PRINCIPLES AND SYSTEMS OF DRUG DELIVERY · SEMINARS 11–12

Controlled-release dosage forms: from principle to preclinical testing

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

After these seminars you will be able to

1. Classify oral controlled-release forms: matrix, reservoir, osmotic, multiparticulate
2. Explain how an osmotic push–pull tablet gives zero-order release
3. Describe gastro-retentive and colon-targeted systems
4. Explain dose dumping and the alcohol interaction test
5. Outline QbD (QTPP, CQA, CPP) and the stages of preclinical evaluation

Oral controlled-release systems

Hydrophilic matrix

HPMC swells into a gel; diffusion + erosion. Most common, cheap.

Inert matrix

Ethylcellulose, wax: drug leaches through pores; √t release.

Reservoir

Pellets or tablet coated with a release-controlling film.

Osmotic

Semipermeable membrane + orifice; independent of pH and food.

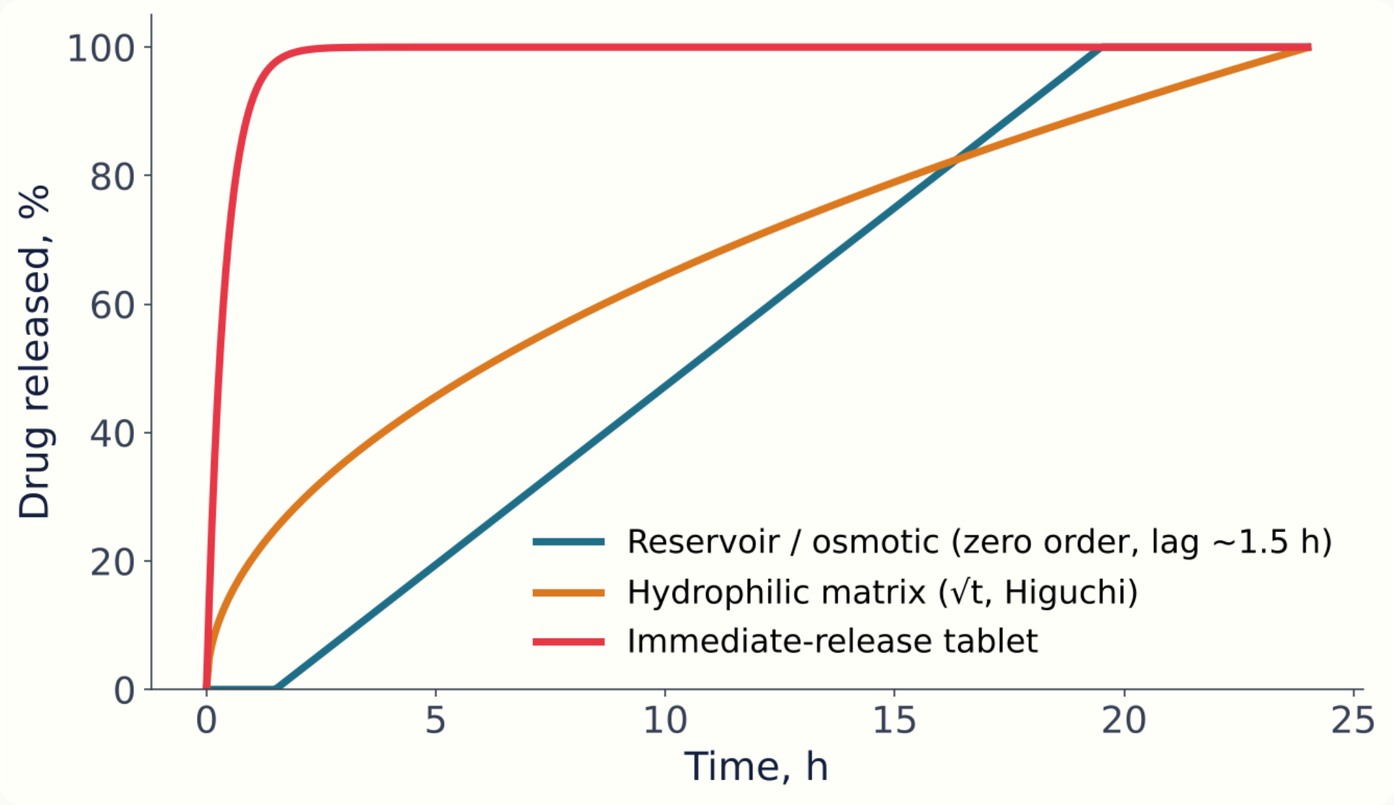
Gastro-retentive

Floating or swelling forms stay in the stomach for hours.

Ion exchange

Drug–resin complex; often for liquid ER suspensions.

Different systems, different release curves

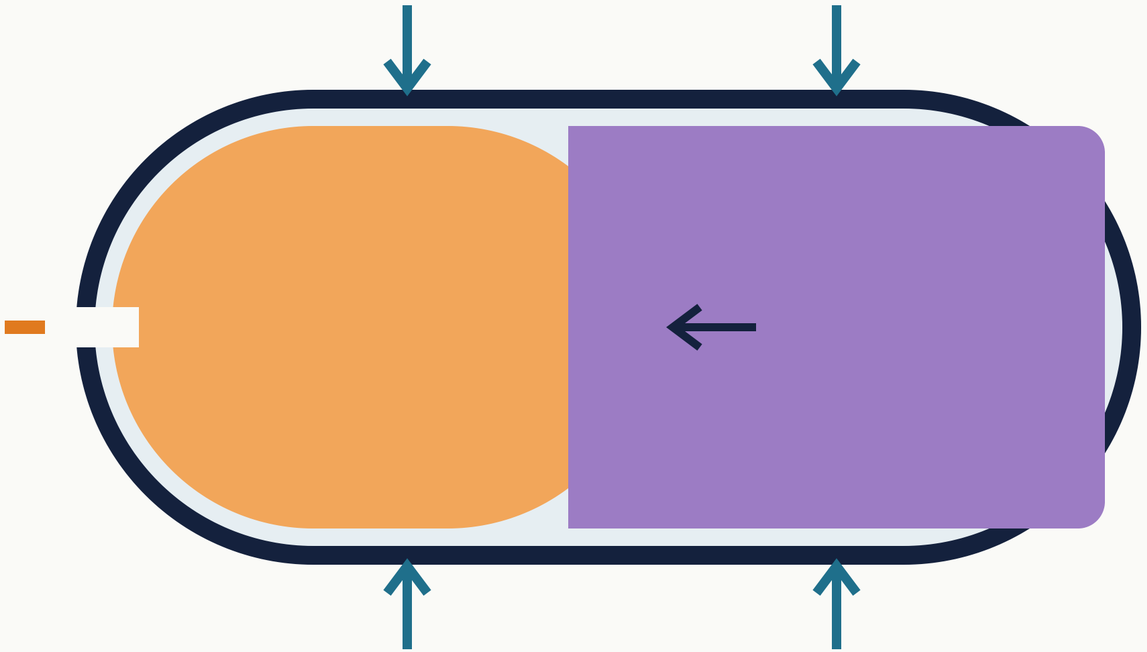


IR: whole dose in ~1 h

Matrix: fast at first, then slower (path grows)

