Unit-1

Novel Drug Delivery Systems

B.Pharma 7 Sem Notes

Unit: 1

Controlled drug delivery systems:

Introduction, terminology/definitions and rationale, advantages, disadvantages, selection of drug candidates.Approaches to design controlled release formulations based on diffusion, dissolution and ion exchange principles. Physicochemical and biological properties of drugs relevant to controlled release formulations

Polymers:

Introduction, classification, properties, advantages and application of polymers in formulation of controlled release drug delivery

CONTROLLED DRUG DELIVERY SYSTEMS

Introduction to Controlled Drug Delivery Systems

Conventional drug delivery systems such as tablets, capsules, syrups, injections, and suppositories release drugs immediately after administration. These systems produce fluctuating drug plasma concentrations that may oscillate between toxic and sub-therapeutic levels, leading to inadequate therapy.

Controlled Drug Delivery Systems (CDDS) were developed to overcome these limitations. They are designed to deliver the drug at a pre-determined rate, at a specific site, and for a specified period of time, thereby maintaining constant therapeutic drug levels in the body.

📌 **Note:** Controlled drug delivery is defined as a system that delivers a drug at a predetermined rate locally or systemically, for a specified period of time.

Historical Background

- 1950s: First sustained-release products (e.g., Dexedrine Spansules) were introduced.
- 1960s: Concept of zero-order drug release was introduced.
- 1970s: Development of osmotic pump systems and transdermal patches began.
- 1980s onwards: Emergence of polymer-based, biodegradable, and targeted drug delivery systems.
- Present: Nanotechnology, liposomes, nanoparticles, and smart drug delivery systems are in focus.

Terminology and Definitions

Understanding the key terms used in controlled drug delivery is essential for designing effective formulations.

Term	Definition
Controlled Release (CR)	A system designed to deliver drug at a pre-determined, controlled rate.

Sustained Release (SR)	Prolongs drug action by continuously releasing drug over an extended period after administration.
Prolonged Release (PR)	Provides slow release of drug to maintain therapeutic effect for a longer time.
Extended Release (ER/XR)	Allows at least a twofold reduction in dosing frequency compared to conventional dosage form.
Delayed Release (DR)	Drug is released at a time other than immediately after administration (e.g., enteric-coated tablets).
Modified Release (MR)	Includes ER, DR, and pulsatile release formulations with modified release pattern.
Zero-Order Release	Drug is released at a constant rate, independent of drug concentration.
First-Order Release	Drug release rate is proportional to the drug concentration remaining in the formulation.
Pulsatile Release	Drug is released in pulses at specific time intervals.
Targeted Delivery	Drug is delivered selectively to a specific organ, tissue, or cell type.
Bioavailability	Fraction of administered drug that reaches systemic circulation unchanged.
MTC (Min. Toxic Conc.)	Minimum plasma drug concentration at which toxic effects begin to appear.
MEC (Min. Effective Conc.)	Minimum plasma drug concentration required to produce desired therapeutic effect.
Therapeutic Window	Range of drug concentration between MEC and MTC.

Rationale for Controlled Drug Delivery

The rationale behind development of CDDS is based on pharmacokinetic and pharmacodynamic principles aimed at improving therapeutic outcomes and patient compliance.

Limitations of Conventional Drug Delivery

- Peak and valley plasma concentration profiles leading to toxicity or therapeutic failure.
- Frequent dosing schedules reducing patient compliance.
- Rapid degradation of drugs with short biological half-life ($t_{1/2} < 2$ hours).
- First-pass metabolism reducing bioavailability.

- Localized side effects from high peak concentrations.
- Drug waste due to rapid elimination.

Goals of Controlled Drug Delivery

- Maintain drug concentration within therapeutic window for prolonged duration.
- Reduce dosing frequency (e.g., once daily instead of 3–4 times daily).
- Minimize side effects by avoiding peak plasma concentrations.
- Improve patient compliance and convenience.
- Protect labile drugs from enzymatic degradation.
- Achieve site-specific or targeted delivery.
- Reduce total amount of drug used, minimizing cost.

📌 **Note:** The ideal controlled release system should provide drug at a rate that matches the biological requirement of the patient over the entire dosing interval.

