Unit-4

Novel Drug Delivery Systems

B.Pharma 7 Sem Notes

Unit: 4

Targeted drug Delivery:

Concepts and approaches advantages and disadvantages, introduction to liposomes, niosomes, nanoparticles, monoclonal antibodies and their applications

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TARGETED DRUG DELIVERY

Figure 1: Overview of Targeted Drug Delivery Systems — Key Concepts and Carrier Types

Introduction to Targeted Drug Delivery

Targeted Drug Delivery (TDD) refers to a method of drug delivery designed to concentrate the therapeutic agent at the intended site of action (target site) while minimizing drug exposure to non-target tissues. This approach aims to maximize therapeutic efficacy and minimize systemic side effects — particularly important in cancer chemotherapy, where conventional drugs damage healthy tissues along with tumors.

📌 **Key Point:** Targeted Drug Delivery = Right drug + Right dose + Right site + Right time. The goal is to achieve maximum therapeutic effect with minimum toxic side effects by delivering drug selectively to the target organ, tissue, cell, or sub-cellular compartment.

Historical Milestones

Year	Milestone

1906	Paul Ehrlich coined the concept of 'Magic Bullet' — drug that kills disease without harming host.
1964	First liposomes described by Bangham et al.
1975	First monoclonal antibodies produced by Köhler and Milstein (Nobel Prize 1984).
1980s	Polymer nanoparticles and drug-polymer conjugates for cancer targeting explored.
1995	Doxil (PEGylated liposomal doxorubicin) — FIRST FDA-approved nano-drug for cancer.
1997	Rituxan (Rituximab) — first therapeutic mAb approved for cancer (Non-Hodgkin lymphoma).
2000s	Active targeting with ligand-conjugated nanoparticles and ADCs developed.
2013	Kadcyla (ado-trastuzumab emtansine) — first HER2-targeted ADC approved for breast cancer.
2020s	mRNA-LNP vaccines (COVID-19: Pfizer BNT162b2, Moderna mRNA-1273) — breakthrough in lipid nanoparticle delivery.

Need for Targeted Drug Delivery

- Conventional drugs distribute non-selectively throughout the body — causing systemic toxicity.
- Cytotoxic anticancer drugs damage bone marrow, GI mucosa, hair follicles — causing myelosuppression, nausea, alopecia.
- Many drugs have narrow therapeutic window — targeting allows effective dosing at tumor while protecting normal tissue.
- Some diseases (brain tumors, intracellular parasites, HIV-infected macrophages) require drug delivery to specific sites.
- Poor drug stability, rapid metabolism, or short half-life may require targeted formulations to improve therapeutic outcomes.

Concepts in Targeted Drug Delivery

Levels of Targeting

Level	Description	Example
First-order targeting (Organ-level)	Selective drug delivery to a target organ or tissue	Liver-targeted liposomes; Lung-targeted microspheres
Second-order targeting (Cell-level)	Selective delivery to specific cell type within the target organ	Tumor cell-targeted NPs with folate ligand; hepatocyte-targeted galactosylated carriers
Third-order targeting (Intracellular)	Delivery to specific subcellular organelle (nucleus, mitochondria, lysosome)	Nuclear-targeted gene delivery vectors; mitochondria-targeted antioxidants

Passive Targeting

Passive targeting exploits the natural physiological differences between diseased and normal tissues — without active ligand-receptor interaction.

- **EPR Effect (Enhanced Permeability and Retention):** The most important passive targeting mechanism. Tumor blood vessels are fenestrated (have gaps of 200–2000 nm) due to rapid angiogenesis. Nanoparticles (100–400 nm) leak through these gaps and accumulate in tumor tissue. Impaired lymphatic drainage retains them (retention effect).
- **pH-responsive targeting:** Tumor microenvironment is acidic (pH 6.4–6.8 vs normal pH 7.4). pH-sensitive polymers (Eudragit, polyhistidine) release drug selectively in acidic tumor environment.
- **Temperature-responsive targeting:** Thermosensitive liposomes release drug at elevated temperatures (tumor hyperthermia, 42–45°C).
- **Lymphatic targeting:** Drug-loaded nanoparticles absorbed by lymphatics after SC injection — target lymph nodes for cancer staging/treatment.

Active Targeting

Active targeting uses targeting ligands (antibodies, peptides, aptamers, vitamins) conjugated to drug carriers. Ligands bind specifically to overexpressed receptors or antigens on target cells — improving selectivity beyond passive EPR effect.