Osmotic: lag while the core hydrates, then constant

Inside an osmotic push–pull tablet



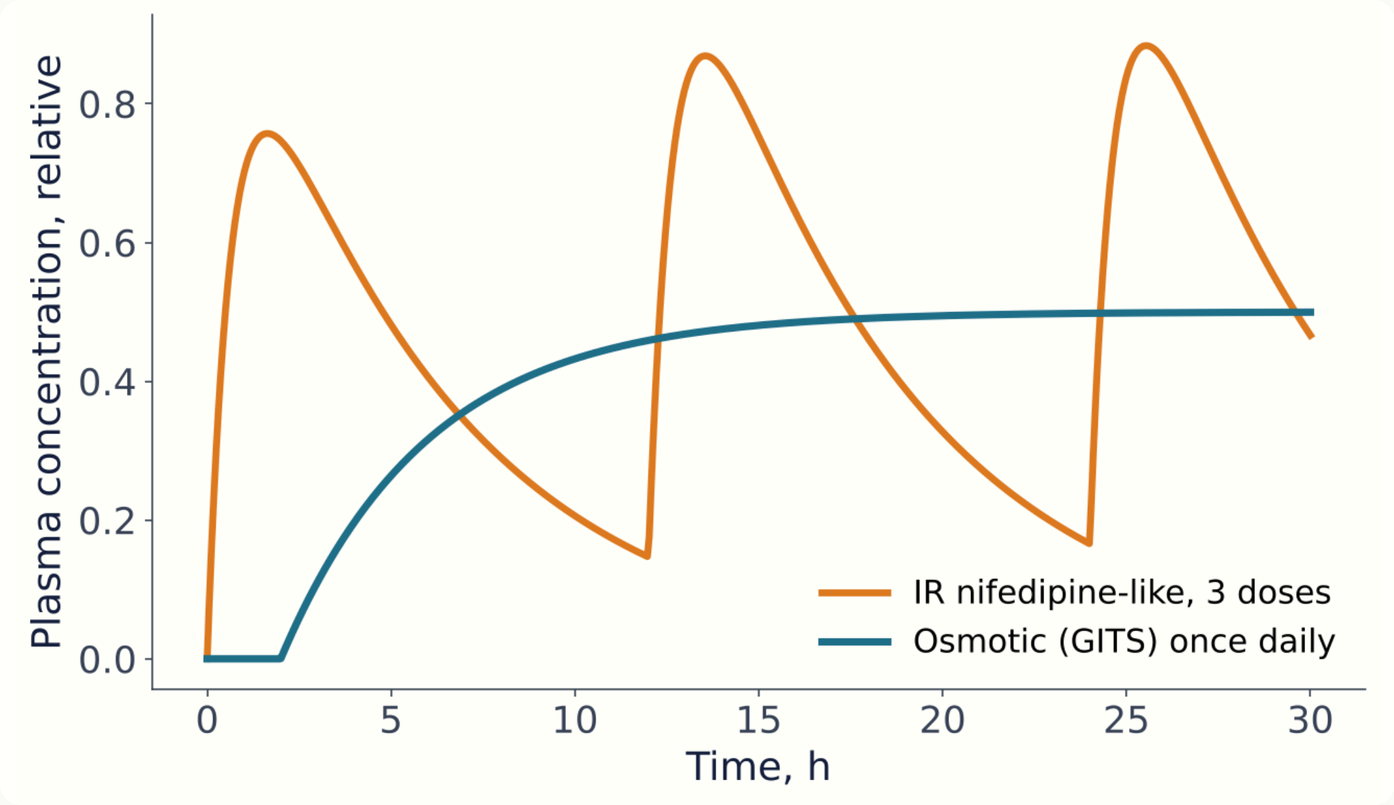
Water enters through the cellulose acetate membrane

Drug layer forms a suspension

Push layer (polyethylene oxide + NaCl) swells

Drug leaves through a **laser-drilled orifice** at a constant rate

Clinical effect: flat plasma levels once daily



IR nifedipine: rapid peaks → reflex tachycardia, flushing

GITS: smooth 24-hour level → better tolerated, once daily

A delivery system changed the clinical safety profile of the same molecule.