Advantages of Controlled Drug Delivery Systems

Advantage	Explanation
Reduced dosing frequency	Drug is released slowly, reducing the number of doses from 3–4/day to 1/day.
Improved patient compliance	Less frequent dosing improves adherence to therapy.
Maintained therapeutic levels	Avoids peak and trough fluctuations; keeps drug within therapeutic window.
Reduced side effects	Lower peak concentrations minimize adverse effects.
Reduced total drug dose	Efficient drug utilization reduces overall dose needed.
Overnight protection	Sustained-release allows drug to be effective through the night.
Site-specific delivery	Targeting delivers drug directly to the site of action.
Protection of drug	Polymeric coatings protect drug from degradation in GI tract.
Improved bioavailability	Avoids first-pass effect in some transdermal/buccal formulations.
Better management of chronic diseases	Ideal for conditions like hypertension, asthma, diabetes.

Disadvantages of Controlled Drug Delivery Systems

Disadvantage	Explanation
High cost of development	Advanced excipients, polymers, and technologies increase manufacturing cost.
Dose dumping risk	Accidental rupture of coating can release entire dose at once, causing toxicity.
Unpredictable in-vivo release	GI motility, pH, and food effects can alter drug release pattern.
Poor dose flexibility	Fixed dose per unit; cannot be easily titrated for individual patients.
First-dose lag time	Some systems have delayed onset of action, unsuitable for acute conditions.
Requires specialized machinery	Manufacturing demands sophisticated equipment and expertise.
Drug leaching	Drug may leach from matrix if solubility changes in GI environment.

Not suitable for all drugs	Drugs with very long or very short t½, or narrow therapeutic index may not be suitable.
In vitro–in vivo correlation	Difficult to establish IVIVC for complex formulations.
Patient manipulation	Patients may crush or chew CR tablets, destroying the release mechanism.

Selection of Drug Candidates for Controlled Release

Not all drugs are suitable candidates for controlled release formulation. The selection is based on both pharmacokinetic and pharmacodynamic properties of the drug.

Ideal Pharmacokinetic Properties

Parameter	Ideal Value / Criteria
Biological half-life (t½)	3–8 hours (too short = too frequent dosing; too long = no advantage)
Dose size	Low to moderate (high dose drugs are difficult to formulate in small CR units)
Therapeutic index	Wide therapeutic index preferred (narrow index = dose dumping risk)
Absorption	Uniform and complete absorption throughout GI tract
Protein binding	Not excessively protein-bound
Metabolism	Not extensively metabolized in the GI wall or liver
Intrinsic activity	Sufficient to allow administration of dose in controlled release form
Oral bioavailability	Should be reasonable (>10%)

Drugs NOT Suitable for Controlled Release

- Drugs with very long t½ (> 24 hours): e.g., Digoxin — already controlled naturally.
- Drugs with very short t½ (< 1 hour): require impractically large amounts of polymer.
- Drugs with narrow therapeutic index: e.g., Warfarin, Phenytoin — dose dumping is dangerous.
- Drugs absorbed by active transport at specific GI sites.

- Drugs with poor aqueous solubility throughout the GI tract.
- Drugs that are highly irritating to the GI mucosa.
- Drugs requiring precise dosing titration.
- Highly toxic drugs where dose must be precisely controlled.

Examples of Suitable and Unsuitable Drug Candidates

Category	Examples of Drugs	Reason
Suitable	Theophylline, Nifedipine, Metoprolol, Diclofenac, Diltiazem	Moderate t½, good absorption, wide therapeutic window
Partially suitable	Captopril, Propranolol	Short t½ but moderate absorption characteristics
Unsuitable (long t½)	Digoxin, Warfarin, Chlordiazepoxide	Already have prolonged action
Unsuitable (narrow window)	Phenytoin, Carbamazepine, Lithium	Risk of toxicity from dose dumping
Unsuitable (poor absorption)	Penicillin G (acid labile)	Poor GI stability or site-specific absorption

Approaches to Design Controlled Release Formulations

The fundamental approaches for controlling drug release are based on physical and chemical mechanisms. The three major approaches are: diffusion-controlled, dissolution-controlled, and ion exchange-based systems.

Diffusion-Controlled Systems

In diffusion-controlled systems, the rate of drug release is governed by diffusion of drug molecules through a rate-controlling membrane or matrix.

Reservoir Systems (Membrane-Controlled)

The drug core is surrounded by a rate-controlling polymeric membrane. Drug diffuses through the membrane at a controlled rate.

- Drug is present in a core surrounded by a membrane.
- Drug release rate depends on membrane permeability, thickness, and drug concentration gradient.

- Can achieve near zero-order drug release.
- Examples: Transdermal patches, Ocusert (ocular), Progestasert (IUD), ethylene-vinyl acetate matrix.

