Unit-2

Novel Drug Delivery Systems

B.Pharma 7 Sem Notes

Unit: 2

Microencapsulation:

Definition, advantages and disadvantages, microspheres/microcapsules, microparticles, methods of microencapsulation, applications

Mucosal Drug Delivery system:

Introduction, Principles of bioadhesion /mucoadhesion, concepts, advantages and disadvantages, transmucosal permeability and formulation considerations of buccal delivery systems

Implantable Drug Delivery Systems:

Introduction, advantages and disadvantages, concept of implantsand osmotic pump

MICROENCAPSULATION

Definition of Microencapsulation

Microencapsulation is a technology by which solid particles, liquid droplets, or gases are enclosed within a thin wall of coating material (shell/membrane) to form small capsules called microcapsules or microspheres, generally ranging from 1 to 1000 micrometers (1 µm – 1 mm) in diameter.

📌 **Key Point:** Microencapsulation = Process of enclosing a core material (drug) within a shell material (polymer/coating) to produce microparticles of 1–1000 µm diameter.

Definitions

Term	Definition
Microcapsule	A miniature capsule with a distinct wall (membrane) surrounding the core drug material.
Microsphere	A matrix system where drug is dispersed or dissolved uniformly throughout the polymer matrix without a distinct membrane.
Microparticle	General term for both microcapsules and microspheres with particle size 1–1000 µm.
Core material	The substance to be encapsulated (drug, enzyme, liquid, gas, or solid).
Shell/Wall material	The coating polymer that surrounds the core (gelatin, HPMC, wax, Eudragit, PLGA, etc.).
Nanoparticle	Similar to microparticles but size < 1 µm (100–1000 nm); nanoscale drug delivery.
Coating efficiency	Percentage of core material successfully enclosed within the shell material.
Loading efficiency	Amount of drug incorporated in microcapsules relative to the total drug used.
Encapsulation efficiency	(Actual drug content / Theoretical drug content) × 100%

Advantages and Disadvantages of Microencapsulation

Advantages

Advantage	Explanation / Example
Controlled drug release	Shell controls rate and site of drug release; achieves zero/first-order kinetics.
Taste and odor masking	Coating masks bitter/unpleasant taste of drugs like Chloramphenicol, Potassium chloride.
Protection of drug	Shields drug from moisture, oxygen, light, and GI acid/enzymes (e.g., peptide drugs).
Improved stability	Reduces degradation of labile drugs; increases shelf life.
Conversion of liquid to solid	Oils and liquid drugs (e.g., fish oil, volatile oils) converted to free-flowing powders.
Reduced GI irritation	Gradual release reduces local drug concentration; e.g., aspirin microspheres vs. plain aspirin.
Separation of incompatible components	Two incompatible drugs/excipients can be encapsulated separately in same dosage form.
Site-specific delivery	Enteric-coated microcapsules deliver drug to intestine/colon; pH-sensitive shells used.
Improved patient compliance	Taste-masked, once-daily controlled-release systems improve adherence.
Reduced dose frequency	Controlled release from microspheres reduces dosing from multiple times to once daily.
Targeted delivery	Magnetic microspheres and bioadhesive microspheres enable targeted drug delivery.

Disadvantages

Disadvantage	Explanation
High cost	Specialized equipment, polymers, and processes make manufacturing expensive.
Complex technology	Scale-up from lab to industrial scale is technically challenging.
Limited drug loading	High drug loading may compromise integrity of shell and affect release.
Poor encapsulation efficiency	Small molecules and water-soluble drugs may leak through walls.

Regulatory challenges	Novel materials and processes require extensive validation and approval.
Risk of dose dumping	Mechanical damage to microcapsule shell can release entire dose at once.
In vitro–in vivo correlation	Difficult to establish IVIVC for complex microencapsulated products.
Particle agglomeration	Microcapsules may aggregate during storage — requires anti-caking agents.
Not suitable for all drugs	Very high dose drugs, NTI drugs, or extensively metabolized drugs may not benefit.

Microspheres vs. Microcapsules vs. Microparticles

Feature	Microsphere	Microcapsule
Structure	Matrix system — drug uniformly dispersed in polymer	Reservoir system — drug core surrounded by distinct polymer shell
Membrane	No distinct membrane; drug in polymer matrix	Distinct wall/membrane surrounds drug core
Drug release	Diffusion through matrix; erosion-controlled	Diffusion through membrane; membrane controls rate
Drug distribution	Homogeneous throughout the matrix	Core-shell arrangement; drug concentrated in center
Release kinetics	First-order or Higuchi model	Zero-order (reservoir = predictable constant rate)
Examples	PLGA microspheres (Lupron Depot)	Spansule beads, gelatin microcapsules
Dose dumping risk	Lower — matrix erodes gradually	Higher — shell rupture releases all drug at once
Manufacturing	Simpler (emulsion-solvent evaporation)	More complex (coacervation, interfacial polymerization)

📌 **Key Point:** Microparticles is the umbrella term encompassing both microspheres and microcapsules with sizes between 1–1000 µm.

Types Based on Size

Size Range	Name	Examples
< 1 µm (100–1000 nm)	Nanoparticles / Nanocapsules	Albumin nanoparticles, PLGA nanoparticles
1–1000 µm	Microparticles (Microspheres / Microcapsules)	PLGA microspheres, gelatin microcapsules
> 1000 µm (> 1 mm)	Macroparticles / Pellets	Compressed pellets, wax pellets

Methods of Microencapsulation

Microencapsulation can be achieved by various physical, chemical, and physicochemical methods. The choice of method depends on the physicochemical properties of core and wall materials, desired particle size, and intended application.

Physicochemical Methods

Coacervation / Phase Separation

Coacervation is the most widely used method for microencapsulation. It involves separation of a polymer-rich phase (coacervate) from the solution, which deposits around the core material.