Targeting Ligand	Receptor / Target	Disease Application
Folic acid (Folate)	Folate receptor (FR-α) — overexpressed on many tumor cells	Ovarian, cervical, breast, lung cancers
Transferrin	Transferrin receptor (TfR) — overexpressed on cancer cells and BBB	Brain tumors, leukemia; BBB crossing
Galactose	Asialoglycoprotein receptor (ASGPR) — on hepatocytes	Liver targeting — hepatitis, liver cancer
Mannose	Mannose receptor — on macrophages, dendritic cells	Macrophage-targeted delivery (HIV, TB, leishmaniasis)
RGD peptide	Integrin αvβ3 — on tumor vasculature	Anti-angiogenic therapy; tumor targeting
HER2 antibody (Trastuzumab)	HER2/neu receptor — overexpressed in breast cancer	HER2+ breast cancer (Herceptin, Kadcyla)
EGFR antibody (Cetuximab)	EGFR — overexpressed in colorectal, head/neck cancers	Colorectal cancer, NSCLC
Aptamers	PSMA — on prostate cancer cells	Prostate cancer targeting
Hyaluronic acid	CD44 receptor — on cancer stem cells	Breast, lung, ovarian cancers

Biotin	Biotin receptor — overexpressed on tumor cells	Various cancers

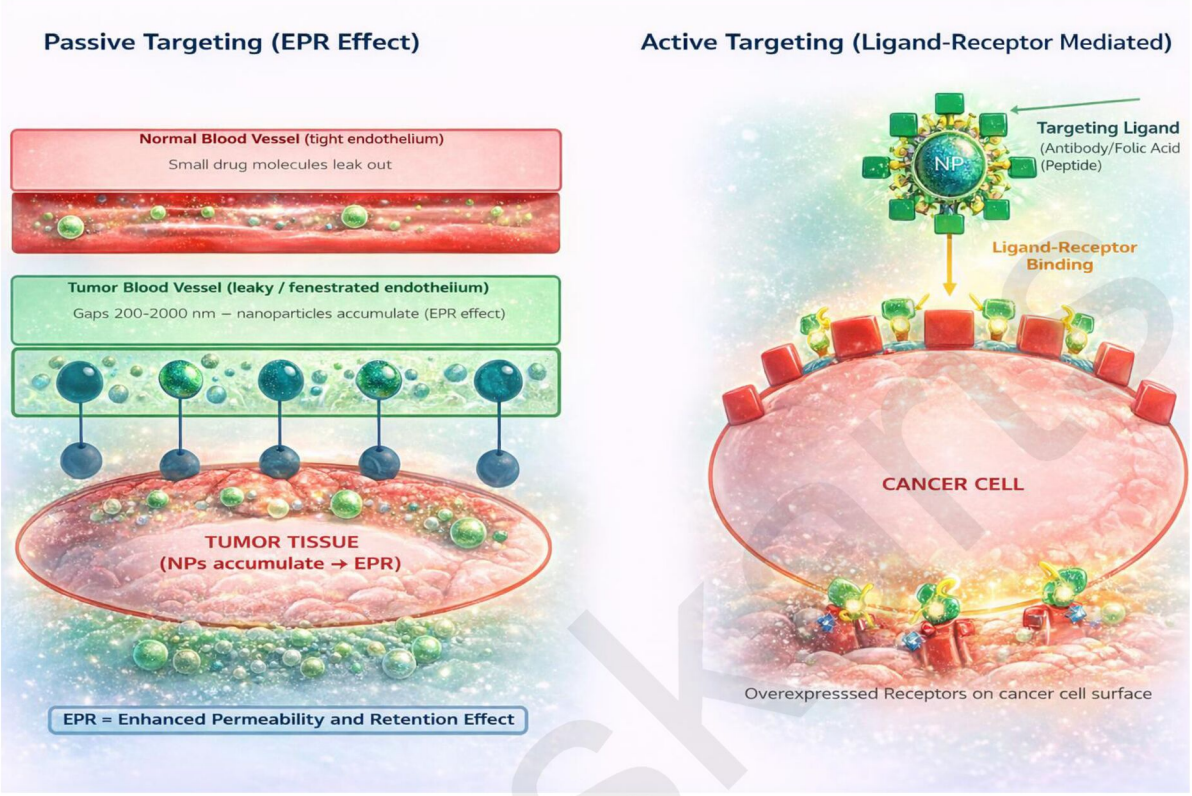

Figure 2: Passive Targeting via EPR Effect (Left) and Active Targeting via Ligand-Receptor Interaction (Right)