Fick's First Law of Diffusion (governing equation):

$$J = -D \times (dC/dx)$$

Where: J = flux (amount of drug/unit area/unit time), D = diffusion coefficient, dC/dx = concentration gradient across membrane

For membrane systems, rate of drug release:

$$dM/dt = D \times A \times K \times \Delta C / h$$

Where: D = diffusion coefficient in membrane, A = surface area, K = partition coefficient, ΔC = concentration difference, h = membrane thickness

Matrix Systems (Monolithic)

Drug is homogeneously dispersed throughout a polymer matrix. Drug is released by diffusion through the matrix pores.

- Drug dissolved/dispersed in hydrophilic or hydrophobic matrix.
- Drug release follows Higuchi equation (first-order kinetics initially, approaching square-root-of-time relationship).
- Examples: Wax matrices (Carnauba wax), HPMC matrices, Carbopol matrices.

Higuchi Equation (for matrix systems):

$$Q = [D(2A - Cs)Cs \times t]^{(1/2)}$$

Where: Q = amount of drug released per unit area at time t, D = diffusion coefficient, A = total drug concentration, Cs = drug solubility in matrix, t = time

Microreservoir Systems

- Combination of reservoir and matrix systems.
- Drug core is dispersed as micro-reservoir units within a matrix.
- Each micro-reservoir is coated with a rate-controlling membrane.
- More complex manufacturing but provides robust release profiles.

Dissolution-Controlled Systems

Drug release is controlled by the rate of dissolution of the drug or the surrounding coating/matrix. Dissolution can be controlled by modifying the drug particle size, crystal form, or by using slowly dissolving coatings.

Coated Bead Systems / Microencapsulation

- Drug particles are coated with slowly dissolving polymers (e.g., shellac, beeswax, carnauba wax, glycerol monostearate).
- Beads with different coating thicknesses are mixed to provide extended drug release.
- Example: Spansule capsule (SK&F) — contains beads with varying coating thicknesses.

Slowly Dissolving Coatings

- Enteric-coated tablets: dissolve at higher pH in intestine, not in stomach.
- Wax coatings: slowly erode in GI fluids.
- Examples: Cellulose acetate phthalate (CAP), Eudragit L and S coatings.

Matrix Dissolution Systems

- Drug is embedded in a slowly dissolving hydrophilic matrix (e.g., HPMC, HPC, Na-CMC).
- As matrix hydrates, it forms a gel layer — drug is released by erosion of the gel.
- Example: HPMC-based sustained-release tablet (hydrophilic matrix).

Fat-Embedded Matrix (Lipid Matrix)

- Drug is dispersed in a hydrophobic lipid matrix (beeswax, hydrogenated castor oil).
- Drug release depends on the melting and erosion of lipid in GI fluids.
- Suitable for drugs with poor taste (taste masking) and moisture-sensitive drugs.

Ion Exchange-Based Systems

In ion exchange-controlled systems, drug is bound to an ion exchange resin through ionic interaction. Drug release occurs by exchange of drug ions with ions present in the GI fluid.

Mechanism of Ion Exchange

- Drug (D+) is complexed with a cation exchange resin (R-) forming D+R-.
- In the GI tract, Na+ and H+ ions from intestinal fluid exchange with drug ions:
  - D+R- + Na+ → Na+R- + D+ (drug is released)
- For basic drugs, cationic exchange resins are used (e.g., Amberlite IRP-69).
- For acidic drugs, anionic exchange resins are used.

Factors Affecting Ion Exchange Release

- Ion concentration in GI fluid: Higher Na+ and Cl- concentrations increase drug release.
- Cross-linking of resin: Higher cross-linking slows diffusion and release.
- pH: Affects ionization and exchange efficiency.
- Drug-resin ratio: Determines drug loading.

Examples and Applications

- Delsym (Dextromethorphan Polistirex): Cough suppressant with ion exchange resin.
- Tussionex (Hydrocodone Polistirex): Extended-release hydrocodone.
- Advantages: Dose dumping is less likely; good masking of bitter taste; stable complex.

Comparison of Release Mechanisms

Feature	Diffusion	Dissolution	Ion Exchange
Release control	Membrane/matrix permeability	Solubility of coat/drug	Exchange of ions in GI fluid
Release order	Zero or first order	First order or erosion	Dependent on ion concentration
Polymers used	EVA, EC, Eudragit RL/RS	HPMC, CAP, Eudragit L/S	Amberlite, Purolite resins

Dose dumping risk	Moderate (reservoir)	Low (matrix)	Very low
Examples	Transdermal patches, Ocusert	Spansules, enteric-coated	Delsym, Tussionex
Key advantage	Predictable zero-order kinetics	Simple manufacturing	Taste masking + CR

Physicochemical and Biological Properties of Drugs Relevant to Controlled Release

Selection and formulation of a drug for controlled release requires thorough understanding of its physicochemical and biological properties. These determine the feasibility, mechanism, and design of the controlled release system.