- Two types of coacervation:
  - Simple coacervation: Uses one polymer; phase separation induced by adding salt, non-solvent, or temperature change.
  - Complex coacervation: Uses two oppositely charged polymers (e.g., gelatin + gum arabic); electrostatic interaction causes phase separation.
- Steps in coacervation process:
  - Step 1: Core material dispersed/emulsified in polymer solution.
  - Step 2: Coacervate phase is induced (by salting out, pH change, temperature change, or non-solvent addition).
  - Step 3: Coacervate deposits around core forming liquid shell.
  - Step 4: Shell is solidified by crosslinking (glutaraldehyde), cooling, or drying.
  - Step 5: Microcapsules are collected, washed, and dried.

- Wall materials: Gelatin, gum arabic, CAP (cellulose acetate phthalate), ethyl cellulose.
- Applications: Encapsulation of oils, vitamins, flavors, pharmaceuticals.
- Advantages: Applicable to both water-soluble and oil-soluble core materials.

Solvent Evaporation / Emulsion Solvent Evaporation

The most commonly used method for pharmaceutical microspheres, especially biodegradable PLGA microspheres.

- Process (for hydrophobic drugs — O/W emulsion):
  - Step 1: Drug + polymer (PLGA) dissolved in organic solvent (DCM, EtOAc, acetone).
  - Step 2: Organic phase emulsified in aqueous PVA solution — forms O/W emulsion.
  - Step 3: Organic solvent evaporated under vacuum or stirring.
  - Step 4: Microspheres harden as solvent evaporates; collected by filtration/centrifugation.
  - Step 5: Washed and lyophilized (freeze-dried).
- For hydrophilic drugs: W/O/W double emulsion method is used.
- Key variables: Stirring speed, PVA concentration, polymer:drug ratio, solvent type, temperature.
- Wall materials: PLGA, PLA, PCL, EC, Eudragit.
- Applications: PLGA microspheres for parenteral controlled release (Lupron Depot, Risperdal Consta).
- Advantage: Simple, scalable, widely used; suitable for peptides and proteins.

Spray Drying

- Liquid feed (drug + polymer solution or suspension) is atomized into hot drying chamber.
- Solvent rapidly evaporates; dry microspheres/microcapsules form.
- Process steps: Feed preparation → Atomization → Drying → Separation.
- Wall materials: HPMC, EC, lactose, PVP, gelatin, starch.

- Advantages: Rapid, continuous process; suitable for heat-stable compounds; good yield.
- Disadvantages: High temperature may degrade heat-sensitive drugs; requires expensive equipment.
- Applications: Inhalation microparticles, taste-masked granules, reconstitutable powders.

Spray Congealing (Spray Chilling)

- Similar to spray drying but uses wax/lipid as wall material that congeals on cooling.
- Molten lipid + drug is atomized into cool chamber — lipid solidifies to form microspheres.
- Wall materials: Beeswax, carnauba wax, hydrogenated castor oil, glyceryl monostearate.
- Advantages: No solvents needed; suitable for water-sensitive drugs.
- Applications: Taste masking, sustained-release granules, vitamin encapsulation.

Chemical Methods

Interfacial Polymerization

- Monomer in organic phase reacts with monomer in aqueous phase at the interface to form polymer shell.
- Core (usually liquid/aqueous drug solution) is dispersed in organic phase.
- Monomers polymerize spontaneously at the O/W interface — forming thin, tough membrane.
- Examples: Polyamide (nylon), polyurethane, polyurea capsule walls.
- Applications: Encapsulation of aqueous solutions of drugs, insecticides, dyes.
- Advantage: Very thin, uniform membranes; fast process.
- Disadvantage: Residual monomers may be toxic.

In-situ Polymerization

- Monomer present only in the continuous phase (not in both phases like interfacial polymerization).
- Monomer diffuses to the surface of dispersed core droplets and polymerizes there.
- Example: Urea-formaldehyde microcapsules (carbonless paper technology).
- Applications: Industrial encapsulation (fragrance, adhesive, agricultural).

Physical / Mechanical Methods

Pan Coating

- Oldest method; widely used for tablets and pellets.
- Core particles/tablets are tumbled in a rotating pan while coating solution is sprayed.
- Air flow dries the coating — layer builds up gradually.
- Suitable for: Sugar coating, film coating, enteric coating of pellets.
- Wall materials: Shellac, CAP, HPMC, Eudragit.
- Advantage: Well-established, simple, good control.
- Disadvantage: Slow; not suitable for very small particles (<100 µm).

Fluidized Bed Coating (Air Suspension / Wurster Process)

- Core particles are suspended in an upward-moving stream of air (fluidized).
- Coating solution sprayed from the bottom (Wurster) or top onto suspended particles.
- Uniform, thin coatings produced on small particles (50–5000 µm).
- Wall materials: HPMC, EC, Eudragit, PVP, shellac.
- Applications: Enteric-coated pellets, sustained-release granules, taste-masked particles.
- Advantages: Uniform coating, applicable to small particles, continuous process.

Electrostatic Deposition

- Charged polymer particles deposited onto oppositely charged core material using electrostatic forces.
- Produces thin, uniform polymer coatings without solvents.
- Applications: Specialty encapsulation; pharmaceutical dry powder coatings.

Extrusion / Centrifugal Extrusion

- Core material extruded through nozzle co-axially with shell material — forms concentric droplets.
- Droplets hardened by cooling, crosslinking, or solvent removal.
- Suitable for: Liquid core materials (oils, flavors).
- Advantage: Controlled particle size and shell thickness.