Single-unit versus multiparticulate forms

Feature	Single unit (tablet)	Multiparticulate (pellets)
Gastric emptying	All-or-none, variable	Gradual, reproducible
Dose dumping risk	Higher if coat fails	Lower: failure of one pellet is minor
Combined profiles	Difficult	Easy: mix IR and ER pellets
Swallowing	Whole tablet	Capsule can be opened onto food
Manufacture	Simple	Extrusion–spheronisation, coating

Example: omeprazole capsules contain enteric-coated pellets (MUPS tablets disintegrate into pellets).

Releasing in the right part of the GI tract

Stomach: gastro-retentive

- Floating (low density, CO_2-generating)
- Swelling above pylorus size (> 12–15 mm)
- Mucoadhesive
- Drugs with an upper-GI absorption window: metformin, gabapentin

Colon: targeted

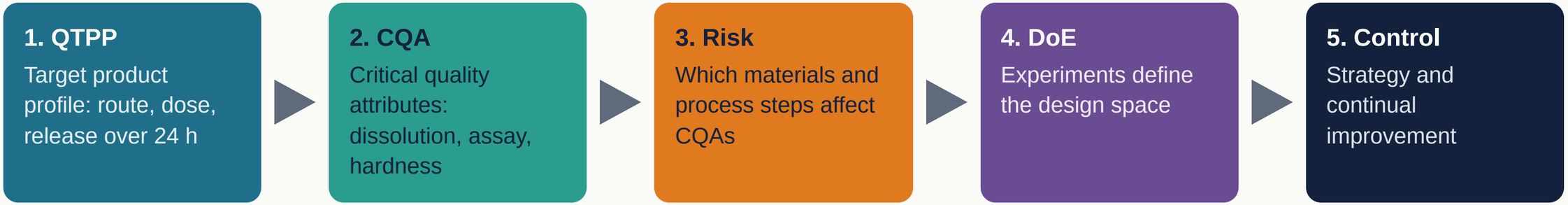
- pH-dependent coat: Eudragit S dissolves at pH ≥ 7
- Bacterial enzymes degrade polysaccharides
- Time-dependent (lag) coatings
- Mesalazine and budesonide for ulcerative colitis

DOSE DUMPING: WHEN THE CONTROL FAILS

In 2005 FDA asked for the withdrawal of Palladone, an extended-release hydromorphone capsule, because alcohol made it release the dose much faster

Since then regulators expect in vitro dissolution tests in 5–40% ethanol for extended-release opioids and other risky products.

Designing a new form with Quality by Design



Example for an HPMC matrix: CPPs are HPMC viscosity grade and content, compression force; the CQA is the release at 2, 8 and 20 h.

Preclinical evaluation of a new DDS

In vitro

- Release and dissolution
- Stability (ICH)
- Cell uptake, cytotoxicity
- Caco-2 permeability

Ex vivo

- Franz cells with skin
- Excised mucosa, cornea
- Everted gut sac
- Blood compatibility

In vivo (animals)

- Pharmacokinetics, biodistribution
- Efficacy in disease models
- Local tolerance
- Toxicity under GLP

The 3Rs principle — **replace, reduce, refine** — guides animal use; EU Directive 2010/63/EU makes it law.

Choosing the model for the route

Route	In vitro / ex vivo	Animal model
Oral	USP apparatus 1–4, Caco-2 cells	Rat, dog (GI similar to human)
Transdermal	Franz cell, human or pig skin	Pig, hairless rat
Ocular	Excised pig or bovine cornea	Rabbit
Pulmonary	Cascade impactor, Calu-3 cells	Rat, mouse; dog for devices
Parenteral depot	Release in buffer at 37 °C, accelerated tests	Rat, rabbit (injection site)

Questions for discussion

1. Why does food have little effect on release from an osmotic tablet?
2. Why do patients sometimes find the shell of a tablet in their stool?
3. Give two advantages of pellets over a single matrix tablet.
4. Why is pH alone an unreliable trigger for colon delivery?
5. Name the QTPP, one CQA and one CPP for a once-daily matrix tablet.
6. Why is pig skin preferred to rat skin for transdermal studies?

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