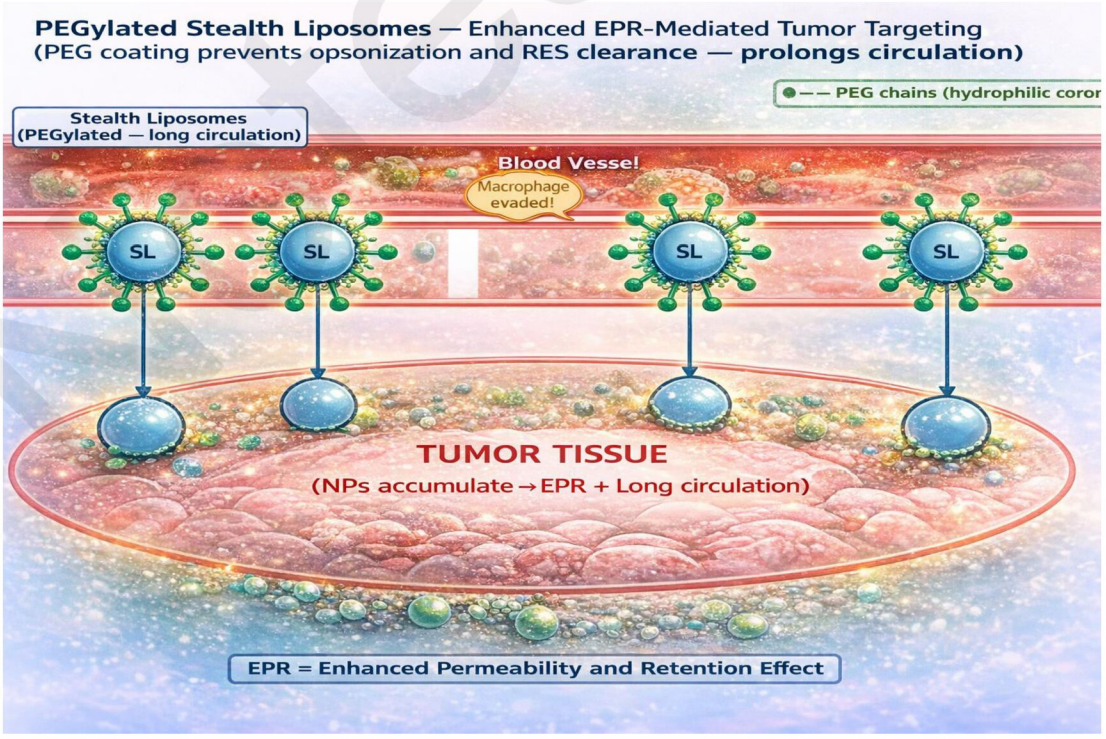

Figure 3: PEGylated Stealth Liposomes Exploiting EPR Effect — Enhanced Tumor Accumulation

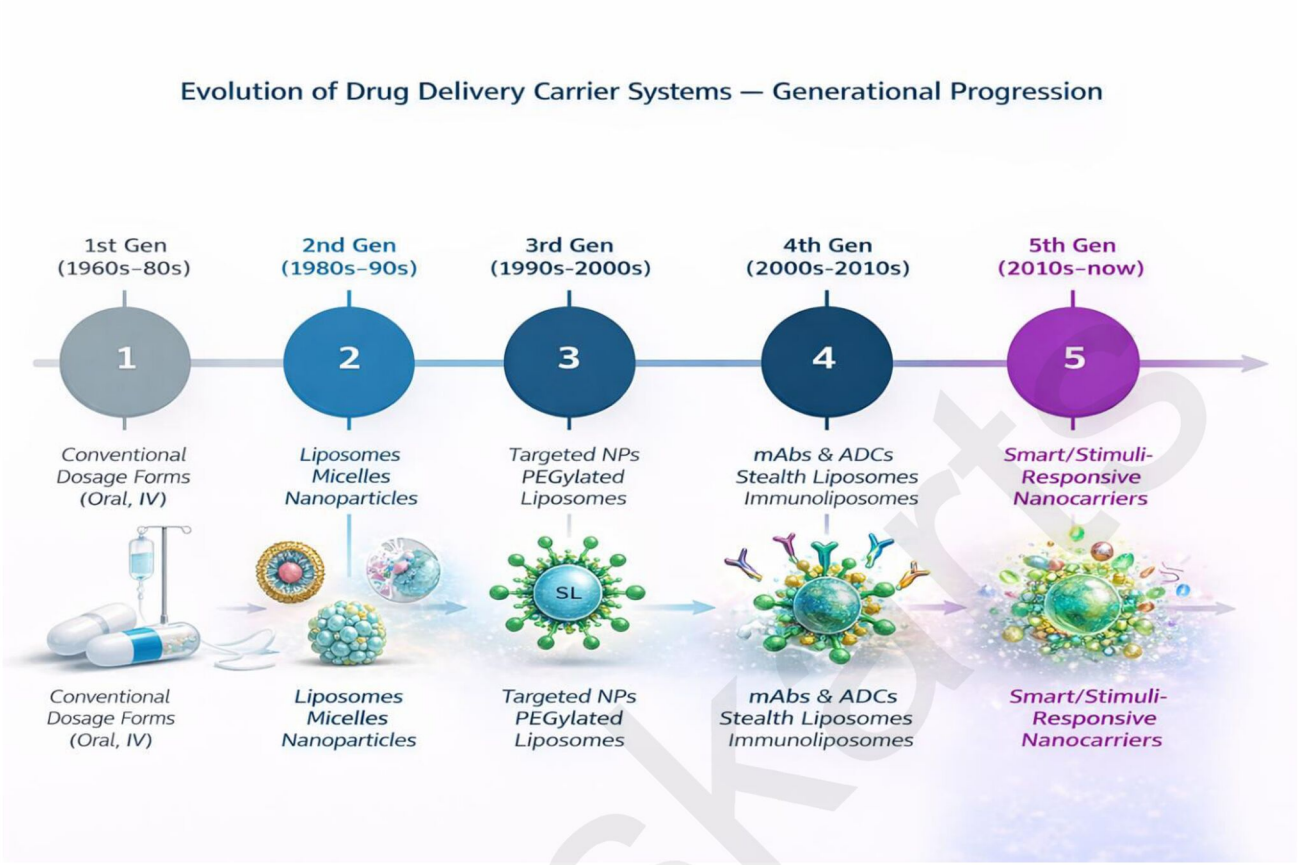

Figure 4: Evolution of Drug Delivery Carrier Systems — From 1st to 5th Generation

