

2.1 Principles and fundamentals

A rate controlled drug delivery system is designed so that the release rate, not the body's absorption or elimination, decides the plasma profile. The fundamental idea is simple: if the drug input rate is known and constant, and the body handles the drug by first order elimination, the plasma level settles to a predictable steady state, $C_{ss} = \text{input rate} / \text{clearance}$. The formulator therefore designs the input, and physiology does the rest.

Rate control can be engineered at three levels:

- **Rate preprogrammed systems:** the release rate pattern is fixed during manufacture (membrane reservoir systems, osmotic pumps). The system cannot change its rate in the body, but it delivers that rate faithfully.
- **Activation modulated systems:** release stays off or minimal until an activation force switches it on or speeds it: mechanical force, pH change, enzymes or osmotic pressure. These are the modulated systems of this unit.
- **Feedback regulated systems:** a sensor detects a body signal (for example glucose) and the system responds by releasing drug in proportion to the signal. This is the closed loop concept, the most advanced level.

The general design requirements repeat across all types: a rate controlling element (membrane, matrix, osmotic core), a drug reservoir protected from the environment until release, reproducibility between units, and stability of the rate over the whole dosing period.

2.2 Types of rate controlled systems

By mechanism, the working classification used in the standard texts is:

Rate controlled drug delivery systems

1. Rate preprogrammed
 - Polymer membrane permeation controlled (reservoir with membrane)
 - Polymer matrix diffusion controlled (monolithic matrix)
 - Microreservoir partition controlled (drug in microscopic reservoirs in a matrix)
2. Activation modulated
 - Mechanically activated - pH activated
 - Enzyme activated - Osmotic activated
 - Also listed: magnetic, ultrasound, iontophoresis and hydration activated
3. Feedback regulated
 - Bioerosion regulated, bioresponsive, self regulated systems

- **Membrane permeation controlled:** saturated drug reservoir behind a rate controlling polymer membrane; while solid drug remains, the activity inside is constant and release is near zero order.
- **Matrix diffusion controlled:** drug dispersed in a polymer slab, cylinder or sphere; release falls with the square root of time (Higuchi) as the depleted zone thickens.
- **Microreservoir systems:** the drug is first dissolved or dispersed in microscopic compartments (for example an aqueous drug solution emulsified into a polymer matrix, as in the Nitrodisc type design), combining reservoir behaviour at micro scale with a matrix at macro scale.

2.3 Mechanically activated drug delivery systems

In these systems a mechanical force applied by the patient or by a device drives delivery, which gives on demand dosing.

- **Infusion pumps:** external electromechanical pumps deliver drug (classically insulin) through a catheter at programmed basal rates with patient triggered bolus doses. Implantable pumps do the same inside the body for long term therapy.
- **Metered dose inhalers and nasal sprays:** each actuation (a mechanical press) releases a fixed metered volume through a valve. The metering valve is the rate and dose controlling element.
- **Working principle to state in exams:** energy for delivery comes from an external mechanical action, not from the formulation, so dose accuracy depends on device engineering and patient technique; the formulation mainly needs stability and compatibility with the device.

2.4 pH activated drug delivery systems

These systems exploit the pH gradient of the body, above all the gastrointestinal tract: stomach pH about 1 to 3, small intestine about 6 to 7.5, colon near neutral, and specific sites such as the vagina or inflamed tissue having their own values.

- **Enteric systems:** polymers such as cellulose acetate phthalate and methacrylic acid copolymers (Eudragit L, dissolves above pH 6; Eudragit S, above pH 7) stay intact in acid and dissolve in the intestine. Used to protect acid labile drugs (for example erythromycin, pancreatic enzymes, proton pump inhibitors) and to protect the stomach from irritant drugs (for example enteric coated aspirin and NSAIDs).
- **Colon targeted systems:** pH alone is unreliable for the colon, so pH polymers are combined with time dependent or enzyme degradable layers (see also 2.5) to release drugs for ulcerative colitis and Crohn disease (mesalamine products are the standard example).
- **pH sensitive hydrogels and particles:** polymers carrying acidic or basic groups swell or shrink as pH changes, squeezing out or releasing the drug; studied for oral insulin protection through the stomach with release in the intestine.
- **Limitation to remember:** gastrointestinal pH varies with food, disease and co-medication (a patient on a proton pump inhibitor has a raised gastric pH), so pH triggering is a probability, not a switch, and good designs add a second safeguard.