Summary of Microencapsulation Methods

Method	Principle	Wall Material	Application
Complex Coacervation	Electrostatic interaction of two polymers	Gelatin + Gum arabic	Oils, vitamins, pharma
Simple Coacervation	Salting out / temperature change	Gelatin, EC	Oil encapsulation
Solvent Evaporation (O/W)	Solvent removed from emulsion; polymer hardens	PLGA, PLA, EC	Parenteral microspheres
Double Emulsion (W/O/W)	Aqueous drug in inner phase	PLGA, PLA	Peptides, proteins
Spray Drying	Atomization + hot-air drying	HPMC, PVP, Lactose	Inhalation, oral
Spray Congealing	Atomization + cooling congelation	Beeswax, wax	SR granules, taste mask
Interfacial Polymerization	Reaction at O/W interface	Polyamide, polyurea	Aqueous drug solutions
Pan Coating	Spray coating in rotating pan	Shellac, CAP, Eudragit	Tablets, pellets
Fluidized Bed (Wurster)	Coating of fluidized particles	HPMC, EC, Eudragit	Pellets, granules
In-situ Polymerization	Monomer diffusion + polymerization	Urea-formaldehyde	Industrial use

Applications of Microencapsulation

Pharmaceutical Applications

Application	Example
Controlled/Sustained drug release	PLGA microspheres: Lupron Depot (leuprolide), Risperdal Consta (risperidone)
Enteric drug delivery	Enteric-coated microspheres of Omeprazole, Diclofenac sodium
Taste and odor masking	Chloramphenicol palmitate microcapsules, Potassium chloride, Erythromycin
Parenteral depot formulations	Sandostatin LAR (octreotide), Vivitrol (naltrexone)
Inhalation delivery	Budesonide DPI microspheres, salbutamol inhaler particles
Targeted drug delivery	Magnetic microspheres, hepatocyte-targeted galactosylated microspheres
Cell and enzyme encapsulation	Pancreatic islet cell encapsulation for diabetes treatment
Vaccine delivery	Antigen-loaded PLGA microspheres for single-shot vaccination
Topical drug delivery	Microcapsules in creams for skin drug delivery (retinol, hydrocortisone)

Non-Pharmaceutical Applications

- Food industry: Encapsulation of vitamins, flavors, fish oil, probiotics, sweeteners.
- Cosmetics: Encapsulation of perfumes, retinol, skin-active ingredients in creams.
- Agriculture: Pesticide/herbicide encapsulation for slow, targeted release.
- Carbonless copy paper: Pressure-rupture microcapsules containing dye precursors.
- Textile industry: Phase-change materials encapsulated in fabrics for temperature regulation.
- Biotechnology: Encapsulation of microorganisms, enzymes, cells for bioreactors.

MUCOSAL DRUG DELIVERY SYSTEMS

Introduction to Mucosal Drug Delivery Systems

Mucosal drug delivery refers to the administration of drugs via mucosal membranes lining various body cavities and organ surfaces. Mucosal surfaces are moist, vascularized, and have large surface areas — making them ideal routes for systemic as well as local drug delivery.

Mucosal Route	Location	Examples
Buccal / Sublingual	Oral cavity (cheek, under tongue)	Buccal tablets, sublingual films/tablets
Nasal	Nasal cavity (nasal mucosa)	Nasal sprays, nasal gels, insufflators
Rectal	Rectum and lower colon	Suppositories, rectal gels, enemas
Vaginal	Vaginal mucosa	Vaginal tablets, rings, gels, creams
Ocular	Conjunctival and corneal mucosa	Eye drops, inserts, ocular gels
Pulmonary	Bronchial and alveolar mucosa	Inhalers (MDI, DPI), nebulizers

📌 **Key Point:** The oral mucosa is the most accessible mucosal surface for drug delivery and is the focus of buccal drug delivery systems.

Principles of Bioadhesion and Mucoadhesion

Bioadhesion is the ability of a material to adhere to biological tissue surfaces. When adhesion occurs specifically to the mucous membrane (mucus layer), it is called mucoadhesion.

Definitions

Term	Definition
Bioadhesion	Adhesion between a synthetic or biological material and a biological tissue (skin, mucosa, hard tissue).
Mucoadhesion	Specific form of bioadhesion involving adhesion to the mucous coat of a mucosal tissue.

Mucoadhesive drug delivery	Drug delivery system that exploits mucoadhesion to prolong contact time with mucosal surface.
Mucus	Viscoelastic glycoprotein gel secreted by goblet cells; contains mucin (glycoprotein), water (95%), lipids, electrolytes.
Mucin	High molecular weight glycoprotein (0.5–40 MDa); main structural component of mucus; provides anionic charge at physiological pH.
Bioadhesive strength	Force required to detach a bioadhesive material from the biological substrate.

Theories of Mucoadhesion

Several theories have been proposed to explain the mechanism of mucoadhesion:

Electronic Theory

- Mucoadhesive material and mucus layer have different electronic charges.
- Electron transfer occurs between the two surfaces forming an electrical double layer.
- Adhesive forces arise from electrostatic attraction between surfaces at the interface.
- Limitation: Does not fully explain mucoadhesion in all systems.

Adsorption Theory

- Surface adhesion due to secondary forces: van der Waals forces, electrostatic forces, hydrogen bonding, hydrophobic interactions.
- Mucoadhesive polymer functional groups (–COOH, –OH, –NH2) interact with mucin functional groups (–COOH, –OH, –SO4H, –NH2).
- Most accepted theory for mucoadhesive polymers.

Wetting Theory

- Applicable to liquids and spreadable systems (gels, ointments).
- Spreading coefficient determines whether mucoadhesive will spread on the mucosal surface.
- Contact angle and work of adhesion measured by wettability experiments.