Advantages and Disadvantages of Targeted Drug Delivery

Advantages

Advantage	Explanation / Example
Increased therapeutic efficacy	Higher drug concentration at target site → better pharmacological response with lower dose.
Reduced systemic toxicity	Non-target tissues receive less drug — fewer side effects. e.g., Doxil causes less cardiotoxicity than free doxorubicin.
Improved therapeutic index	Ratio of toxic to effective dose widens — safer drugs.
Protection of labile drugs	Encapsulation in nanocarriers protects proteins, peptides, nucleic acids from enzymatic degradation.
Overcoming biological barriers	Nanocarriers cross BBB, GI epithelium, tumor stroma that free drugs cannot penetrate.
Reduced dose and dosing frequency	Efficient delivery requires less total drug; prolonged release reduces dosing frequency.

Multifunctionality	Nanocarriers can simultaneously deliver drug + imaging agent (theranostics) + targeting ligand.
Bypassing MDR (Multidrug Resistance)	Nanoparticle endocytosis bypasses P-glycoprotein efflux pump — overcomes MDR in cancer cells.
Site-specific action	Local delivery to brain tumor (Gliadel), eye (Ozurdex), joint (IA corticosteroid NPs).
Improved patient compliance	Less frequent dosing; reduced side effects improve adherence to therapy.

Disadvantages

Disadvantage	Explanation
High development cost	Synthesis, characterization, and scale-up of nanocarriers is expensive.
Complex manufacturing	Requires specialized equipment (high-pressure homogenizers, extruders, spray dryers).
Regulatory challenges	Novel carriers require extensive toxicology, stability, and efficacy data for approval.
In vitro-in vivo disconnect	Targeting that works in cell culture often fails in complex in vivo environment.
Protein corona formation	Plasma proteins adsorb on nanoparticle surface in vivo — alter targeting ligand accessibility.
RES clearance	Macrophages in liver (Kupffer cells), spleen, bone marrow rapidly clear foreign nanoparticles.
Heterogeneity of tumors	Not all cancer cells overexpress the same receptors — incomplete targeting.
Limited drug loading	Some nanocarriers have low drug encapsulation efficiency — high carrier dose needed.
Stability on storage	Liposomes, nanoparticles may aggregate, leak drug, or degrade on storage.
Scale-up challenges	Lab-scale synthesis difficult to reproduce at industrial scale with consistent quality.

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LIPOSOMES

Liposomes

Liposomes are spherical, self-assembled colloidal vesicles composed of one or more phospholipid bilayers surrounding an aqueous core. They can encapsulate both hydrophilic drugs (in aqueous core) and lipophilic drugs (in phospholipid bilayer). Liposomes are the most clinically advanced nanocarrier system with multiple FDA-approved products.

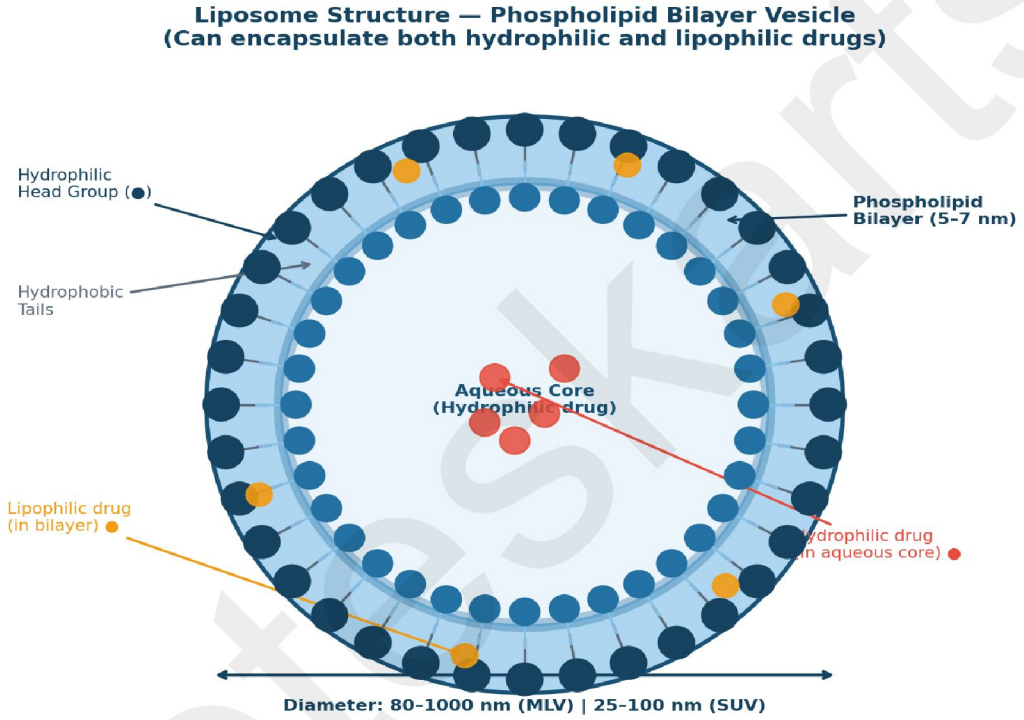

Figure 5: Liposome Structure — Phospholipid Bilayer Vesicle Showing Drug Loading in Aqueous Core and Bilayer