Physicochemical Properties

Aqueous Solubility

- Highly soluble drugs (>1 mg/mL): Easily released from matrix — difficult to control release rate. Use hydrophobic matrices.
- Poorly soluble drugs (<0.1 mg/mL): Slow dissolution limits absorption — challenges in achieving therapeutic levels.
- Ideal solubility: 0.1–10 mg/mL. Allows manipulation of release rate using polymers.
- BCS Classification relevance:
  - Class I (high sol, high perm): Good candidates for CR. Absorption not limiting.
  - Class II (low sol, high perm): Challenging; dissolution is rate-limiting step.
  - Class III & IV: Special formulation techniques needed.

Partition Coefficient (Log P)

- Lipophilicity of the drug governs membrane permeability and diffusion through polymer coatings.
- Log P 1–3 considered ideal for oral controlled release.
- Too high Log P: poor aqueous solubility, may precipitate in GI tract.
- Too low Log P (very hydrophilic): poor membrane permeability, erratic absorption.

pKa and Ionization

- Ionization of drug depends on pKa and pH of GI fluid.
- Unionized form: higher lipophilicity, better membrane permeability.
- pH varies along GI tract: Stomach pH 1–3; Small intestine pH 5–7; Colon pH 7–8.
- Drug ionization affects absorption window — important for site-specific delivery.
- Weakly acidic drugs (e.g., Ibuprofen): absorbed better from stomach.
- Weakly basic drugs (e.g., Atenolol): absorbed better from intestine.

Molecular Weight and Size

- Lower MW drugs diffuse more easily through polymer membranes.
- High MW drugs (>500 Da): slower diffusion through membranes, may limit CR use.
- Molecular size influences diffusion coefficient (Stokes-Einstein equation): $D = kT / 6\pi\eta r$

Crystal Structure and Polymorphism

- Polymorphic forms of drug have different solubilities and dissolution rates.
- Amorphous form: higher solubility, faster dissolution than crystalline form.
- Example: Chloramphenicol palmitate — Polymorph B (inactive) vs. Polymorph A (active).
- Must characterize and stabilize polymorphic form during manufacturing.

Drug Stability

- Hydrolysis, oxidation, photodegradation can reduce drug content in CR formulation.
- pH-dependent stability must be considered with respect to GI pH changes.
- Interactions between drug and polymer/excipients must be evaluated.
- Use of protective coatings or appropriate excipients for stabilization.

Protein Binding

- Highly protein-bound drugs have reduced free drug concentration for pharmacological action.

- Only free drug diffuses across membranes and is pharmacologically active.
- High protein binding (>95%) may reduce effective therapeutic response.

Biological Properties

Biological Half-life (t½)

- Ideal t½ for CR formulation: 2–8 hours.
- Short t½ (< 2 hrs): Requires large amounts of drug to maintain therapeutic levels over extended period.
- Long t½ (> 24 hrs): No need for CR — already provides extended action.
- t½ determines:
  - Dosing frequency
  - Amount of drug needed in CR formulation
  - Time to reach steady state

Absorption Site and Window

- Most oral drugs are absorbed in the small intestine (duodenum and jejunum).
- Some drugs have narrow absorption windows (e.g., Riboflavin, Metformin — absorbed in upper GI).
- For narrow absorption window drugs: CR systems must release drug before passing the absorption window.
- Use of mucoadhesive systems or gastric retentive formulations (GRDF) can help retain drug at absorption site.

Absorption Rate Constant (Ka)

- For effective controlled release, Ka should be greater than release rate constant (Kr).
- If Ka < Kr: drug accumulates in GI tract without absorption — no therapeutic benefit.
- High Ka indicates good absorption potential — favorable for CR formulation.

First-Pass Metabolism

- Drugs with high first-pass effect have reduced bioavailability when administered orally.

- CR formulations may increase extent of first-pass metabolism due to prolonged contact with gut wall enzymes.
- Alternative routes (transdermal, buccal, sublingual) can bypass hepatic first-pass effect.
- Examples: Nitroglycerin, Testosterone, Estradiol — given transdermally.

Margin of Safety (Therapeutic Index)

- Wide therapeutic index: better and safer candidates for CR (e.g., Theophylline, Diclofenac).
- Narrow therapeutic index: dose dumping from CR system can be fatal.
- For NTI drugs: extra precautions needed if CR is attempted — in vitro/in vivo correlation essential.