Diffusion Theory (Interpenetration Theory)

- Most widely accepted theory for polymer-based mucoadhesive systems.
- Mucoadhesive polymer chains interpenetrate and entangle with mucin chains.

- Depth of interpenetration depends on diffusion coefficient, contact time, flexibility of polymer chains, MW, and concentration.
- Greater interpenetration = stronger mucoadhesion.
- Mucoadhesive polymers must have flexible chains, appropriate MW, and free –OH and –COOH groups.

Fracture Theory

- Analyzes force required to separate two surfaces after mucoadhesion.
- Adhesive strength = maximum tensile stress at point of fracture.
- Useful for measuring/comparing mucoadhesive strength of different polymers.

Mechanical Theory

- Adhesion due to mechanical interlocking of adhesive material into surface irregularities of mucosa.
- Porous surfaces show stronger mucoadhesion by mechanical interlocking.

Stages of Mucoadhesion

Stage	Description
Contact Stage	Physical contact between mucoadhesive formulation and mucosal surface.
Consolidation Stage	Moisture activates mucoadhesive material, chains become mobile, interpenetration begins.
Entanglement Stage	Polymer chains diffuse into and entangle with mucin network — adhesive bond formed.
Adhesion Stage	Stable mucoadhesive bond maintained; drug is released from formulation.
Detachment Stage	Bond weakens over time due to mucus turnover, dilution, or mechanical forces.

Factors Affecting Mucoadhesion

Polymer-Related Factors

- Molecular weight: Higher MW = more chain entanglement = stronger adhesion. Optimum MW ~100,000–4,000,000 Da.
- Flexibility of polymer chains: More flexible chains interpenetrate deeper into mucus.
- Concentration: Optimal concentration gives maximum adhesion; too high concentration may reduce adhesion (chains fold back).

- Hydration: Water swells polymer chains, allowing mobility and interpenetration. Over-hydration reduces adhesion (forms slippery gel).
- Functional groups: –COOH, –OH, –NH2, –SO3H groups participate in hydrogen bonding with mucin.
- Spatial configuration: Linear chains interpenetrate better than branched chains.

Environmental Factors

- pH: Affects ionization of both polymer and mucin. Most mucoadhesive polymers (carbopol, HPMC) are optimally adhesive at pH 5–7.
- Mucus layer thickness: Thick mucus (stomach, small intestine) provides more chains for entanglement.
- Mucus turnover rate: Fast turnover (stomach) reduces residence time of mucoadhesive systems.
- Disease state: Inflammation, disease alter mucus composition and viscosity.

Mucoadhesive Polymers (Classification)

Category	Polymer	Feature
First generation (non-covalent)	Carbopol (PAA), Na-CMC, HPMC, Chitosan, Sodium Alginate, Hyaluronic acid	Hydrogen bonding, ionic interaction with mucin
Second generation (covalent)	Thiolated polymers (Chitosan-TBA, PAA-cysteine)	Form covalent disulfide bonds with cysteine-rich mucin — superior adhesion
Lectins	Wheat germ agglutinin (WGA), Tomato lectin	Specific binding to glycan moieties of mucin — targeted adhesion
Invasomes / Cell-penetrating	Polycationic polymers (Chitosan)	Tight junction opening, paracellular transport

Concepts in Mucosal Drug Delivery

Mucoadhesion vs. Bioadhesion

- Bioadhesion is the broader term (adhesion to any biological surface).
- Mucoadhesion specifically refers to adhesion to mucus-coated surfaces.
- Mucoadhesion is reversible — mucus is continually secreted and shed (turnover every 4–6 hours in GI tract).
- For effective delivery, mucoadhesive formulation must adhere longer than mucus turnover time.

First and Second Generation Mucoadhesive Systems

Generation	Mechanism	Examples	Limitation
First Generation	Non-covalent bonds: hydrogen bonding, electrostatic, van der Waals	Carbopol, HPMC, CMC, Chitosan, alginate	Reversible; limited adhesion time; mucus turnover limits residence
Second Generation (Thiomers)	Covalent disulfide bonds between thiol groups of polymer and cysteine in mucin	Chitosan-TBA, PAA-cysteine, PVP-cysteine	Much stronger and prolonged adhesion; better drug permeation

Transmucosal Absorption Pathways

Pathway	Description	Drug type
Transcellular (through cells)	Drug passes through epithelial cell membranes — passive or active transport	Lipophilic drugs; moderate permeability
Paracellular (between cells)	Drug passes through tight junctions between cells	Small hydrophilic drugs; penetration enhancers open TJs
Endocytosis	Vesicular uptake of drug — pinocytosis or receptor-mediated	Proteins, peptides, nanoparticles
Carrier-mediated	Active transport via specific membrane transporters	Amino acid-like structures, nucleosides

Advantages and Disadvantages of Mucosal Drug Delivery

Advantages

Advantage	Explanation
Bypass first-pass metabolism	Drug absorbed via buccal/sublingual mucosa enters systemic circulation directly — avoiding hepatic first-pass effect.
Rapid onset of action	Sublingual route provides faster absorption than oral route (e.g., Nitroglycerin).
Avoidance of GI degradation	Drugs unstable in GI (peptides, proteins) can be delivered via nasal, buccal, or rectal routes.
Non-invasive	Avoids needles/injections; patient-friendly and suitable for self-administration.

Easy drug withdrawal	Formulation can be removed from mucosa if necessary (e.g., buccal patches).
Improved bioavailability	Avoids pre-systemic degradation; higher bioavailability than oral for many drugs.
Site-specific action	Local mucosal conditions (ulcers, infection) treated locally with topical mucosal formulations.
Extended drug contact time	Mucoadhesive systems prolong contact with mucosa for extended drug absorption.
Suitable for unconscious patients	Nasal, rectal, and buccal routes usable when patient cannot swallow.
Permeation enhancers applicable	Absorption can be enhanced by safe chemical enhancers.