Composition of Liposomes

Component	Examples	Role
Phospholipids	DPPC, DSPC, DMPC, Egg-PC, Soy-PC, DPPE, DSPE	Form bilayer; determine membrane fluidity, permeability, and stability
Cholesterol	Cholesterol (20–50 mol%)	Stabilizes bilayer; reduces membrane permeability; modulates fluidity
Charged lipids (anionic)	DPPG, DOPG, DOPS, Cardiolipin	Provide negative charge; reduce aggregation; used in targeted liposomes

Charged lipids (cationic)	DOTAP, DOTMA, DC-Chol	Positive charge — bind anionic DNA/siRNA for gene delivery
PEG-lipids	DSPE-PEG2000, DSPE-PEG5000	Steric stabilization (stealth); extend circulation time; prevent RES uptake
Targeting ligands	Antibodies, folate, transferrin (conjugated to PEG-lipid)	Active targeting to cancer cells, brain, liver
Aqueous phase	PBS, citrate buffer, normal saline	Contains hydrophilic drug; provides osmotic balance

Classification of Liposomes

Based on Size and Number of Bilayers

Type	Abbreviation	Size	Description
Small Unilamellar Vesicle	SUV	20–100 nm	Single bilayer; prepared by sonication or extrusion; high drug release rate
Large Unilamellar Vesicle	LUV	100–400 nm	Single bilayer; prepared by extrusion; better encapsulation
Giant Unilamellar Vesicle	GUV	1–100 µm	Very large single bilayer; research use; electroporation, electroformation
Multilamellar Vesicle	MLV	0.1–10 µm	Multiple concentric bilayers (onion-like); high drug loading for lipophilic drugs
Multivesicular Vesicle	MVV	1–30 µm	Multiple smaller vesicles enclosed in larger vesicle; very high drug loading

Based on Composition and Function

Type	Description	Example
Conventional liposomes	Neutral or anionic lipids; no targeting; short circulation	Early liposomal amphotericin B
Stealth liposomes (PEGylated)	PEG-coated; evades immune system; long circulation (24–48 h)	Doxil (PEG-liposomal doxorubicin) — t½ ~45 h vs. 5 min for free drug
Immunoliposomes	Antibody (mAb or Fab) conjugated to liposome surface for active targeting	Anti-HER2 immunoliposomes for breast cancer
Cationic liposomes	Positively charged; form complexes (lipoplexes) with DNA/siRNA	Gene therapy vectors; mRNA-LNP vaccines (Pfizer COVID-19)
Thermosensitive liposomes	Lipids with phase transition temperature 40–42°C; release drug at tumor hyperthermia	ThermoDox (doxorubicin) in clinical trials

pH-sensitive liposomes	PE-based liposomes; destabilized at acidic pH of endosomes or tumor	DOPE-based liposomes for endosomal escape
Virosomes	Liposomes containing viral envelope proteins for cell entry	Epaxal (Hepatitis A vaccine), Inflexal V (flu vaccine)
Archaeosomes	Made from archaeal ether lipids; extreme stability	Vaccine adjuvants; thermostable formulations

Methods of Preparation of Liposomes

Method	Steps / Principle	Liposome Type Produced
Thin Film Hydration (Bangham method)	Lipids dissolved in organic solvent → solvent evaporated → thin lipid film → hydrated with aqueous drug solution → MLVs formed	MLV → SUV (after sonication) or LUV (after extrusion)
Probe Sonication	MLV suspension sonicated using titanium probe → small unilamellar vesicles	SUV (20–50 nm); metal contamination possible
Extrusion	MLV or LUV passed through polycarbonate membrane filters (50–200 nm pores)	Monodisperse LUV with controlled size
Solvent injection (Ethanol injection)	Lipids dissolved in ethanol → injected rapidly into aqueous phase → liposomes form spontaneously	SUV; simple; residual ethanol may be issue
Reverse Phase Evaporation (REV)	W/O emulsion formed → solvent evaporated → LUV with high aqueous capture	LUV with high encapsulation of hydrophilic drugs
Microfluidic mixing	Lipids in ethanol + drug in aqueous phase — mixed in microfluidic chip → uniform LNP	Precise LNP (used for mRNA-LNP vaccines)
Dehydration-Rehydration (DRV)	Liposomes dehydrated (freeze-dried) with drug → rehydrated → drug trapped during rehydration	High drug encapsulation; good for proteins

Drug Loading into Liposomes

- **Passive loading:** Drug present during hydration step. Drug encapsulated in aqueous core (hydrophilic) or intercalated in bilayer (lipophilic). Simple but low efficiency.
- **Active loading (Remote loading):** Drug loaded after liposome formation. e.g., pH gradient method — ammonium sulfate creates pH gradient → doxorubicin accumulates in acidic interior. High efficiency (>90%). Used for Doxil manufacture.
- **Encapsulation efficiency (EE%):** EE% = (Drug in liposomes / Total drug) × 100%. Typical: 20–90% depending on method and drug properties.