2.5 Enzyme activated drug delivery systems

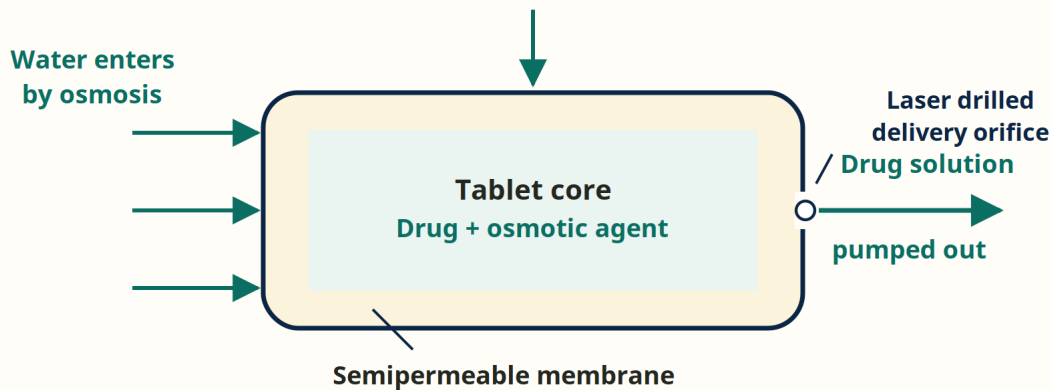
Here an enzyme performs the activation step, so release is linked to a biochemical event at the site.

- **Enzyme triggered release in the colon:** coatings and matrices of polysaccharides (pectin, guar gum, chitosan, dextran) and azo polymer systems survive the upper gut but are degraded by colonic bacterial enzymes (azoreductase, glycosidases). Azo prodrugs are the drug level version: sulfasalazine is split by colonic azoreductase into sulfapyridine and 5-aminosalicylic acid, the active part for bowel disease.
- **Enzyme responsive hydrogels and carriers:** a carrier cross linked by peptide bonds is cleaved by enzymes that are raised at a diseased site (for example matrix metalloproteinases in tumours and inflamed tissue), releasing the drug where the enzyme activity is highest.
- **Design checks:** enzyme levels differ between patients and with diet and antibiotics (which can wipe out the colonic flora the system depends on), so the formulator must test release with and without the enzyme and treat the system as site assisted rather than perfectly site specific.

2.6 Osmotic activated drug delivery systems

Osmotic systems are the most reliable route to true zero order oral delivery, so this section deserves careful study.

Osmotic Pump (OROS Principle)



Water influx is constant, so drug leaves at a steady zero order rate

Figure: The elementary osmotic pump: water drawn in through the semipermeable membrane pushes drug solution out of the orifice at a constant rate.

Principle: water crosses a semipermeable membrane (classically cellulose acetate) into a core containing an osmotically active substance. The incoming water creates hydrostatic pressure that pushes the drug solution or suspension out through a small delivery orifice drilled in the membrane. The release rate depends on the membrane area, thickness and permeability, the osmotic pressure difference and the orifice size, and stays constant as long as solid osmotic agent remains to keep the incoming fluid saturated. In simple words: constant water inflow, constant drug outflow, largely independent of pH, food and agitation, which is why in vitro and in vivo rates match unusually well for these systems.

The elementary osmotic pump (EOP): a core of drug with or without added osmogen, coated with the semipermeable membrane, with one laser drilled hole. Rose and Nelson's early pump and Theeuwes' elementary osmotic pump are the textbook line of development. It works best for moderately soluble drugs; a very insoluble drug leaves as a solution only in small amount, and a very soluble drug needs membrane and osmogen balancing.

Push pull osmotic pump (PPOP): two layer core. The push layer contains a swellable polymer and osmogen; the drug layer contains the drug, often poorly soluble, in a suspendable form. Water enters both layers, the push layer expands and squeezes the drug suspension out of the orifice at a constant rate. Most modern once daily products (for example nifedipine GITS, glipizide and paliperidone systems) use this design. GITS (gastrointestinal therapeutic system) is the trade name family for these.