Disadvantages

Disadvantage	Explanation
Mucosal irritation	Some drugs and excipients may cause local irritation or inflammation of mucosa.
Limited drug loading	Small surface area limits dose size — not suitable for high-dose drugs.
Swallowing reflex	Patients may inadvertently swallow buccal formulations — reducing efficacy.
Mucus barrier	Mucus is a physical and biochemical barrier — reduces drug diffusion to epithelium.
Enzymatic degradation	Aminopeptidases, esterases in mucosal tissue degrade peptides and proteins.
Variable permeability	Mucosal permeability varies with disease state, age, and individual differences.
Taste and comfort	Some buccal formulations may have unpleasant taste or cause discomfort.
Mucus turnover	Rapid mucus clearance limits residence time of mucoadhesive systems.
Not all drugs suitable	Highly irritating, large molecules, or highly lipophilic drugs poorly absorbed mucosally.

Transmucosal Permeability

Transmucosal permeability refers to the ability of a drug to permeate across the mucosal epithelium into the systemic circulation. Permeability determines bioavailability via mucosal routes.

Factors Governing Transmucosal Permeability

Physicochemical Properties of Drug

- Lipophilicity (Log P): Lipophilic drugs permeate transcellularly more easily. Optimal Log P = 1–3 for buccal absorption.
- Molecular weight: Low MW (<500 Da) drugs permeate more readily.
- Ionization (pKa): Unionized form permeates better. pH of mucosal environment determines fraction unionized.
- Molecular size and shape: Smaller, compact molecules permeate faster.

Mucosa-Related Factors

- Thickness of mucosa:
  - Sublingual: 100–200 µm — thinnest, fastest absorption.
  - Buccal: 500–800 µm — thicker, slower but sustained absorption.
  - Gingival: 200 µm — keratinized, less permeable.
- Degree of keratinization: Non-keratinized mucosa (buccal, sublingual, ventral tongue) more permeable than keratinized (palate, gingiva).
- Blood flow: Rich vascular supply (sublingual > buccal) enhances drug absorption.
- Salivary pH and flow: Saliva (pH 6.2–7.4) affects drug ionization; high flow dilutes drug.
- Mucus thickness and composition: Acts as diffusion barrier; enzyme content affects drug stability.

Enhancement of Transmucosal Permeability

Chemical Permeation Enhancers

Category	Examples	Mechanism
Fatty acids and esters	Oleic acid, Sodium caprate, Lauric acid	Fluidize lipid bilayer of cell membrane
Surfactants	Sodium lauryl sulfate (SLS), Polysorbate 80	Disrupt membrane integrity; increase permeability
Bile salts	Sodium deoxycholate, Sodium glycocholate	Disrupt tight junctions; increase paracellular transport
Chelating agents	EDTA, Citric acid	Bind Ca^{2+} → open tight junctions → paracellular transport
Polymers (mucoadhesive)	Chitosan, Polycarbophil	Open tight junctions; increase paracellular drug permeation

Cyclodextrins	HP-β-CD, methyl-β-CD	Enhance drug solubility and membrane partitioning
Azone (Laurocapram)	Azone (1-dodecylazacycloheptan-2-one)	Fluidizes intercellular lipids; enhances transcellular transport

Physical Enhancement Methods

- Iontophoresis: Application of low electric current drives ionized drug through mucosa.
- Electroporation: Brief high-voltage pulses create transient pores in mucosa.
- Microneedles: Micrometer-scale needles create micropores without pain.
- Ultrasound (Sonophoresis): Low-frequency ultrasound enhances mucosal permeability.

Buccal Drug Delivery Systems

The buccal route utilizes the mucosa of the inner cheek (buccal mucosa) for drug administration. The buccal mucosa is non-keratinized, has good vascular supply, is accessible, and allows controlled drug delivery.

Anatomy of Buccal Mucosa

- Buccal mucosa lines the inner surface of cheeks.
- Area: ~50 cm2 (total oral mucosal area ~170 cm2; buccal ~50 cm2; sublingual ~26 cm2).
- Epithelium: Non-keratinized stratified squamous epithelium — 40–50 cell layers.
- Thickness: ~500–800 µm.
- Blood supply: Buccal artery — rich vascular supply ensures rapid systemic absorption.
- Salivary glands: Parotid gland duct opens near upper second molar — provides salivary flow.
- Permeability order: Sublingual > Buccal > Palatal > Gingival.

Formulation Considerations for Buccal Delivery

Bioadhesive Polymers (Must-have ingredient)

- Must adhere to buccal mucosa for prolonged time.

- Commonly used: Carbopol 934P, HPMC K4M/K15M, HPC, Na-CMC, Chitosan, Polycarbophil, Hyaluronic acid.
- Polymer concentration, MW, and functional groups determine adhesion strength.

Permeation Enhancers

- Required for drugs with poor buccal permeability.
- Examples: Sodium glycocholate, SLS, EDTA, fatty acids, azone, chitosan (also mucoadhesive).
- Must be safe for repeated mucosal exposure; should be reversible.

Drug Solubility and Partition

- Drug must dissolve in salivary fluid and partition into buccal epithelium.
- Optimal Log P: 1–3 for passive transcellular transport.
- Hydrophilic drugs: Use paracellular pathway + permeation enhancers.

pH and Buffering

- Saliva pH: 6.2–7.4. Formulation should be buffered to maintain desired pH.
- pH affects degree of ionization and permeability of drug.
- Acidic pH (5–6): May be optimal for basic drugs (unionized at this pH).
- Buffering agents: Citrate buffer, phosphate buffer.