Advantages of Liposomes

Advantage	Explanation

Amphiphilic drug loading	Can carry both hydrophilic (aqueous core) and lipophilic (bilayer) drugs — versatile carrier.
Biocompatible & biodegradable	Phospholipids are natural membrane components — safe, metabolized to natural lipids.
Reduced toxicity	Encapsulation reduces peak drug concentration in normal tissues — e.g., Doxil: reduced cardiotoxicity.
Prolonged circulation	PEGylated (stealth) liposomes circulate for 24–48 hours vs. minutes for free drug.
EPR-mediated tumor accumulation	Long-circulating stealth liposomes accumulate in tumor via EPR effect.
Surface modification	Easy to attach targeting ligands, PEG, antibodies via lipid conjugation chemistry.
Protection of encapsulated drug	Shield labile drugs (proteins, nucleic acids, antibiotics) from degradation.
Controlled release	Lipid composition, cholesterol content, and surface PEGylation control release rate.
Approved products available	Multiple FDA/EMA-approved products confirm clinical safety and efficacy.

Disadvantages of Liposomes

Disadvantage	Explanation
Physical and chemical instability	Phospholipids undergo oxidation and hydrolysis — limited shelf life in aqueous form.
Leakage of drug	Hydrophilic drugs may leak through bilayer over time — reduces encapsulation efficiency on storage.
High manufacturing cost	Specialized equipment (extruders, microfluidics, lyophilizer); high-purity lipids are expensive.
Short circulation (conventional)	Conventional liposomes cleared by RES (liver, spleen) within minutes–hours.
Batch-to-batch variability	Difficult to achieve consistent size distribution and drug loading across batches.
Scale-up challenges	Lab-to-industrial scale-up maintains quality is technically demanding.
Protein corona	Plasma proteins adsorb on surface → alter pharmacokinetics and targeting.
Limited drug loading for some drugs	Encapsulation efficiency < 20% for some water-soluble drugs.

FDA-Approved Liposomal Drug Products

Brand Name	Drug	Liposome Type	Indication
Doxil / Caelyx	Doxorubicin HCl	PEGylated liposome	Ovarian cancer, breast cancer, multiple myeloma, AIDS-related KS
AmBisome	Amphotericin B	Unilamellar liposome	Fungal infections (less nephrotoxic than conventional amphotericin B)
DaunoXome	Daunorubicin	SUV liposome	HIV-associated KS
Myocet	Doxorubicin	Conventional liposome	Metastatic breast cancer
Marqibo	Vincristine sulfate	Sphingomyelin/cholesterol liposome	Relapsed/refractory ALL
Onivyde	Irinotecan	PEGylated liposome	Metastatic pancreatic cancer
Vyxeos	Daunorubicin + Cytarabine	Liposome (fixed 5:1 ratio)	AML (acute myeloid leukemia)
Exparel	Bupivacaine	Multivesicular liposome (DepoFoam)	Local post-surgical analgesia (up to 72 hours)
DepoCyte	Cytarabine	Multivesicular liposome (DepoFoam)	Lymphomatous meningitis
Comirnaty (Pfizer BNT162b2)	mRNA (SARS-CoV-2 spike)	Lipid nanoparticle (LNP)	COVID-19 vaccine — mRNA delivery

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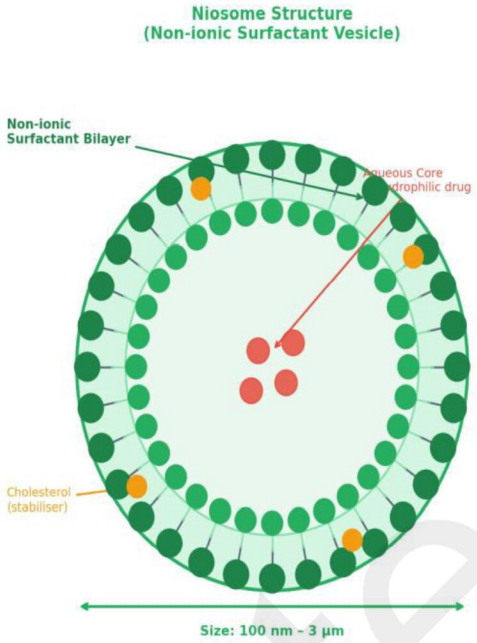
NIOSOMES

Niosomes

Niosomes (Non-ionic surfactant vesicles) are self-assembled bilayer vesicles formed from non-ionic surfactants (such as Span, Brij, or Tween series) with or without incorporation of cholesterol. They are structurally similar to liposomes but use synthetic non-ionic surfactants instead of phospholipids — offering better chemical stability and lower manufacturing cost.