Drug Metabolism Considerations

- CYP enzyme kinetics affect bioavailability.
- Prolonged drug presence in GI may induce or saturate metabolic enzymes — altering pharmacokinetics.
- Presystemic metabolism in gut wall (CYP3A4, P-gp efflux) must be evaluated.

Property	Favorable for CR	Unfavorable for CR
Aqueous solubility	Moderate (0.1–10 mg/mL)	Very high or very low
Biological t½	2–8 hours	< 1 hr or > 24 hrs
Absorption	Uniform throughout GI	Limited to narrow window
Therapeutic index	Wide	Narrow (NTI drugs)
Dose size	Small (< 0.5 g/dose)	Very large dose
Protein binding	Moderate	Very high (> 95%)
Log P	1–3	< 0 or > 5
First-pass effect	Low to moderate	Very extensive
Stability	Stable in GI pH	Acid/base labile

POLYMERS IN CONTROLLED RELEASE

Introduction to Polymers in Drug Delivery

Polymers are high molecular weight macromolecules composed of repeating structural units (monomers) connected by covalent bonds. They are the backbone of modern controlled drug delivery technology. Polymers serve as matrix formers, membrane coatings, binders, and carriers in CDDS.

The choice of polymer determines the release mechanism, rate, and site of drug release. The interaction between the drug and polymer influences the overall performance of the controlled release formulation.

📌 **Note:** A polymer used in drug delivery must be biocompatible, non-toxic, chemically stable under storage conditions, and compatible with the drug and other excipients.

Historical Development of Polymers in Drug Delivery

- 1950s: Natural polymers (shellac, wax, gelatin) used as film coatings.
- 1960s: Synthetic polymers (cellulose ethers, polyacrylates) introduced.
- 1970s: Biodegradable polymers (PLA, PLGA) explored for implantable systems.
- 1980s: Water-swellable hydrogels developed for oral/transdermal delivery.
- 1990s onwards: Smart/stimuli-responsive polymers, dendrimers, and nano-carriers.

Classification of Polymers

Based on Origin / Source

Category	Sub-type	Examples
Natural Polymers	Polysaccharides	Cellulose, Starch, Guar gum, Xanthan gum, Chitosan, Sodium alginate, Pectin
Natural Polymers	Proteins	Gelatin, Albumin, Casein, Collagen, Silk fibroin
Natural Polymers	Rubber	Natural rubber (polyisoprene)

Semi-synthetic Polymers	Cellulose derivatives	HPMC, HPC, MC, EC, CAP, HPMCP, Na-CMC
Semi-synthetic Polymers	Starch derivatives	Hydroxypropyl starch
Synthetic Polymers	Non-biodegradable	Polyacrylates (Eudragit), Polyvinyl acetate (PVAc), EVA, Polysulfone
Synthetic Polymers	Biodegradable	PLA, PGA, PLGA, PCL, Polyanhydrides, Polyorthoesters
Synthetic Polymers	Hydrogels	PVA, PVP, Polyacrylamide, Carbopol (carbomer)

Based on Biodegradability

- Biodegradable polymers: Undergo chemical/enzymatic degradation in the body.
  - Examples: PLGA, PLA, PGA, Chitosan, Gelatin, Albumin, PCL, Polyhydroxybutyrate
  - Applications: Injectable microspheres, implants, sutures, tissue engineering scaffolds
- Non-biodegradable polymers: Chemically inert, not degraded in the body; must be removed or pass through.
  - Examples: Eudragit RS/RL, Ethyl cellulose, EVA, Silicone rubber
  - Applications: Oral matrix tablets, membrane coatings, transdermal patches, IUDs

Based on Solubility / Swelling

- Hydrophilic polymers: Soluble/swellable in water. Form gel layer controlling drug release.
  - Examples: HPMC, HPC, PVP, Sodium alginate, Carbopol, PEO
- Hydrophobic polymers: Insoluble in water. Drug release by diffusion through polymer matrix.
  - Examples: Ethyl cellulose (EC), Eudragit RS/RL, Beeswax, Carnauba wax, PLA

Based on Electrical Charge (for Ion Exchange)

- Cationic resins: Negatively charged; exchange with positively charged (basic) drugs.
  - Example: Amberlite IRP-69 (sulfonic acid groups) — used for basic drugs like pseudoephedrine
- Anionic resins: Positively charged; exchange with negatively charged (acidic) drugs.
  - Example: Amberlite IRA-400 (quaternary ammonium groups)

Based on Response to Stimuli (Smart Polymers)

- pH-responsive: Swell/dissolve at specific pH.
  - Examples: Eudragit L (pH > 6), Eudragit S (pH > 7), Eudragit E (pH < 5)
- Temperature-responsive (thermo-responsive): Sol-gel transition at LCST.
  - Examples: PNIPAM (poly-N-isopropylacrylamide), Poloxamers (Pluronic)
- Redox-responsive: Release triggered by redox potential.
  - Examples: Disulfide-containing polymers
- Glucose-responsive: Used in diabetes management (insulin delivery).