Enzyme Inhibitors

- Buccal mucosa contains aminopeptidases, esterases, and cytochrome P450 enzymes.
- Enzyme inhibitors protect peptide/protein drugs from presystemic degradation.
- Examples: Aprotinin (protease inhibitor), Bestatin (aminopeptidase inhibitor).

Plasticizers

- Required in film/patch formulations to improve flexibility and adhesion.
- Examples: Glycerol, propylene glycol, polyethylene glycol (PEG 400), triethyl citrate.

Types of Buccal Drug Delivery Formulations

Dosage Form	Description	Example Drug / Product
Buccal tablets	Bioadhesive tablet placed against buccal mucosa; releases drug for 4–8 hours	Prochlorperazine (Buccastem), Nitroglycerine
Buccal films / patches	Thin flexible patch placed on buccal mucosa; unidirectional or bidirectional release	Onsolis (fentanyl buccal film), Suboxone film
Buccal gels	Mucoadhesive gel applied to buccal mucosa; conforms to surface	Aphthous ulcer gels (Orabase, Kenalog)
Buccal lozenges	Drug-containing lozenge that releases drug slowly as it dissolves	Nicotine lozenges, antiseptic lozenges
Mucoadhesive discs	Disc-shaped bioadhesive systems; one surface releases drug, other surface is impermeable	Pilocarpine disc, estradiol buccal disc
Sublingual tablets	Dissolve under tongue; rapid drug absorption (< 5 min)	Nitroglycerin SL, Buprenorphine SL
Chewing gum	Drug released on chewing; absorbed through buccal mucosa	Nicotine gum (Nicorette), aspirin gum

Design Considerations for Buccal Patches/Films

- Backing membrane: Impermeable layer (ethyl cellulose, Eudragit RL) prevents drug loss to saliva side.
- Drug-containing layer: Mucoadhesive polymer + drug (e.g., Carbopol + HPMC + drug).
- Membrane-controlled release: Optional rate-controlling membrane between drug layer and mucosa.
- Unidirectional vs. bidirectional systems:
  - Unidirectional (preferred): Backing layer prevents drug loss to oral cavity; all drug directed toward mucosa.
  - Bidirectional: Drug released from both surfaces — higher salivary loss.
- Key evaluation parameters: Mucoadhesive strength, swelling index, surface pH, drug content uniformity, in vitro release, ex vivo permeation.

⚠ **Important:** For buccal delivery: Always include backing membrane for unidirectional drug release to reduce salivary drug loss and improve bioavailability.

IMPLANTABLE DRUG DELIVERY SYSTEMS

Introduction to Implantable Drug Delivery Systems

Implantable drug delivery systems (IDDS) are devices surgically placed under the skin or within a body cavity to deliver drugs at a controlled rate for an extended period ranging from weeks to years. They provide sustained systemic or local drug action without the need for repeated injections or oral dosing.

📌 **Key Point:** Implantable drug delivery systems = Devices placed inside the body by surgical or minimally invasive means to release drug at a controlled rate over extended periods (months to years).

Historical Background

- 1964: First silicone implant reported by Folkman and Long for sustained drug release.
- 1966: Subdermal silicone implants for contraception explored.
- 1983: Norplant (levonorgestrel subdermal implant) developed.
- 1990: Rose implants for cancer treatment introduced.
- 2000s onwards: PLGA-based biodegradable implants; Gliadel wafer for glioblastoma.
- Present: Osmotic pumps (ALZET), biosensor-integrated smart implants.

Routes of Implantation

Route	Site	Example
Subcutaneous	Under the skin (arm, abdomen, hip)	Norplant, Implanon, insulin implants
Intramuscular	Within muscle tissue	Drug-loaded biodegradable rods
Intraocular	Within the eye (vitreous cavity)	Vitrasert (ganciclovir), Ozurdex (dexamethasone)
Intracranial / Intracerebral	Brain parenchyma	Gliadel wafer (carmustine — brain tumor)
Intravaginal	Vaginal cavity (non-surgical)	NuvaRing (vaginal ring)
Intra-articular	Synovial joint space	Corticosteroid depot for arthritis

Intravascular	Blood vessel wall	Drug-eluting stents (sirolimus, paclitaxel)

Advantages and Disadvantages of Implantable Drug Delivery

Advantages

Advantage	Explanation
Extended drug release	Single implant can release drug for months to years — eliminating daily dosing.
Improved patient compliance	Patient does not need to remember to take medication; removes human error.
Bypass GI degradation	Drugs unstable in GI tract (peptides, proteins) delivered without oral dosing.
Bypass first-pass metabolism	No hepatic first-pass effect; higher and more consistent bioavailability.
Zero-order release possible	Osmotic pumps and membrane-controlled implants can deliver at constant zero-order rate.
Local drug delivery	Drugs delivered directly to target site (brain, eye, joint) at high local concentration.
Avoidance of peak-trough fluctuations	Steady-state plasma levels maintained.
Reversibility (some types)	Implants like Norplant can be removed; drug effect stops immediately.
Reduced total drug dose	Efficient delivery reduces total amount needed vs. oral/IV therapy.
Suitable for low-dose drugs	Very potent drugs (hormones, cancer drugs) can be incorporated in small implants.

Disadvantages

Disadvantage	Explanation

Surgical procedure required	Implantation and removal (for non-biodegradable) require surgical interventions.
Risk of infection	Surgical insertion creates risk of wound infection.
Local tissue reaction	Implant materials may cause inflammation, fibrosis, or foreign body reaction.
Irreversibility (some types)	Biodegradable implants cannot be removed once placed; cannot stop therapy rapidly.
High cost	Implants are expensive to manufacture; surgical cost adds to therapy cost.
Drug loading limitation	Small implant size limits total amount of drug that can be incorporated.
Difficult dose adjustment	Cannot easily increase or decrease dose once implanted.
Device failure risk	Mechanical failure of pump/device can cause dose dumping or cessation of therapy.
Limited to potent drugs	Only low-dose, highly potent drugs can be delivered by implants of practical size.
Patient acceptance	Some patients reluctant to have surgical procedure for a drug delivery device.