Liposome vs. Niosome Comparison

Feature	Liposome	Niosome
Bilayer material	Phospholipids (natural/synthetic)	Non-ionic surfactants (Span, Brij, Tween)
Cholesterol	Required (stability)	Required (rigidity)
Charge	Neutral / Anionic / Cationic	Neutral (non-ionic)
Cost	High	Low (surfactants cheaper)
Stability	Less stable (oxidation)	More stable (no double bonds)
Drug loading	Hydrophilic + Lipophilic	Hydrophilic + Lipophilic
Size range	25 nm – 1 µm	100 nm – 3 µm
Entrapment eff.	Moderate–High	Moderate–High
Preparation	Complex (extrusion, probe sonication)	Simpler (Ether injection, film)
Scale-up	Difficult	Easier
Applications	Anticancer, antifungals, vaccines	Dermal, oral, nasal, anticancer

Figure 6: Niosome Structure (Left) and Comprehensive Liposome vs. Niosome Comparison Table (Right)

Composition of Niosomes

Component	Examples	Function
Non-ionic surfactants	Span 20, 40, 60, 80 (Sorbitan esters); Brij 52, 72, 92; Tween 20, 80; Polysorbates; Poloxamers	Form bilayer; HLB value determines vesicle-forming ability (HLB 4–8 ideal)
Cholesterol	Cholesterol (30–50 mol%)	Stabilizes bilayer; controls membrane fluidity and permeability; reduces drug leakage
Charge inducers	Dicetyl phosphate (DCP — negative); Stearylamine (SA — positive)	Provide charge to prevent aggregation of niosomes; improve zeta potential

Aqueous phase	Phosphate buffer, saline, drug solution	Fills aqueous core; contains hydrophilic drug
Targeting ligands	Antibodies, folate, lectins (optional)	Active targeting — convert niosomes to targeted vesicles
PEG derivatives	PEG-cholesterol, PEG-surfactant (optional)	Stealth niosomes — extended circulation time

Methods of Preparation of Niosomes

Method	Procedure	Notes
Thin film hydration	Surfactant + cholesterol dissolved in organic solvent → evaporated → hydrated with aqueous drug solution → MLV niosomes	Most commonly used; scalable
Ether injection	Surfactant solution in diethyl ether slowly injected into heated aqueous phase → SUV niosomes	Simple; solvent residue concern
Reverse phase evaporation	W/O emulsion → solvent evaporated → niosomes; high aqueous drug encapsulation	Good for hydrophilic drugs
Sonication	MLV suspension sonicated → SUV niosomes	Reduces particle size; generates heat
Transmembrane pH gradient	Acidic/basic interior created → drug loaded by gradient similar to liposome active loading	High EE% for ionizable drugs
Bubble method	Surfactant hydrated with aqueous phase; N_2 gas bubbled through at 70°C → vesicles	One-step; no organic solvent

Classification of Niosomes

- **Based on size:** Small (SUV — 10–100 nm), Large (LUV — 100 nm–1 µm), Multilamellar (MLV — 1–10 µm).
- **Based on lamellarity:** Unilamellar (single bilayer) vs. Multilamellar (concentric bilayers).
- **Based on charge:** Neutral (most), Anionic (with DCP), Cationic (with stearylamine).
- **Proniosomes:** Dry powder precursor of niosomes (surfactant coated on mannitol or sorbitol carriers). Reconstituted to niosomes by adding water — superior stability on storage.
- **Discomes:** Disc-shaped niosomes prepared using solulan C24 (polysorbate ester). Size > 16 µm. Used for ocular drug delivery as they lodge in cul-de-sac.
- **Elastic niosomes (Flexosomes):** Incorporate edge activators (surfactants like Tween 80, sodium laurate) — deform and pass through skin layers. Used in transdermal delivery.

Advantages of Niosomes

Advantage	Explanation

Better chemical stability	Ether lipids (not phospholipids) — no oxidation of double bonds; longer shelf life.
Lower cost	Non-ionic surfactants are synthetic and cheaper than natural phospholipids.
No special storage conditions	Stable at room temperature (phospholipids require cold chain).
Amphiphilic drug loading	Like liposomes: hydrophilic in core, lipophilic in bilayer.
Biocompatible	Non-ionic surfactants are generally GRAS (Generally Recognized As Safe).
Suitable for oral delivery	Stable in acidic gastric environment unlike some liposomes.
Flexible surface modification	PEGylation, antibody conjugation feasible on niosome surface.
Controlled drug release	Bilayer composition and charge inducers control release rate.
Enhance transdermal delivery	Elastic/deformable niosomes (flexosomes) enhance skin permeation.

Disadvantages of Niosomes

Disadvantage	Explanation
Drug leakage on storage	Aqueous suspension form: hydrolysis and aggregation occur over time.
Aggregation and fusion	Niosomes may aggregate and fuse — increasing particle size on storage.
Scale-up difficulties	Maintaining uniform size and lamellarity at industrial scale is challenging.
HLB optimization required	Only surfactants with HLB 4–8 form bilayer vesicles — limits surfactant choice.
Not as extensively studied as liposomes	Fewer clinical data; no major FDA-approved injectable products yet.
Proniosome reconstitution step	Proniosomes need preparation just before use — inconvenient for patients.

