PRINCIPLES AND SYSTEMS OF DRUG DELIVERY · SEMINARS 13–14

Quality control, bioavailability and bioequivalence of modified-release forms

Educational program “Pharmacy” · 4th year · Al-Farabi Kazakh National University

Quality control of a modified-release product

Dissolution

At least 3 time points: early (no dumping), middle, end (complete release)

Assay, uniformity

HPLC content; uniformity of dosage units (Ph. Eur. 2.9.40)

Solid state

XRPD and DSC: polymorph, amorphous content

Coating, structure

Film thickness, SEM, micro-CT; integrity of osmotic orifice

Alcohol test

Dissolution in 5–40% ethanol for at-risk products

Stability

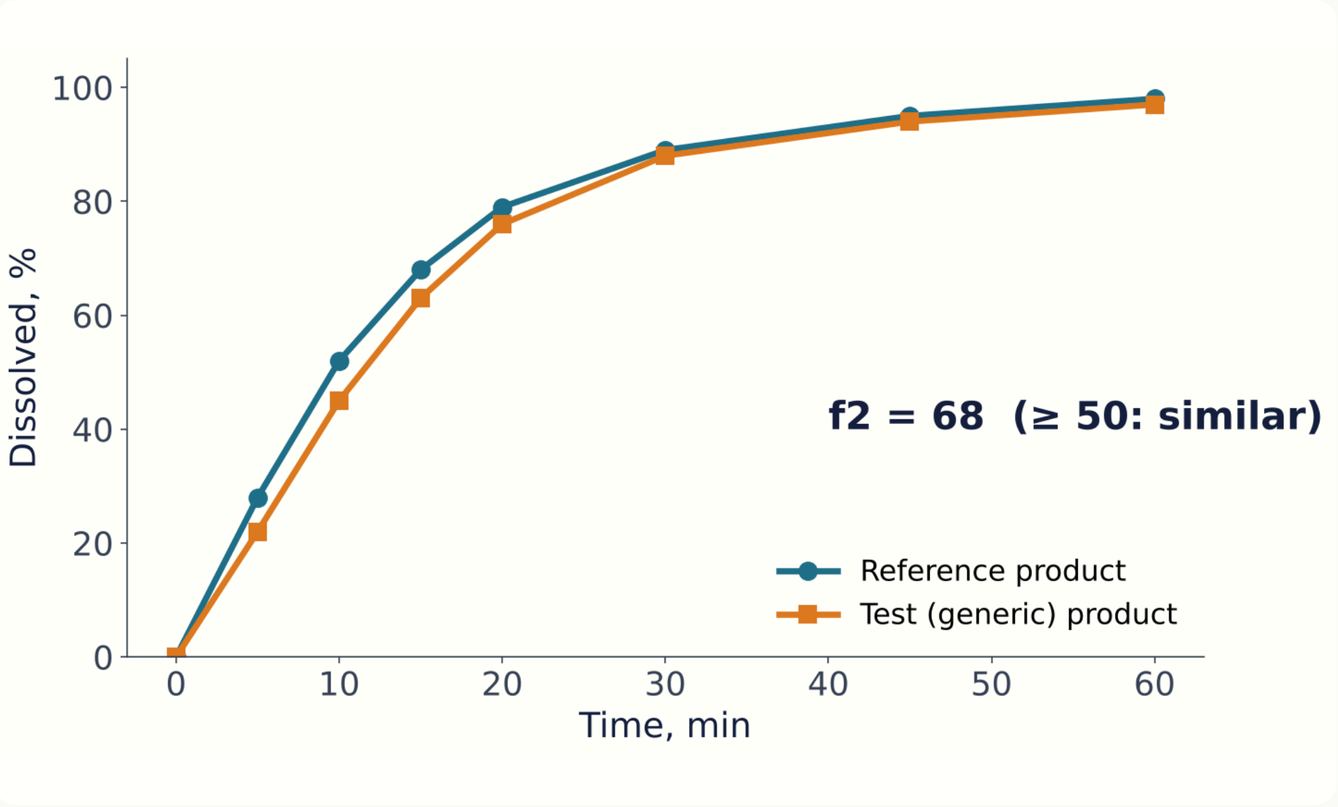
Release profile must not change over shelf life (ICH Q1A)

Dissolution apparatus (USP <711>, Ph. Eur. 2.9.3)

Apparatus	Principle	Typical use
1 – Basket	Rotating mesh basket, 50–100 rpm	Capsules, floating forms
2 – Paddle	Rotating paddle, 50–75 rpm	Most tablets, ER matrices
3 – Reciprocating cylinder	Moves through rows of media (pH change)	ER beads; simulates GI transit
4 – Flow-through cell	Fresh medium pumped past the sample	Poorly soluble drugs, implants, microspheres
5, 6, 7	Paddle over disk, cylinder, reciprocating holder	Transdermal patches

Conditions: 900 mL, 37 ± 0.5 °C; for enteric forms 2 h in 0.1 M HCl, then pH 6.8 buffer.

