

Unit 1: Sustained Release and Controlled Release Formulations, Polymers and Dosage Forms for Personalized Medicine

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Drug Delivery System, subject code MPH102T, is a core Semester 1 subject of M.Pharm Pharmaceuticals. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. This subject teaches how a drug delivery system is designed so that the drug reaches the right site, at the right rate, for the right length of time. A conventional tablet releases its drug quickly and the blood level rises and falls with every dose. The systems in this subject change that behaviour: they sustain or control the release rate, hold the dosage form in the stomach or on a mucosal surface, carry the drug across the skin or the eye, protect fragile protein drugs, and deliver vaccines in new ways. A student who completes this subject should be able to select a suitable drug and polymer for a delivery system, explain the mechanism by which the system releases the drug, and describe how such a system is formulated and evaluated. The seven units move from the basic concepts of sustained and controlled release, through rate controlled, gastro-retentive, buccal, ocular and transdermal systems, to protein, peptide and vaccine delivery.

1.1 Introduction and basic concepts

When a conventional immediate release dosage form is given repeatedly, the plasma concentration rises after each dose and falls before the next one. If the interval between doses is long compared with the half life of the drug, the concentration spends part of the time below the minimum effective concentration (MEC) and, with a narrow therapeutic index drug, part of the time near or above the minimum toxic concentration (MTC). The aim of a modified release system is to flatten this curve.

Some basic terms must be clear before any design work:

- **Sustained release (SR):** a dosage form that releases the drug slowly over an extended period, so that the dosing frequency is reduced, usually from three or four times a day to once or twice a day. The release rate is prolonged but is not necessarily constant, and the system does not target a specific site.
- **Controlled release (CR):** a system that releases the drug at a constant, predetermined rate, ideally zero order, so that the plasma concentration stays nearly constant for the period of therapy. Controlled release is the stricter term: rate control is designed into the system and is largely independent of the biological environment.
- **Extended release, prolonged release and delayed release** are related labels. Delayed release means release begins after a lag, for example an enteric coated tablet that releases only in the intestine. Extended and prolonged release are used loosely for systems that release over a longer time than a conventional form.
- **Loading dose and maintenance dose:** many SR/CR designs contain an immediate release portion that produces the therapeutic level quickly (the loading part), followed by a slow release portion that maintains it. The total dose is therefore higher than a single conventional dose, which is one reason dose dumping is a safety concern.

The rationale for SR/CR is strongest for drugs with a half life of about 2 to 8 hours, a wide enough therapeutic index, uniform absorption from the gastrointestinal tract, and a dose that is not too large to fit into one unit.

1.2 Advantages and disadvantages of SR/CR formulations

Advantages:

- Reduced frequency of dosing, which improves patient compliance, especially in chronic therapy such as hypertension, diabetes and arthritis.
- More constant plasma levels: fewer peaks and troughs, so fewer peak related side effects and fewer periods of lost effect, including better night time control.
- Reduced total drug usage in some cases, because the drug is used more efficiently and first pass loss per dose event is spread out.
- Better safety margin in therapy where fluctuation itself is harmful, for example antianginal and antihypertensive therapy.
- Reduced gastrointestinal irritation for some drugs, because the local concentration released at one spot at one time is lower, though this depends on the design.
- Economic and nursing time savings in hospitals because fewer administrations are needed.

Disadvantages and limitations:

- Higher cost per unit than conventional forms, because of polymers, coating and process technology.
- Dose dumping: if the system fails (a cracked coat, chewing of a matrix tablet, alcohol induced failure of some coatings), the whole large dose can be released at once and cause toxicity.
- The dosage form cannot be crushed, split or chewed in most cases, which is a problem for patients who cannot swallow whole units and for feeding tube administration.
- Poor correlation sometimes between in vitro release and in vivo performance, because gut motility, food and pH vary between patients.
- Retrieval of the drug is difficult once the dose is taken: therapy cannot be stopped quickly if an adverse reaction occurs.
- Not every drug is suitable. Very short half life drugs need too large a dose, very long half life drugs do not need the technology, poorly soluble or site specific absorption drugs behave unpredictably, and large dose drugs cannot fit.