Properties of Polymers Relevant to Controlled Release

Molecular Weight and Molecular Weight Distribution

- Higher MW polymers: Form stronger, denser matrices — slower drug release.
- Lower MW polymers: Weaker films, faster drug release.
- Polydispersity Index (PDI): Measure of MW distribution breadth. Low PDI indicates uniform polymer.
- Viscosity of polymer solutions depends on MW — important for coating and granulation.

Glass Transition Temperature (Tg)

- Temperature at which polymer transitions from glassy (rigid) to rubbery (flexible) state.
- Below Tg: Polymer is hard and brittle — low drug diffusion.
- Above Tg: Polymer is soft and rubbery — higher drug diffusion.
- Plasticizers are added to reduce Tg of polymers in film coatings.
- Examples: HPMC Tg ~180°C; Eudragit RS Tg ~55°C

Swelling Behavior

- Hydrophilic polymers absorb water → swell → form gel layer.
- Degree of swelling determines gel strength and drug diffusion rate.
- Crosslinked hydrogels: Exhibit controlled, limited swelling. Used in beads and implants.
- Swelling index: (Ws - Wd)/Wd × 100%, where Ws = swollen weight, Wd = dry weight

Permeability and Diffusivity

- Drug permeability through polymer film depends on polymer free volume and polarity.
- Diffusion coefficient (D) of drug in polymer determines release rate.
- Ethyl cellulose: Low permeability — ideal rate-controlling membrane.
- HPMC: High permeability — used for hydrophilic matrix systems.
- Plasticizers increase free volume → increase permeability.

Chemical and Physical Stability

- Polymer must be chemically stable in GI fluids (acid, alkali, enzymes).
- Must not degrade, crosslink, or change properties during storage.
- Physical stability: No crystallization, phase separation, or cracking of polymer film on storage.
- Compatibility with drug and other excipients is essential (check by DSC, FTIR).

Biocompatibility and Toxicity

- Polymers must be non-toxic, non-immunogenic, and non-carcinogenic.
- Biodegradable polymer degradation products must also be biocompatible.
- Example: PLGA degrades to lactic acid and glycolic acid — naturally occurring, safe metabolites.
- Polymer safety must be established through regulatory toxicology studies (ICH guidelines).

Solubility and Film-Forming Ability

- Good film-forming ability is required for coating applications.
- Polymer must dissolve or disperse in suitable solvents (aqueous or organic).
- Aqueous-based coating polymers are preferred (e.g., Eudragit L 30 D, HPMC aqueous dispersions).

Viscosity

- Viscosity of polymer solutions used in film coating must be controlled for uniform coating.
- Higher viscosity: Thicker, more consistent films; used in matrix tablet formulation.
- Lower viscosity: Better spray atomization in coating processes.
- HPMC viscosity grades: 5, 15, 50, 100 cps — higher grades give slower drug release.

Advantages of Using Polymers in Controlled Release Formulations

Advantage	Explanation
Flexible drug release profiles	Different polymers and combinations provide zero-order, first-order, or pulsatile release.
Protection of drug	Polymers protect labile drugs from GI degradation (acid, enzymes).
Site-specific delivery	Enteric polymers (Eudragit L, S) dissolve only at specific pH for targeted release.
Taste and odor masking	Drug coated with polymer hides bitter taste — improves patient compliance.
Improved stability	Polymer films reduce moisture and oxygen exposure, increasing drug shelf life.
Biodegradable options	PLGA, PLA can be used for injectable implants — no surgical removal needed.
Mucoadhesion	Polymers like Carbopol, Chitosan adhere to mucous membranes — prolonged contact time.
Biocompatibility	Generally well-tolerated, non-toxic, non-irritant in the body.
Versatility	Applicable across oral, topical, transdermal, parenteral, ocular, and nasal routes.
Tunable properties	Chemical modification, crosslinking, blending allows customization of release rate.