Comparing dissolution profiles: the f2 factor



f2 = 50·log{100 / √[1 + (1/n)Σ(Rt − Tt)²]}

f2 = 100: identical; **f2 ≥ 50**: similar (≤ 10% mean difference)

Rules: ≥ 3 points, ≤ 1 point after 85%, CV ≤ 20% early, ≤ 10% later

In vitro–in vivo correlation (IVIVC)

Level A

Point-to-point: % dissolved vs % absorbed (deconvolution). Strongest; can replace bioequivalence studies.

Level B

Mean dissolution time vs mean residence time. Statistical, not point-to-point.

Level C

One dissolution value vs one PK parameter (AUC or Cmax). Weakest.

A validated Level A IVIVC turns the dissolution test into a **surrogate** for clinical performance.

Biopharmaceutics Classification System

Class I: high S, high P
Metoprolol, paracetamol — biowaiver possible

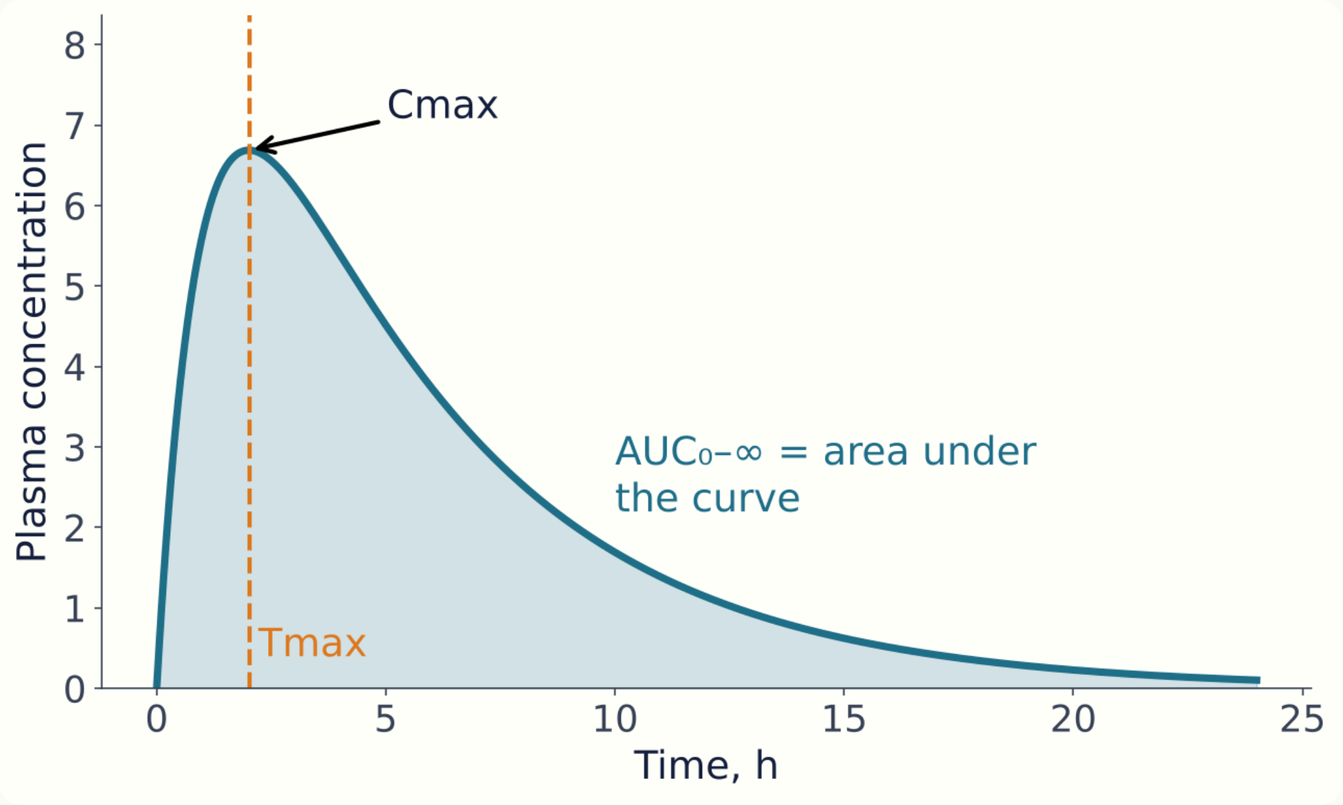
Class II: low S, high P
Ibuprofen, carbamazepine — dissolution limits

Class III: high S, low P
Atenolol, metformin — permeability limits

Class IV: low S, low P
Furosemide, hydrochlorothiazide — hardest

High solubility: highest dose dissolves in 250 mL over pH 1.2–6.8. High permeability: ≥ 85% absorbed.

