BP306T · UNIT IV

# BP306T Pharmaceutical Dosage Forms I

## Unit IV — Modified-Release Solids

B.Pharm Semester III · Theory Notes

Modified-release tablets: sustained release, controlled release, formulation design, mechanisms, polymers and evaluation

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# Chapter 4: Modified-Release Tablets (Sustained-Release and Controlled-Release)

## 4.1 Learning Objectives

After studying this chapter, the student will be able to:

1. Define sustained-release and controlled-release tablets and differentiate them.
2. Explain the concept, need, advantages, and disadvantages of modified release.
3. Describe formulation design and drug-release mechanisms.
4. List polymers used for sustained and controlled release.
5. Describe evaluation tests for modified-release dosage forms.

## 4.2 Definitions

- **Modified-release dosage form:** A formulation designed to change the timing or rate of drug release compared to an immediate-release product.
- **Sustained-release (SR):** Releases drug slowly over an extended time so dosing frequency is reduced. The release rate is not necessarily constant.
- **Controlled-release (CR):** Delivers drug at a predetermined, predictable (often near-constant) rate for a specified period.
- **Delayed-release:** Releases drug after a delay (e.g., enteric-coated tablets that release in the intestine, not the stomach). A type of modified release.
- **Immediate-release (IR):** Conventional tablet that releases drug quickly after swallowing.

## 4.3 Terminology (Teach from Zero)

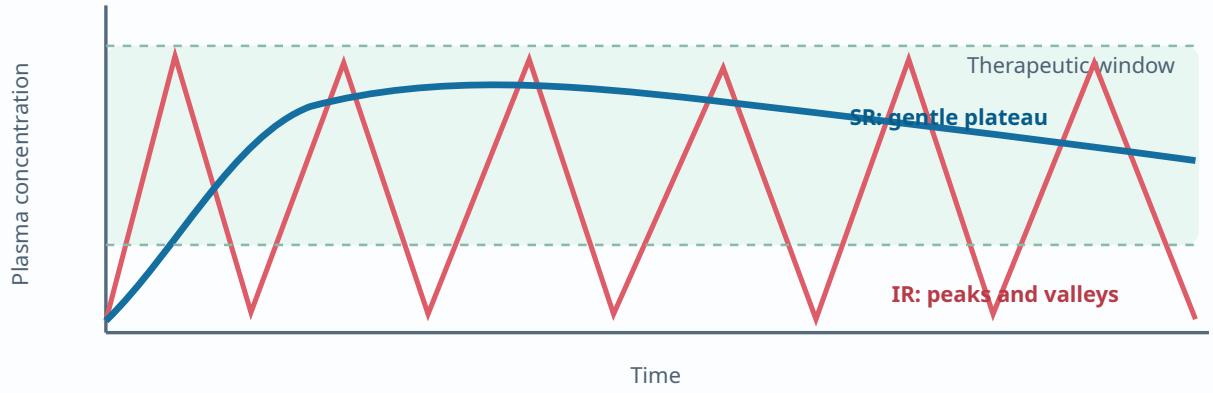
- **Plasma concentration:** Amount of drug in blood over time — the curve we try to flatten with SR/CR.
- **Therapeutic window:** The blood-level range where the drug works without toxic side effects.
- **Dosing frequency:** How often the patient takes the medicine (once daily vs three times daily).
- **Burst release:** An unwanted large initial release from an SR product — a defect.
- **Dose dumping:** Sudden release of the entire SR dose at once — dangerous.
- **Matrix tablet:** Drug uniformly mixed in a polymer network; release happens as fluid enters and drug diffuses out.
- **Reservoir system:** Drug core surrounded by a polymer membrane that controls release.
- **Osmotic pump:** Tablet that uses water entering through a membrane to push drug out of a laser-drilled hole at constant rate.
- **Polymer:** A long-chain molecule used to control drug release (e.g., HPMC, ethylcellulose).
- **In-vitro dissolution:** Lab test of drug release in beakers; predicts in-body behaviour.

## 4.4 Concept and Need

> **Technical concept:** Conventional tablets give peaks (possible toxicity) and troughs (loss of effect) in blood levels. Modified-release flattens this curve, keeping drug in the therapeutic window longer with fewer doses.

**Simple explanation:** A normal tablet is like pouring a bucket of water on a plant — flood, then drought. A sustained-release tablet is like a drip-irrigation pipe — steady water all day. Fewer doses, steadier effect.

**Diagram (describe):** Draw two blood-level-vs-time curves on one graph: the IR curve shows sharp peaks and valleys crossing above (toxic) and below (ineffective) the therapeutic window; the SR curve stays as a gentle plateau inside the window. Mark dosing points: IR needs 3 doses, SR needs 1.




Immediate-release peaks and valleys versus a sustained-release plateau within the therapeutic window.

**Need for modified release:**

- Drugs with short half-life needing frequent dosing.
- Improve patient compliance (once-daily beats thrice-daily).
- Reduce side effects from high peaks.
- Night-time or chronic conditions needing steady levels (hypertension, pain).