Application of Polymers in Controlled Release Drug Delivery

Oral Controlled Release Applications

Polymer	Application / Dosage Form	Examples of Products
HPMC (K4M, K15M, K100M)	Hydrophilic matrix tablets; extended-release core	Metformin SR, Theophylline CR
Ethyl Cellulose (EC)	Film coating of beads/pellets; hydrophobic matrix	Theo-Dur, Nitrospan
Eudragit L 100, S 100	Enteric coating; releases at pH > 6 or pH > 7	EC-coated Diclofenac, Mesalazine

Eudragit RS/RL	Extended-release membrane coating; water-insoluble but permeable	Paliperidone ER, Diltiazem SR
Sodium Alginate	Ionic gelation beads; mucoadhesive granules	Alginate microspheres
Chitosan	Mucoadhesive matrix; ion exchange systems; H-matrix tablets	Chitosan microspheres
Carbopol (Carbomer)	Mucoadhesive matrix; buccal tablets; hydrogels	Zilactin, buccal mucoadhesive tablets
PVP (Povidone)	Film former; binder; solid dispersion carrier	PVP-Itraconazole dispersions
Shellac (Lac resin)	Delayed-release enteric coating	Enteric-coated aspirin

Transdermal Drug Delivery Systems (TDDS)

- EVA (ethylene vinyl acetate): Rate-controlling membrane in reservoir patches.
  - Example: Nitroglycerin patch (Transderm-Nitro), Scopolamine patch (Transderm-Scop)
- Polyisobutylene (PIB): Pressure-sensitive adhesive layer in patches.
- Polyurethane: Backing membrane providing flexibility and water resistance.
- Acrylate copolymers: Drug-in-adhesive layer for matrix patches.
- Silicone polymers: Used in rate-controlling membrane of some patches.

Injectable / Parenteral Controlled Release

- **PLGA (Poly-lactide-co-glycolide):** Biodegradable microspheres for long-acting injectables.
  - Examples: Lupron Depot (leuprolide), Risperdal Consta (risperidone), Sandostatin LAR
- **PLA (polylactic acid):** Biodegradable rods/implants.
  - Example: Zoladex implant (goserelin acetate)
- **PCL (polycaprolactone):** Slow-degrading implant polymer.
  - Example: Capronor (levonorgestrel subdermal implant)
- **Polyanhydrides:** Used in wafer implants for brain tumors.
  - Example: Gliadel wafer (carmustine) — polyanhydride polymer

Ocular Drug Delivery

- **EVA:** Rate-controlling membrane in Ocusert (pilocarpine) ocular insert.

- Polyacrylic acid (Carbopol): Viscosity enhancer in eye drops for prolonged contact.
- Hyaluronic acid: Viscoelastic gel for intraocular use.
- Collagen shields: Biodegradable collagen used as drug reservoir in ocular delivery.

Nasal and Pulmonary Drug Delivery

- HPMC: Viscosity enhancer in nasal drops and sprays.
- Chitosan: Mucoadhesive polymer for nasal drug delivery (vaccine delivery).
- PLGA nanoparticles: For pulmonary delivery of proteins and peptides.

Vaginal / Intrauterine Drug Delivery

- Silicone elastomers: Ring-shaped vaginal rings for contraceptive delivery.
  - Example: NuvaRing (etonogestrel/ethinyl estradiol)
- Polyurethane: Used in some IUD designs.
- Polycarbophil: Bioadhesive gel base for vaginal drug delivery.

Commonly Used Polymers: Detailed Overview

Hydroxypropyl Methylcellulose (HPMC)

- Type: Semi-synthetic cellulose ether.
- Properties: Hydrophilic, swells in water to form gel; non-ionic; available in various viscosity grades.
- Mechanism: Forms gel barrier on tablet surface; drug diffuses through gel and gel erodes — combination of diffusion and erosion controls release.
- Viscosity grades: E5, E15, K4M, K15M, K100M — higher viscosity = slower release.
- Applications: Oral matrix tablets, film coating, mucoadhesive systems, eye drops, food additive.
- Commercial products: Methocel (Dow), Metolose (Shin-Etsu).

Ethyl Cellulose (EC)

- Type: Semi-synthetic hydrophobic cellulose ether.
- Properties: Water-insoluble, soluble in organic solvents; forms tough, flexible films.
- Mechanism: Acts as rate-controlling membrane in coated pellets/tablets; drug diffuses through pores in EC film.

- Tg: ~130°C; requires plasticizer (dibutyl sebacate, triethyl citrate) to form flexible films.
- Applications: Film coating of pellets, matrices, taste masking, microencapsulation.
- Commercial products: Ethocel (Dow), Aquacoat ECD (FMC, aqueous dispersion).

Eudragit Polymers (Polymethacrylates)

Eudragit is a registered trademark of Evonik (Röhm GmbH). These are acrylic copolymers with diverse applications.