Bioavailability: Cmax, Tmax and AUC

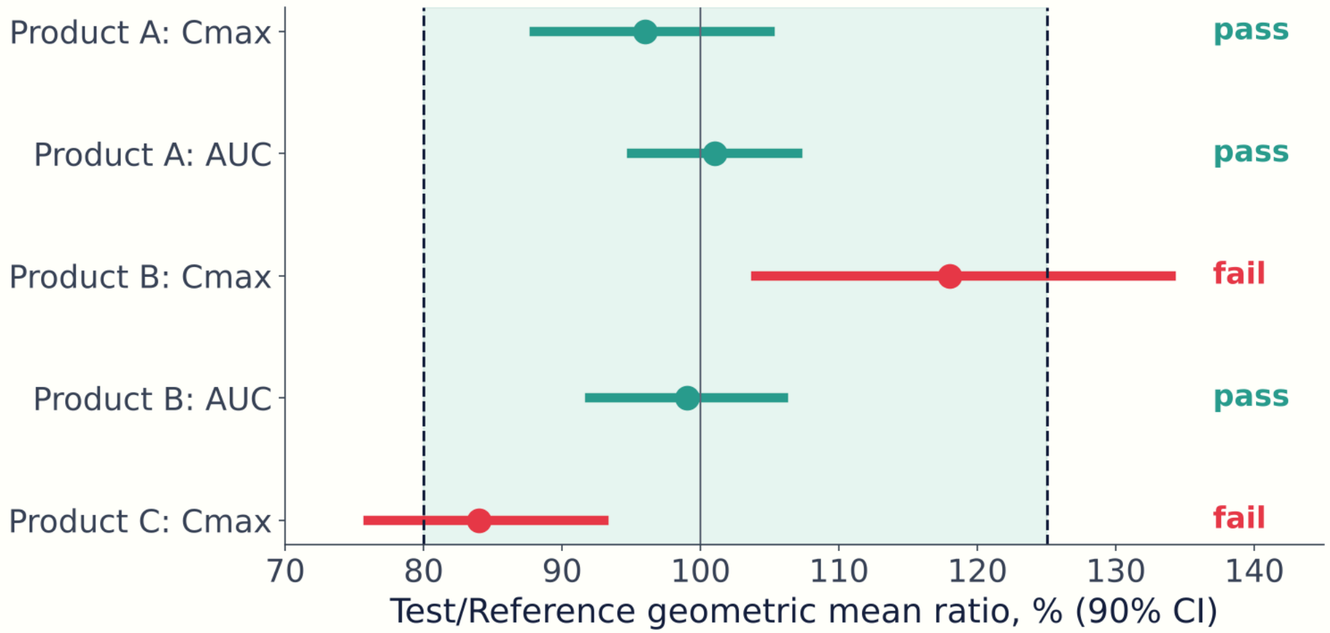


Absolute F = (AUC oral · Dose iv) / (AUC iv·Dose oral)

Relative F: test vs reference product of the same route

For ER forms also: fluctuation index, Cmin at steady state, partial AUC

Bioequivalence: the 80–125% rule



The **whole 90% CI** of test/reference geometric mean ratio must lie within 80.00–125.00% for AUC and Cmax.

ER products (EMA): single dose fasting + fed; multiple dose if accumulation.

Membrane transporters shape bioavailability

Transporter	Direction	Substrates	DDS relevance
P-gp (ABCB1)	Efflux	Digoxin, cyclosporine	Lowers absorption; excipients like TPGS inhibit it
BCRP (ABCG2)	Efflux	Rosuvastatin, topotecan	Limits oral and brain uptake
PEPT1 (SLC15A1)	Uptake	Valacyclovir, β-lactams	Prodrug targeting
OATP1B1	Uptake (liver)	Statins	Interactions, liver targeting

P-gp sits in the gut wall and the blood–brain barrier; it pumps drugs back out. ER forms releasing slowly in the lower gut meet more P-gp and CYP3A4 in some regions.

Questions for discussion

1. Why must an ER specification include an early time point?
2. Which apparatus suits microspheres that release over a month?
3. f2 = 42. Are the profiles similar? What next?
4. Why does a Level A IVIVC have regulatory value?
5. Point estimate 105%, 90% CI 96–128%. Bioequivalent?
6. How can P-gp explain low bioavailability of a soluble drug?

References

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