Concept of Implants

Implants are solid or semisolid dosage forms intended for subcutaneous, intramuscular, or intraperitoneal implantation into the body. They release drug over extended periods through diffusion, erosion, or osmosis.

Classification of Implants

Basis	Type	Examples
Biodegradability	Biodegradable (bio-erodible)	PLGA rods, PLA wafers, Zoladex, Gliadel
Biodegradability	Non-biodegradable (inert)	Silicone rods, EVA implants, Norplant, Implanon
Release mechanism	Diffusion-controlled	Silicone implants (Norplant), EVA implants
Release mechanism	Erosion-controlled	PLGA rods — erosion rate controls release
Release mechanism	Osmotic pressure-controlled	ALZET osmotic pump, DUROS implant
Shape/Form	Rods / cylinders	Norplant, Implanon, Zoladex

Shape/Form	Discs / wafers	Gliadel wafer (carmustine)
Shape/Form	Pellets	Testosterone pellets (Testopel)
Shape/Form	Rings	NuvaRing (vaginal — not truly implanted)
Location	Subdermal	Contraceptive implants, drug depot rods
Location	Intraocular	Vitrasert, Ozurdex implants
Location	Intracranial	Gliadel wafer for glioblastoma

Non-Biodegradable Implants

Silicone Rubber Implants

- Polydimethylsiloxane (PDMS) — biocompatible, flexible, permeable to lipophilic drugs.
- Drug diffuses through silicone membrane at constant rate.
- Release rate proportional to membrane thickness and drug solubility in silicone.
- Examples:
  - Norplant: 6 silicone rubber rods containing levonorgestrel; subcutaneous arm implant; 5-year contraception.
  - Capronor: Polycaprolactone (biodegradable) rod with levonorgestrel.
  - Progestasert: T-shaped IUD containing progesterone in silicone oil — releases for 1 year.

EVA (Ethylene Vinyl Acetate) Implants

- EVA copolymer with tunable drug permeability based on vinyl acetate content.
- Higher vinyl acetate content = more hydrophilic = higher drug permeability.
- Drug loaded in EVA matrix or as reservoir with EVA membrane.
- Example: Implanon/Nexplanon — single EVA rod with etonogestrel; 3-year contraception.

Biodegradable Implants

PLGA-Based Implants

- PLGA degrades by hydrolysis to lactic acid + glycolic acid — metabolized naturally.
- Drug is released as PLGA erodes in body fluids.

- Release rate controlled by LA:GA ratio, MW, and implant geometry.
- Examples:
  - Zoladex (goserelin acetate): Biodegradable PLGA rod; subcutaneous implant; 1-month or 3-month depot.
  - Lupron Depot: PLGA microspheres injected IM; 1, 3, 4, or 6-month formulations.
- Advantages: No surgical removal needed; degradation products are safe.

Polyanhydride Implants — Gliadel Wafer

- Gliadel wafer is a landmark biodegradable implant for glioblastoma (brain cancer).
- Composition: Carmustine (BCNU) loaded in polyanhydride polymer (PCPP:SA = 20:80).
- Placed directly in the surgical cavity after tumor resection (up to 8 wafers).
- BCNU released locally over 2–3 weeks as polymer erodes.
- Advantage: Bypasses blood-brain barrier; delivers high local drug concentration directly to tumor site.
- Approved by FDA in 1996 — first brain cancer implant.

Drug-Eluting Stents (DES)

- Metallic coronary stent coated with polymer containing anti-restenosis drug.
- Drug released over 30–90 days from the stent coating.
- Examples:
  - Cypher stent: Sirolimus (rapamycin) coated on stainless steel stent.
  - TAXUS stent: Paclitaxel in styrene-isobutylene-styrene (SIBS) polymer coating.
  - Xience stent (3rd gen): Everolimus in fluoropolymer coating on cobalt-chromium stent.
- Action: Prevent smooth muscle cell proliferation → prevent restenosis (re-narrowing of artery).

Intraocular Implants

- Vitrasert (ganciclovir): Non-biodegradable EVA/PVA implant; intravitreal; for CMV retinitis in AIDS patients. Releases for 8 months.
- Ozurdex (dexamethasone): Biodegradable PLGA implant; intravitreal; for macular edema and uveitis. Releases for 6 months.
- Iluvien (fluocinolone acetonide): Non-biodegradable polyimide tube; intravitreal; 3-year release for diabetic macular edema.

Concept of Osmotic Pump

Osmotic pumps are drug delivery devices that use osmotic pressure as the driving force for releasing drug at a controlled, constant (zero-order) rate. They are among the most sophisticated and precise controlled release systems.

Principle of Osmotic Drug Delivery

📌 **Key Point:** Osmotic pressure (π) = i × C × R × T (van't Hoff equation). Osmotic pressure drives water into the device through a semipermeable membrane, which in turn pushes drug out of the device at a constant rate.

- A semipermeable membrane allows water to enter but does not allow drug or osmogen to exit.
- Osmogen (osmotic agent) inside the device creates high osmotic pressure.
- Water enters the device → builds up pressure → pushes drug out through a delivery orifice.
- As long as excess solid osmogen remains, the osmotic pressure and hence the delivery rate are constant → zero-order release.