Grade	Type	Solubility	Application
Eudragit L 100	Anionic (methacrylic acid + MA)	pH > 6	Enteric coating; small intestine release
Eudragit S 100	Anionic (methacrylic acid + MA)	pH > 7	Colon-specific release
Eudragit E 100	Cationic (dimethylaminoethyl MA)	pH < 5 (gastric)	Taste masking; gastric release
Eudragit RL 100	Quaternary ammonium (high perm.)	Insoluble but water-permeable	Extended-release membranes
Eudragit RS 100	Quaternary ammonium (low perm.)	Insoluble; low permeability	Extended-release membranes
Eudragit NE 30D	Neutral (ethyl acrylate + MA)	Insoluble; flexible	Extended-release coatings (no plasticizer needed)

Chitosan

- Type: Natural cationic polysaccharide; deacetylated form of chitin (derived from crustacean shells).
- Properties: Mucoadhesive, biodegradable, biocompatible, non-toxic, cationic charge at low pH.
- Mechanism: Forms ionic gelation with polyanions (tripolyphosphate); forms mucoadhesive matrices.
- Applications: Mucoadhesive drug delivery (nasal, vaginal, oral), nanoparticles, wound healing, vaccine delivery.
- Unique feature: Penetration enhancer — opens tight junctions in GI epithelium transiently.

Sodium Alginate

- Type: Natural anionic polysaccharide from brown seaweed (Laminaria sp.).
- Properties: Forms gel with Ca2+ ions; hydrophilic, biodegradable, biocompatible.
- Mechanism: Ionic gelation — Ca-alginate beads formed by dropping Na-alginate into CaCl2 solution.
- Applications: Oral beads/microspheres, wound dressings, dental impressions, food additive.
- Viscosity grades: Low, medium, high — determines gel strength and drug release.

PLGA (Poly-lactide-co-glycolide)

- Type: Synthetic biodegradable polyester.
- Properties: Degrades by hydrolysis to lactic acid and glycolic acid; biocompatible.
- Degradation rate: LA:GA ratio determines rate — more PGA = faster degradation.
  - 50:50 PLGA degrades in ~1 month; 75:25 PLGA degrades in ~3 months; 100% PLA in ~12 months
- Applications: Injectable microspheres, implants, nanoparticles, sutures.
- Products: Lupron Depot (leuprolide), Risperdal Consta, Gliadel wafer, Sandostatin LAR.

Carbopol (Carbomer / Polyacrylic Acid)

- Type: Synthetic crosslinked polyacrylic acid.
- Properties: Mucoadhesive, hydrophilic; forms highly viscous gels at low concentrations (0.5–2%).
- pH-dependent viscosity: Carbopol dispersions show maximum viscosity at pH 6–11.
- Applications: Topical/ophthalmic gels, mucoadhesive buccal/vaginal formulations, rectal gels.
- Common grades: Carbopol 934P, 971P, 974P (pharmaceutical grades).

Polymer	Source	Feature	Main Application in CDDS
HPMC	Semi-synthetic (cellulose)	Gel-forming, hydrophilic	Oral matrix tablets
Ethyl Cellulose	Semi-synthetic (cellulose)	Hydrophobic film former	Coated pellets/beads

Eudragit L/S	Synthetic	pH-dependent dissolution	Enteric/colon delivery
Eudragit RS/RL	Synthetic	Permeable, insoluble membrane	Oral ER coating
Chitosan	Natural (chitin)	Mucoadhesive, cationic	Mucoadhesive/nasal delivery
Sodium Alginate	Natural (seaweed)	Ionic gelation with Ca2+	Oral beads/microspheres
PLGA	Synthetic (biodegradable)	Hydrolytic degradation	Injectable microspheres/implants
Carbopol	Synthetic (crosslinked PAA)	High mucoadhesion, gel former	Topical/mucoadhesive gels
PVP	Synthetic	Film former, solubilizer	Solid dispersions, film coating
EVA	Synthetic	Flexible, rate-controlling	Transdermal patches, implants

🎓📄 Thank You for Reading! 📄🎓

🎧 We hope this book helped you in your studies.

If you want to access 📚 complete notes, 📂 PDFs, and 📖 study material for your course, scan the QR code below. 🚀

📲✨ Scan & Download All Notes ✨📲

👉 **What You'll Get:**

- 📄 B.Pharm & D.Pharm Notes
- 📝 Exam-Oriented PDF Materials
- 🔔 Regular Updates & New Content

✨📣 Stay Connected for More Updates 📣✨

🌐 **Visit: https://noteskarts.com/**

📧 Contact: noteskartsconnect@gmail.com

✔ One Scan = 📲 All Notes at Your Fingertips! 🎯