Elementary osmotic pump, working sequence

Tablet swallowed

- > water enters through semipermeable cellulose acetate coat
- > core dissolves, osmotic pressure builds inside
- > pressure pushes drug solution out of the laser drilled orifice
- > constant rate while solid core material remains (zero order)
- > exhausted shell is finally excreted in the faeces

Other osmotic designs: push pull pump (two layer core for insoluble drugs), osmotic bursting pump (no orifice, coat bursts after a lag), sandwiched and controlled porosity pumps (pore formers in the coat)

Advantages: zero order release, rate set by the device not the patient, reduced food and pH effects, good IVIVC, one daily dosing for many chronic drugs. **Limitations:** cost and laser drilling technology, the spent shell is excreted intact (patients must be told, the "ghost tablet" in stool is expected), the rigid non deformable shell is a caution in patients with severe gastrointestinal narrowing, and a coat defect can release the whole dose.

2.7 Feedback regulated drug delivery systems: principles and fundamentals

A feedback regulated system closes the loop: it senses a biochemical signal, decides, and releases. Three parts are always present:

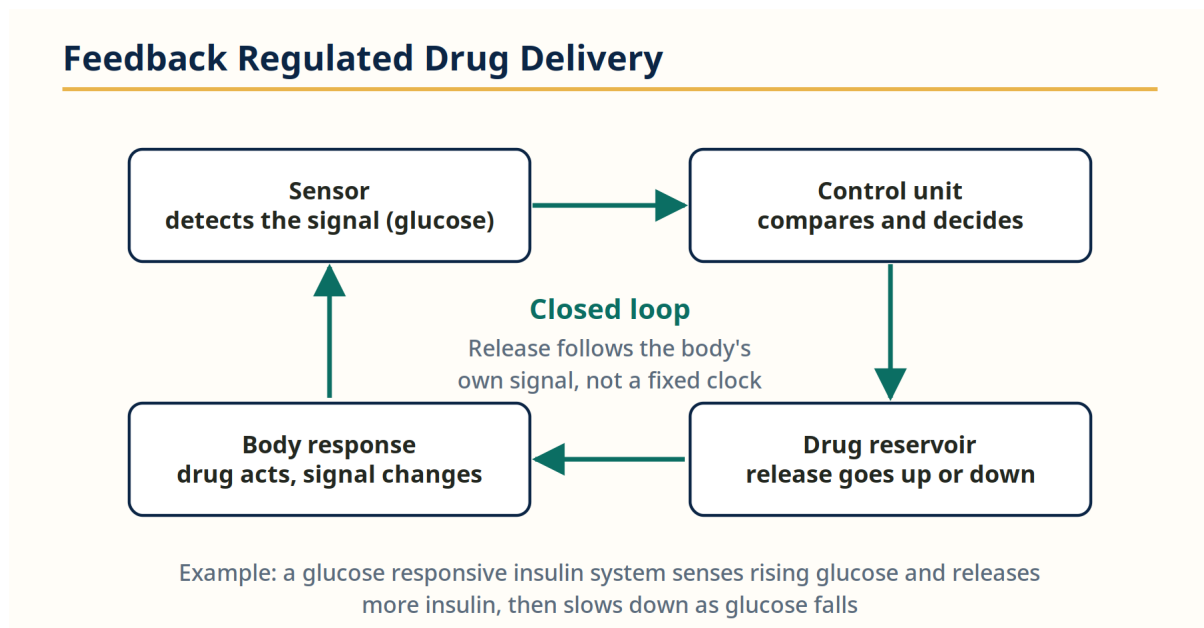


Figure: A feedback regulated system is a closed loop: sense, decide, release, respond, and sense again.

- **A sensor or sensing chemistry** that responds to the signal substance.
- **A rate controlling mechanism** whose permeability or erosion changes with the signal.
- **The drug reservoir**, released in proportion to the signal, and stopping or slowing when the signal falls.

The classic research example is self regulated insulin delivery: glucose oxidase inside a hydrogel converts glucose to gluconic acid, the local pH falls, the pH sensitive gel swells and lets insulin out; when glucose falls, acid production slows, the gel shrinks and release stops. Other studied versions use concanavalin A competitive binding (glucose competes with glycosylated insulin for binding sites, freeing insulin in proportion to glucose) and bioerosion regulated designs where the signal substance triggers surface erosion of the carrier.

Exam level judgement expected: the concept is proven in the laboratory and in animal work, and modern sensor based insulin pumps with electronic feedback (closed loop or artificial pancreas systems) achieve the same goal with devices; a purely chemical self regulated formulation is still not a routine marketed product because sensor response is slow, materials fatigue, and fail safe behaviour is hard to guarantee. That gap between principle and product is exactly why this topic sits at the end of the unit.