**Key takeaway:** **Modified release = steadier blood levels + fewer doses + better compliance.**

## 4.5 Advantages and Disadvantages

| Advantages | Disadvantages |
|---|---|
| Fewer doses → better patient compliance | Higher cost of formulation and manufacture |
| Steadier blood levels, fewer side effects | Dose dumping risk if product fails |
| Less fluctuation, better for chronic disease | Difficult to adjust dose quickly |
| Reduced total drug needed sometimes | Not suitable for all drugs (see below) |
| Convenient (once-daily) | Harder to manufacture; complex QC |

**Drugs NOT suitable for SR/CR:** Very short or very long half-life drugs, drugs absorbed only in a small gut region (narrow absorption window), drugs needing precise dose titration, and drugs unstable in the gut over long times.

**Key takeaway:** **SR/CR helps compliance and steadiness but costs more and cannot rescue unsuitable drugs.**

## 4.6 Formulation Design

> **Technical concept:** Design selects the release mechanism, polymer system, and dose to meet the target release profile.

> **Simple explanation:** Designing an SR tablet is like designing a slow-release fertiliser granule — choose the coating/thickness (polymer), the mechanism (diffusion, erosion), and test until release matches the plan.

**Design steps:**

1. **Define target profile:** How long should release last? (e.g., 12 hours, once-daily.)
2. **Check drug suitability:** Dose size, half-life, solubility, absorption window, stability.
3. **Choose mechanism:** Diffusion, dissolution/erosion, osmosis, or combination.
4. **Select polymer(s):** Hydrophilic matrix (HPMC), hydrophobic matrix (ethylcellulose), or membrane coat.
5. **Set polymer level and tablet design:** Polymer proportion controls release speed — more polymer = slower release.
6. **Test in-vitro dissolution** and adjust until the profile matches the target.
7. **Stability and scale-up** checks.

> **Key takeaway:** **Target profile → suitable drug → mechanism → polymer → test and adjust.**

## 4.7 Drug-Release Mechanisms

### (a) Diffusion-controlled

Drug diffuses through a polymer matrix or membrane. Release slows over time as the diffusion path lengthens (matrix) or stays steady (reservoir membrane).

> **Simple explanation:** Like tea diffusing from a tea bag — flavour comes out through the bag's pores.

### (b) Dissolution/erosion-controlled

Polymer slowly dissolves or erodes, releasing drug as the matrix wears away.

> **Simple explanation:** Like a bar of soap shrinking as you use it — the drug is released as the tablet "melts" away layer by layer.

### (c) Osmotic-controlled

Water enters through a semipermeable membrane, builds pressure, and pushes drug solution out through a tiny drilled orifice at a constant rate.

> **Simple explanation:** Like a water balloon with a pinhole squeezed by incoming water — drug squirts out steadily.

### (d) Combination

Many commercial products combine mechanisms (e.g., diffusion + erosion).

**Comparison table:**

| Mechanism | Release pattern | Example system |
|---|---|---|
| Diffusion (matrix) | Slowing over time | HPMC matrix tablet |
| Diffusion (reservoir) | Near-constant | Membrane-coated tablet |
| Erosion | Depends on erosion | Wax-matrix tablet |
| Osmotic | Near-constant (zero-order) | Osmotic pump tablet |

**Key takeaway:** **Diffusion = through pores; erosion = wearing away; osmotic = water pressure pushes drug out.**

## 4.8 Polymers Used

| Polymer | Type | Role |
|---|---|---|
| HPMC (hydroxypropyl methylcellulose) | Hydrophilic | Matrix former — swells to form gel layer |
| Ethylcellulose | Hydrophobic | Matrix/membrane — slows water entry |
| Eudragit (methacrylate copolymers) | pH-dependent/independent | Coating for delayed or sustained release |
| Carbopol (carbomer) | Hydrophilic | Gel matrix, bioadhesive |
| Sodium alginate | Natural hydrophilic | Matrix former |
| Carnauba wax / beeswax | Hydrophobic | Erosion matrix |
| Cellulose acetate | Semipermeable | Osmotic pump membrane |
| Polyethylene oxide | Hydrophilic | Swellable matrix |

**Simple explanation:** Hydrophilic polymers (HPMC) swell into a jelly layer that drug diffuses through; hydrophobic polymers (ethylcellulose, waxes) block water to slow everything down.

**Key takeaway:** **HPMC = swelling gel matrix (most common); ethylcellulose/waxes = water-blocking; Eudragit = smart pH-based coating.**

## 4.9 Evaluation of Modified-Release Dosage Forms

| Test | Purpose |
|---|---|
| Description | Appearance, coating integrity |
| Identification, assay | Correct drug and strength |
| Content uniformity | Uniform dose |
| In-vitro dissolution profile | Release matches specification at multiple time points (e.g., 1, 4, 8, 12 h) |
| Check for dose dumping | No sudden full release (especially with alcohol — "alcohol-induced dose dumping") |
| Mechanical strength | Tablet survives handling |
| Stability | Release profile unchanged over shelf life |
| In-vivo (bioavailability) studies | Confirms performance in the body |

**Dissolution testing specifics:** Unlike IR tablets (single time point), SR/CR products are tested at several time points with specified ranges (e.g., "not more than X% at 1 hour, between Y–Z% at 6 hours, not less than W% at 12 hours" — exact limits are product- and pharmacopoeia-specific).