Types of Osmotic Pump Systems

Elementary Osmotic Pump (EOP) — Rose-Nelson Pump

- First osmotic pump described by Rose and Nelson (1955) — originally for veterinary use.
- Components:
  - Drug chamber: Contains drug solution/suspension.
  - Salt chamber: Contains inorganic salt (osmogen) e.g., MgSO4 or NaCl.
  - Water chamber: Contains water.
  - Rigid semipermeable membrane between salt and water chambers.
- Mechanism: Water crosses into salt chamber via osmosis → volume increases → pushes drug out through orifice.
- Limitation: Bulky; not suitable for oral use; mainly for parenteral/subcutaneous implantation.

Higuchi-Theeuwes Pump — ALZET Osmotic Pump

- Developed at ALZA Corporation (now J&J) — widely used in laboratory animal research.
- Structure: Flexible impermeable drug reservoir bag + rigid semipermeable membrane housing.
- Osmotic agent (NaCl) between the flexible bag and the outer membrane.

- Mechanism: Water enters through outer semipermeable membrane → compresses flexible reservoir bag → drug pushed out at constant rate.
- Available as subcutaneous implant in rats and mice for research.
- Sizes: From 1-week to 4-week delivery; pump sizes 100 µL to 2 mL reservoir.
- Drug release rate = constant (zero-order) for entire duration.

OROS (Oral Osmotic System) — Theeuwes Pump

OROS is the most commercially significant oral osmotic drug delivery system, developed by ALZA Corporation. Several FDA-approved products use OROS technology.

- Basic OROS structure:
  - Osmotic tablet core: Drug + osmogen (e.g., NaCl, mannitol, sorbitol).
  - Semipermeable membrane coat: Cellulose acetate (CA) — permeable to water, impermeable to drug.
  - Laser-drilled orifice: Tiny hole (0.3–0.5 mm) drilled by laser through which drug is pushed out.
- Mechanism:
  - Water enters through CA membrane driven by osmotic pressure.
  - Osmogen dissolves → creates high osmotic pressure inside tablet.
  - Drug solution/suspension pumped out through laser orifice at zero-order rate.
  - Rate = f (membrane permeability, osmotic pressure, orifice size) — constant as long as osmogen is in excess.
- OROS variants:
  - Push-Pull OROS (L-OROS): Two-layer tablet — push layer (osmotic engine) + pull layer (drug). Push layer expands → pulls drug layer out.
  - Swellable core OROS: Single-layer osmotic tablet.
  - OROS-CT: Colon-targeted OROS system.

- Advantages of OROS:
  - True zero-order drug release — drug delivered at constant rate throughout GI transit.
  - Release rate independent of GI pH, motility, and food effects.
  - Drug release depends only on osmotic pressure and membrane properties.
  - Reproducible pharmacokinetics.
- Disadvantages of OROS:
  - High manufacturing cost (laser drilling, precision coating).
  - Orifice may clog in high-viscosity drug suspensions.
  - Cannot be split or crushed (destroys osmotic system).

- Not suitable for drugs that are poorly soluble or highly viscous.

Commercial OROS Products

Product	Drug	OROS Type	Indication
Procardia XL	Nifedipine 30/60/90 mg	Push-Pull OROS	Hypertension, Angina
Glucotrol XL	Glipizide 5/10 mg	Basic OROS	Type 2 Diabetes
Ditropan XL	Oxybutynin 5/10/15 mg	Push-Pull OROS	Overactive bladder
Covera-HS	Verapamil 180/240 mg	OROS-COER-24	Hypertension (nighttime dosing)
Concerta	Methylphenidate 18/27/36/54 mg	OROS	ADHD
Jurnista	Hydromorphone 8–64 mg	OROS-Push-Pull	Chronic pain
Minipress XL	Prazosin 5 mg	OROS	Hypertension
Efexor XR (SXAS)	Venlafaxine XR	Spheroidal OROS	Depression, Anxiety

DUROS Implant (Implantable Osmotic Pump)

- DUROS = Drug Unilamellar Reservoir Osmotic System.
- A titanium cylinder (4 cm × 4 mm) implanted subcutaneously.
- Contains: Drug reservoir + osmotic engine (NaCl) + semipermeable titanium membrane.
- Water permeates through membrane → compresses osmotic engine → pushes piston → drug released through orifice.
- Delivers drug for 6 months – 1 year at precise zero-order rate.
- Example: Viadur (leuprolide acetate) — DUROS implant for prostate cancer; replaced annually.
- Advantage: Precise, predictable, long-term delivery; no needle injections.

Mechanism and Rate Equation for Osmotic Pumps

- Rate of drug delivery from an osmotic pump:

$$\mathbf{dM/dt = (A \times Lp \times \Delta\pi \times Cs) / h}$$

- Where:
  - dM/dt = rate of drug delivery (mg/hour)

- A = area of semipermeable membrane
- Lp = hydraulic permeability of membrane
- Δπ = osmotic pressure gradient across membrane
- Cs = drug solubility in delivery vehicle
- h = membrane thickness

- Rate is constant (zero-order) as long as: (1) excess solid osmogen present, and (2) drug concentration in reservoir remains constant (saturated).

Comparison: Implant Types vs. Osmotic Pump

Feature	Matrix Implant	Reservoir Implant	Osmotic Pump
Release mechanism	Diffusion/erosion through matrix	Diffusion through membrane	Osmotic pressure
Release kinetics	First order or Higuchi	Approximately zero order	True zero order
Drug dependence	Depends on drug solubility in matrix	Depends on partition coefficient	Independent of drug properties
Effect of pH/food	May be affected	Minimal effect	No effect — independent
Biodegradability	Yes (PLGA, PLA)	No (silicone, EVA)	No (titanium)
Removal	Not removable	Removable (surgical)	Removable annually
Examples	Zoladex, Gliadel	Norplant, Vitrasert	ALZET, Viadur, Procardia XL (oral)
Dose precision	Moderate	Good	Excellent (very precise)

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