	0.1 M HCl 2 h, then phosphate buffer pH 6.8	No disintegration in acid; ≤ 60 min in buffer



Apparatus

- Basket-rack assembly with 6 tubes
- 29–32 cycles per minute
- Medium at 37 ± 2 °C
- Disintegration = no firm core remains

Dissolution shows how the active substance is released



Acceptance (immediate release)

- **S1, 6 units:** each ≥ Q + 5%
- **S2, +6 units:** mean of 12 ≥ Q, none < Q − 15%
- **S3, +12 units:** mean of 24 ≥ Q, ≤ 2 units < Q − 15%, none < Q − 25%
- **Conditions:** paddle 50 rpm or basket 100 rpm, 900 mL, 37 ± 0.5 °C
- **Q** usually 75–80% in 30–45 min

Dissolution links quality and bioavailability

Profile comparison

- **Similarity factor f2:** 50–100 means similar profiles
- Used for changes of process, site, strength
- At least 12 units, ≥ 3 time points
- Not needed if > 85% dissolves in 15 min

Biopharmaceutics Classification System

- **Class I:** high solubility, high permeability
- **Class II:** low solubility, high permeability
- **Class III:** high solubility, low permeability
- **Class IV:** low solubility, low permeability
- **Biowaiver (ICH M9):** possible for classes I and III

PH. EUR. 2.9.7 AND 2.9.8

Tablets must survive packaging and transport

Friability (2.9.7)

- Drum, 25 rpm, 100 rotations
- Sample ≈ 6.5 g (unit ≤ 650 mg) or 10 tablets
- Mass loss ≤ 1.0%, no cracked tablets

Resistance to crushing (2.9.8)

- Force to break the tablet, in newtons
- 10 tablets; mean, min, max reported
- Limits set by the manufacturer

Other parameters

- Thickness and diameter
- Subdivision of scored tablets (monograph 0478)
- Coating integrity and appearance

Balance: tablets must be hard enough to resist handling but must still disintegrate and dissolve

From 20 tablets to a result per tablet

1 Weigh 20 tablets

- Average mass m̄
- e.g. 0.2510 g

2 Powder

Grind to a homogeneous powder

3 Sample

- Weigh a portion of powder
- e.g. 0.1255 g ≈ ½ tablet

4 Extract

- Dissolve, filter, dilute
- Measure vs reference

5 Calculate

Content per tablet = found × m̄ / sample mass



Example: found 49.6 mg in 0.1255 g powder; content per tablet = 49.6 × 0.2510 / 0.1255 = 99.2 mg → 99.2% of 100 mg label claim

Key take-aways

1. **Uniformity of mass:** 20 units, ± 10 / 7.5 / 5% for tablets by mass class
2. **Content uniformity:** $AV = |M - \bar{X}| + k \cdot s \leq 15.0$ ($k = 2.4$ for 10 units)
3. **Disintegration:** uncoated 15 min, film-coated and capsules 30 min, gastro-resistant 2 h acid + buffer
4. **Dissolution:** staged S1–S3 against Q; $f2 \geq 50$ for similar profiles
5. **Friability ≤ 1.0%;** assay calculated per average tablet mass

SELF-CHECK

Control questions and literature

Questions

1. Give the permitted deviations for uniformity of mass of tablets and capsules.
2. When is content uniformity required instead of mass variation?
3. Calculate AV for $\bar{X}$ = 97.0%, s = 3.0% (n = 10). Does the batch comply?
4. State disintegration limits for uncoated, film-coated and gastro-resistant tablets.
5. Describe stages S1–S3 of dissolution testing.
6. What does f2 = 62 mean?
7. How is friability tested and what is the limit?
8. Calculate the content per tablet: found 24.1 mg in 0.150 g powder, average mass 0.310 g.

Sources

- Ph. Eur. 0478 Tablets; 0016 Capsules
- Ph. Eur. 2.9.1, 2.9.3, 2.9.5, 2.9.7, 2.9.8, 2.9.40
- ICH M9 (BCS-based biowaivers)
- State Pharmacopoeia RK, Vol. 1