1.3 Factors influencing SR/CR design

Physicochemical factors of the drug:

- **Aqueous solubility:** very soluble drugs are hard to slow down because they dissolve and diffuse quickly; very insoluble drugs are dissolution rate limited already, and release becomes erratic. A moderate solubility is easiest to work with.
- **Partition coefficient:** the drug must cross lipid membranes after release. Very high lipid solubility can cause the drug to be held in fatty tissue; very low lipid solubility gives poor absorption.
- **Molecular size and diffusivity:** large molecules diffuse slowly through polymer matrices and membranes, which limits some designs and is a central problem for proteins (Unit 6).
- **Drug stability:** the drug must survive the pH range and enzymes of the gut for the whole transit period, because the form releases over many hours.
- **Ionisation (pKa):** only the unionised form crosses membranes well, and solubility changes with pH along the gut, so release and absorption both shift with site.
- **Dose size:** as a working rule, single doses above about 500 to 600 mg are difficult to make into a swallowable SR unit.

Biological factors:

- **Biological half life:** the ideal range is roughly 2 to 8 hours. Drugs below about 1 hour need an impractically large dose in the system; drugs beyond about 12 hours are already sustained by the body itself.
- **Absorption window:** some drugs absorb only in the upper gut (for example many weak bases and drugs carried by transporters). Once the form passes that window, the remaining dose is wasted. This is the exact problem gastro-retentive systems in Unit 3 are built to solve.
- **Absorption rate:** release must be slower than absorption, otherwise the release step cannot control the blood level (the flip flop situation is intended here: the slowest step, release, should govern the profile).
- **Metabolism:** drugs with heavy, variable first pass metabolism give inconsistent levels from any oral system; enzyme induction or saturation also changes the picture during long therapy.
- **Distribution and protein binding:** highly bound or widely distributed drugs have their own buffering, which changes how much benefit release control adds.
- **Disease state, food and motility:** gastric emptying time varies with food, posture, age and disease, so the residence of the form is never fully in the formulator's hands.

1.4 Physicochemical and biological approaches for SR/CR formulation

The practical methods used to build SR/CR products fall into a few repeatable approaches:

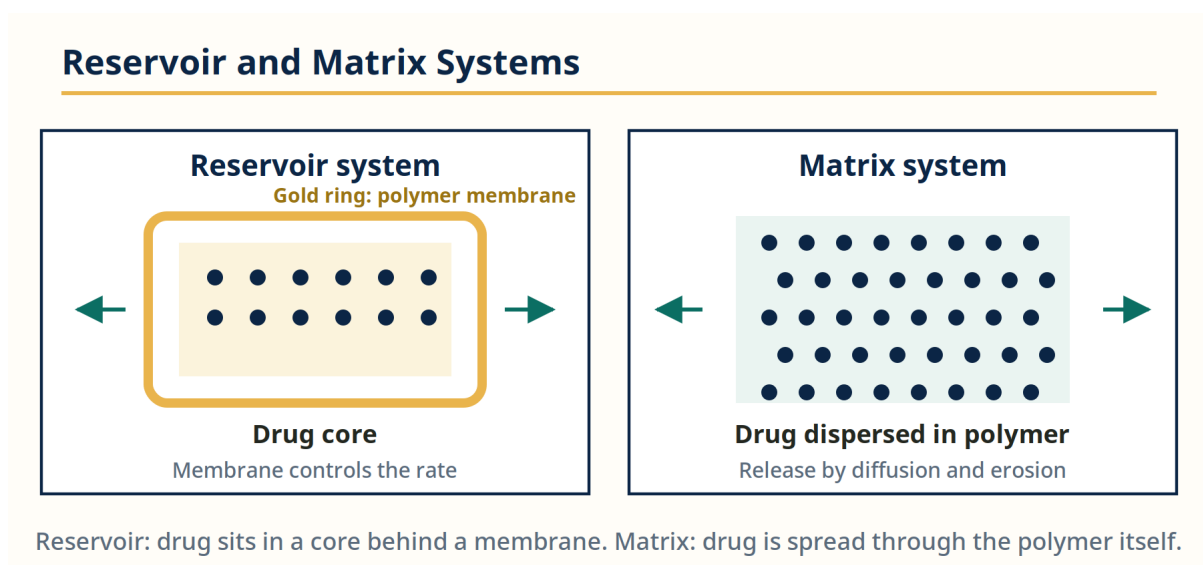


Figure: Reservoir and matrix systems, the two basic diffusion controlled designs for SR and CR formulations.

Physicochemical approaches:

- **Matrix (monolithic) systems:** the drug is dispersed in a polymer matrix and release happens as the medium penetrates, dissolves the drug and lets it diffuse out, or as the matrix itself erodes. Hydrophilic matrices (for example HPMC) swell and form a gel layer; inert plastic matrices (for example ethyl cellulose, polyethylene) keep their shape and release by diffusion through pores; wax and fatty matrices erode slowly.
- **Reservoir systems:** the drug core is enclosed by a polymer membrane and release is by diffusion across that membrane. Coated pellets, microcapsules and membrane coated tablets belong here. A pinhole or crack in the coat can dump the dose, so coat quality is critical.

- **Ion exchange resin complexes:** the drug is bound to an ion exchange resin and is released in the gut by exchange with sodium, potassium or hydrogen ions. Useful for taste masking plus sustained action.
- **Osmotic systems:** water enters through a semipermeable membrane and pushes the drug out through a laser drilled hole at a constant rate. Covered in detail in Unit 2.
- **Prodrugs and drug modification:** chemical change of the drug itself, for example an insoluble salt or ester, slows dissolution and prolongs action. This is a drug level approach rather than a dosage form approach.
- **pH dependent coatings and solubility modifiers:** release is tied to the pH of the region, or the microenvironment pH inside the form is adjusted with buffers to hold solubility steady.

Biological approaches:

- Using the body's own slow step: designing for a drug whose elimination is naturally slow is not formulation, so biological approaches mainly mean enzyme based or site based ideas: prodrugs activated by enzymes at the target region (for example colon targeted prodrugs split by colonic bacteria), antibody or ligand directed carriers studied in targeted delivery, and systems timed with biological rhythms (chronotherapy), where release is matched to the time of day the disease is worst, such as early morning asthma or blood pressure surge.

1.5 Mechanism of drug delivery from SR/CR formulations

Three mechanisms explain nearly every SR/CR product:

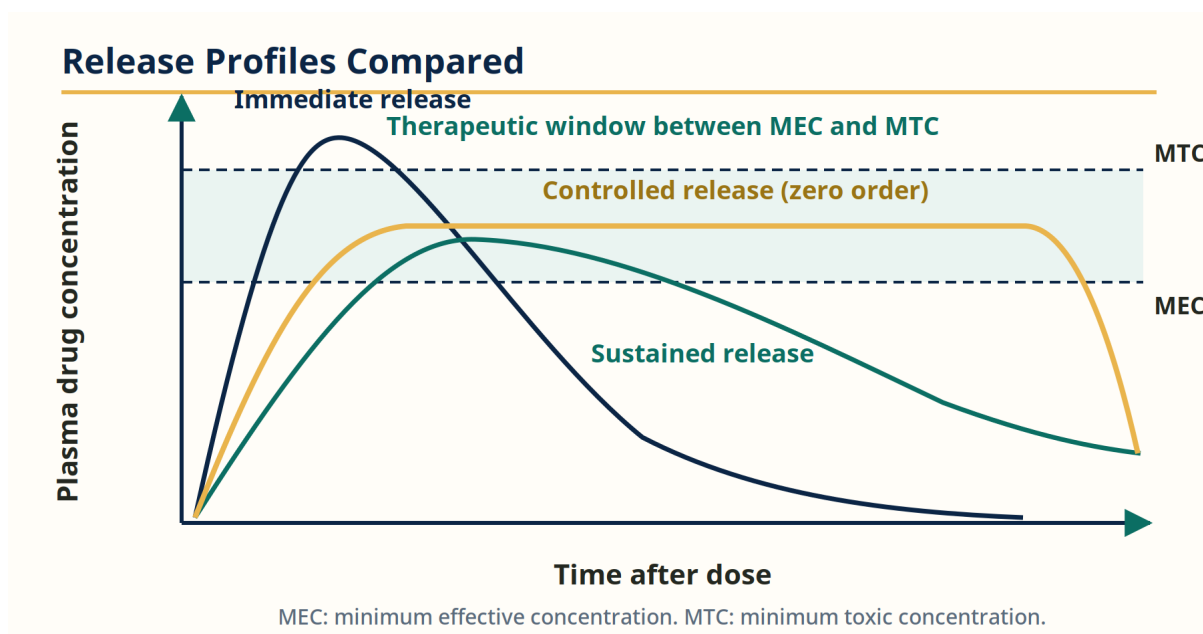


Figure: Plasma profiles compared: immediate release peaks and falls fast, sustained release is lower and broader, controlled release holds a flat zero order plateau inside the therapeutic window.

- **Dissolution controlled release:** the rate limiting step is the dissolution of the drug or of a coating around it. Encapsulation dissolution control coats drug particles with a slowly dissolving material of graded thickness; matrix dissolution control embeds the drug in a slowly dissolving wax matrix. Release follows the Noyes Whitney relationship: the slower the surface dissolves, the slower the supply of dissolved drug.
- **Diffusion controlled release:** the drug diffuses through a polymer. In reservoir systems the membrane gives near zero order release while solid drug remains inside, because the concentration gradient across the membrane stays constant. In matrix systems the amount released grows with the square root of time

(the Higuchi relationship for a planar matrix), because the diffusion path length increases as the drug depletes from the outer layer inward. Students should remember: reservoir membrane systems are the classic route to zero order; homogeneous matrices are not, they slow down with time.

- **Combined diffusion and erosion, and osmotic release:** many real systems mix mechanisms, for example a swelling HPMC matrix releases by diffusion through the gel plus erosion of the gel surface. Fitting release data to models (zero order, first order, Higuchi, Hixson Crowell for erosion, and Korsmeyer Peppas, whose release exponent n indicates Fickian diffusion, non Fickian transport or case II erosion controlled release) is the standard way the mechanism is identified in evaluation work.

Drug release mechanisms from SR/CR systems	
Dissolution controlled	-> slow dissolving coat or matrix limits supply of drug
Diffusion controlled	-> drug diffuses through membrane (reservoir) or matrix
Erosion controlled	-> polymer surface wears away and exposes fresh drug
Osmotic controlled	-> water inflow pushes drug out at a constant rate
Most real products	-> a combination, most often diffusion plus erosion

1.6 Polymers: introduction, definition, classification, properties and application

A **polymer** is a very large molecule built by joining many small repeating units called monomers. In drug delivery, polymers are the working material of almost every system in this subject: they form matrices, membranes, coatings, gels, implants and microparticles, and they decide the release rate more than any other excipient.

Classification:

- **By source:** natural (for example gelatin, alginate, chitosan, xanthan gum, guar gum), semi synthetic (cellulose derivatives such as HPMC, ethyl cellulose, cellulose acetate phthalate) and synthetic (for example polylactic acid, PLGA, polymethacrylates sold as Eudragit grades, polyethylene oxide, silicones, carbomers).
- **By biodegradability:** biodegradable polymers break down in the body into safe products (PLA, PLGA, polycaprolactone, albumin, gelatin) and suit implants and injectable depots; non biodegradable polymers stay intact (ethyl cellulose, silicone, ethylene vinyl acetate) and must be removable if implanted, or pass harmlessly through the gut if oral.
- **By response to water:** hydrophilic polymers swell or dissolve in water and make gel barriers (HPMC, PEO, carbopol); hydrophobic polymers resist water and slow penetration (ethyl cellulose, waxes, Eudragit RS and RL, which are water insoluble but permeable).
- **By function in the system:** matrix formers, film formers and coating materials, mucoadhesive polymers (Unit 3), enteric polymers that dissolve only above a set pH (cellulose acetate phthalate, Eudragit L and S), and smart or stimulus responsive polymers that change with pH or temperature.