**Key takeaway:** **Evaluation = multi-point dissolution proving the release curve, plus a check against dose dumping.**

## 4.10 Pharmacy Relevance

Once-daily SR tablets for blood pressure, diabetes, and pain are among the most dispensed medicines. Pharmacists must warn patients never to crush, chew, or split SR/CR tablets (destroys the release mechanism → dose dumping), unless the product is specifically designed to be splittable.

## 4.11 India Context

- Indian companies manufacture SR/CR products for domestic use and export; once-daily metformin SR and antihypertensive SR tablets are widely prescribed in India.
- Pharmacists counsel patients in simple language: "yeh dawai dheere-dheere kaam karti hai, ise todna/chew karna mana hai" (this medicine works slowly — do not break or chew it).

## 4.12 Key Points

1. SR = prolonged release, reduced frequency; CR = predetermined, often constant rate.
2. Need: steady blood levels, fewer doses, better compliance, fewer side effects.
3. Mechanisms: diffusion, erosion/dissolution, osmotic, or combined.
4. Key polymers: HPMC (hydrophilic matrix), ethylcellulose (hydrophobic), Eudragit (pH-based), cellulose acetate (osmotic membrane).
5. Not all drugs suit SR (narrow absorption window, very short/long half-life).
6. Never crush SR/CR tablets — dose-dumping danger.
7. Evaluation centres on multi-point dissolution profiles.

## 4.13 Common Confusions

- **SR vs CR:** SR = longer action, rate may vary; CR = rate controlled/predictable. (In casual use the terms overlap; exams expect the distinction.)
- **Delayed vs sustained release:** Delayed = release starts later (enteric); sustained = release stretched over time.
- **Matrix vs reservoir:** Matrix = drug mixed throughout polymer; reservoir = drug core + separate controlling membrane.

## 4.14 Common Mistakes

- Crushing or chewing SR tablets → destroys control → dose dumping.
- Assuming every drug can be made SR — ignoring absorption window and half-life.
- Testing SR products with a single dissolution time point — multi-point profiles are required.

## 4.15 Mnemonics

- **Mechanisms:** "**D**iffusion, **E**rosion, **O**smosis — **DEO** controls the flow."
- **Top polymers:** "**H**PMC, **E**thylcellulose, **E**udragit — **HEE** (He controls release)."

## 4.16 Exam Summary

Modified-release tablets change the timing/rate of drug release. Sustained-release prolongs action and reduces dosing frequency; controlled-release delivers at a predetermined rate. Need: steady therapeutic levels, compliance, fewer side effects. Formulation design: target profile → drug suitability → mechanism → polymer → dissolution testing. Mechanisms: diffusion, erosion/dissolution, osmotic. Polymers: HPMC, ethylcellulose, Eudragit, carbopol, waxes, cellulose acetate. Evaluation: multi-point in-vitro dissolution, dose-dumping check, stability. Patients must not crush SR/CR tablets.

## 4.17 One-Minute Revision

SR = longer, fewer doses; CR = controlled rate. Drip irrigation, not bucket. Mechanisms: diffusion, erosion, osmosis. Polymers: HPMC, ethylcellulose, Eudragit. Never crush. Multi-point dissolution proves it.

## 4.18 Infographic Concept Box

**Title:** "Taming the Blood-Level Curve" Two curves: spiky IR (3 doses, peaks/valleys) vs flat SR plateau (1 dose). Below: three mechanism icons — tea bag (diffusion), melting soap (erosion), pinhole balloon (osmotic). Side panel: "Never crush!" warning triangle.

## 4.19 Exam Questions

**Short answers:**

1. Define sustained-release and controlled-release. Give one difference.
2. List four advantages and three disadvantages of SR tablets.
3. Name four polymers used in SR/CR with one role each.
4. Why should SR tablets not be crushed?

**Long answers:**

1. Explain the concept and need of modified-release dosage forms with a blood-level curve diagram.
2. Describe the mechanisms of drug release from SR/CR tablets with examples.
3. Discuss formulation design and evaluation of modified-release tablets.

**MCQs:**

1. An osmotic pump pushes drug out using: (a) diffusion (b) water entering through a semipermeable membrane ✓ (c) stomach acid (d) chewing
2. HPMC in SR tablets acts as: (a) disintegrant (b) hydrophilic matrix former ✓ (c) lubricant (d) colour
3. Dose dumping means: (a) slow release (b) sudden release of full dose ✓ (c) no release (d) delayed release

**Viva:**

1. Draw and explain the SR blood-level curve.
2. Which drugs are unsuitable for SR? Name two reasons.
3. What is the role of the laser-drilled orifice in an osmotic tablet?

**Application-based:** A hypertensive patient on thrice-daily immediate-release tablets misses doses often. Suggest a formulation approach and counsel the patient. (Once-daily SR matrix tablet with HPMC; counsel: swallow whole with water, do not crush/chew, take at the same time daily.)

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