Key properties a formulator checks: molecular weight and viscosity grade (higher viscosity grade, slower release from a gel matrix), glass transition temperature (decides film flexibility and whether a plasticiser is needed), solubility and swelling behaviour, permeability to the drug, mechanical strength, stability, safety and regulatory acceptance, and the degradation products for biodegradable grades.

Applications: rate controlling membranes of reservoir systems, hydrophilic matrix tablets, film coating, microencapsulation, osmotic pump membranes (cellulose acetate), implants and microspheres (PLGA), transdermal adhesives and matrices (Unit 5), mucoadhesive buccal films (Unit 3), and hydrogels for protein delivery (Unit 6). Polymer selection is therefore not one decision but a matching exercise between drug properties (Section 1.3), target profile and route.

Feature	Hydrophilic matrix polymer (example HPMC)	Hydrophobic polymer (example ethyl cellulose)
Behaviour in water	Swells and forms a gel layer	Does not swell, stays intact
Main release mechanism	Diffusion through gel plus surface erosion	Diffusion through pores and channels
Effect of higher polymer level	Slower, more gel controlled release	Slower, more tortuous diffusion path
Typical use	Once daily matrix tablets	Coating of pellets, inert matrices
Failure risk	Gel can be disrupted by alcohol or strong agitation	Film cracks can cause dose dumping

1.7 Dosage forms for personalized medicine

Personalized medicine means selecting or designing the treatment for the individual patient instead of giving every patient the same drug, dose and form. The syllabus topics under this head are:

- **Pharmacogenetics:** the study of how genetic differences change drug response. Variants in metabolising enzymes (for example CYP2C9, CYP2D6, CYP2C19), transporters and drug targets explain why one patient needs a low dose, another a standard dose and a third gets no effect or toxicity at the same dose. Testing before therapy (as with clopidogrel and CYP2C19, or fluorouracil and DPYD) is the applied form of this idea.
- **Categories of patients for personalized medicines:** broadly, patients can be grouped by genotype (poor, intermediate, extensive and ultra rapid metabolisers), by disease subtype and biomarkers (for example HER2 positive breast cancer treated with trastuzumab), by age and organ function (children, elderly, renal or hepatic impairment), and by lifestyle and adherence pattern. Each group is a candidate for a different strength, release profile or dosage form.
- **Customized drug delivery systems:** delivery designed around one patient or one narrow group: dose flexible forms that allow titration (mini tablets counted per dose, oral films cut or printed to strength), systems matched to a patient's swallowing ability or daily routine, and combination products built for a specific comorbidity pattern.
- **Bioelectronic medicines:** small implantable or wearable devices that deliver electrical stimulation to nerves to treat disease, instead of or alongside a drug (for example vagus nerve stimulation). The delivery thinking is the same as for drugs: dose (stimulus strength), site (the nerve) and duration are controlled by the device.
- **3D printing of pharmaceuticals:** layer by layer fabrication of dosage forms from a digital design. Fused deposition modelling, binder jetting and semi solid extrusion can print tablets with exact individual doses, multiple drugs in one polypill with separate release profiles, and shapes that change surface area and release. The first regulatory approved printed drug product (levetiracetam, Spritam, made by binder jetting) shows the route is practical; the exam points are personalisation of dose, complex internal geometry, and on demand manufacture close to the patient.
- **Telepharmacy:** delivery of pharmacy services at a distance through telecommunications: remote prescription review, counselling by video, remote supervision of dispensing and follow up of adherence. It supports personalized care where a pharmacist is not physically present, and pairs naturally with customized dispensing.

The common thread of this unit: release control starts with the drug and the polymer, but the end point is a system fitted to a patient, not only to a molecule.