Applications of Niosomes

Application Area	Drug / Example	Notes
Anticancer delivery	Doxorubicin, Paclitaxel, Methotrexate niosomes	Enhanced tumor accumulation via EPR; reduced cardiotoxicity of doxorubicin
Antifungal delivery	Amphotericin B niosomes	Reduced nephrotoxicity; alternative to liposomal formulation
Topical / Transdermal	Tretinoin, Acyclovir, Minoxidil niosomes	Enhanced skin penetration; elastic niosomes cross stratum corneum
Ophthalmic delivery	Cyclosporine, Pilocarpine niosomes	Discomes lodge in cul-de-sac; prolong precorneal residence time

Nasal delivery	Insulin, Vaccines (niosomal adjuvants)	Mucosal immune response; systemic absorption via nasal mucosa
Oral drug delivery	Insulin, BSA, poorly soluble drugs	Protect from GI enzymes; enhance absorption
Vaccine adjuvants	Malaria, Leishmaniasis antigens	Niosomes as immunoadjuvants — enhance antigen presentation
Gene delivery	pDNA, siRNA loaded in cationic niosomes	Non-viral transfection; safer than viral vectors

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NANOPARTICLES

Nanoparticles

Nanoparticles (NPs) are solid colloidal particles ranging in size from 1 to 1000 nm (typically 10–500 nm). They can be polymeric, lipid-based, metallic, or carbon-based, and serve as versatile drug delivery carriers capable of encapsulating, adsorbing, or conjugating drugs on their surface. The choice of nanoparticle type depends on the drug properties, route of administration, and target site.

📌 **Key Point:** Nanoparticles = Solid colloidal particles (1–1000 nm) made from polymers, lipids, or metals — used to encapsulate, adsorb, or conjugate drugs for targeted and controlled delivery.

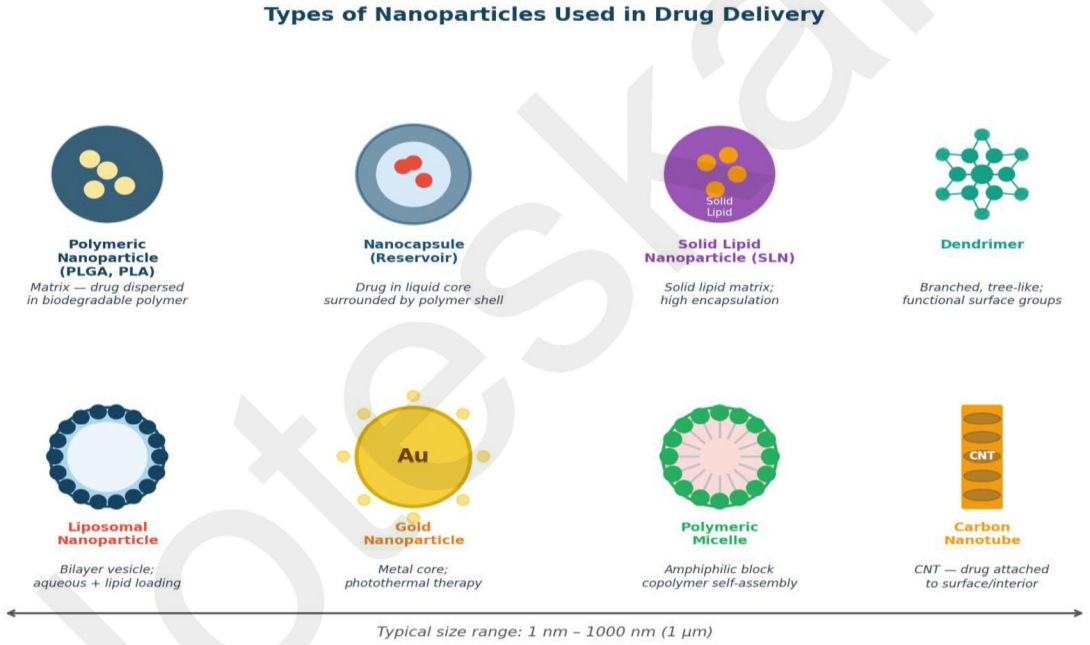

Figure 7: Types of Nanoparticles Used in Drug Delivery Systems

Classification of Nanoparticles

Based on Material Composition

Type	Material	Key Features
Polymeric NPs	PLGA, PLA, PCL, chitosan, albumin, gelatin	Biodegradable; sustained release; surface modification possible

Lipid NPs (SLN & NLC)	Solid lipids (Compritol, Precirol, beeswax) + liquid lipid	High drug loading; lipophilic drugs; low toxicity
Metallic NPs	Gold (AuNP), Silver (AgNP), Iron oxide (SPION)	Photothermal therapy; MRI contrast; magnetic targeting
Polymeric micelles	PEG-PLA, PEG-PCL amphiphilic block copolymers	Self-assembling; hydrophobic drug loading; small size 10–100 nm
Dendrimers	PAMAM, PPI dendrimers	Highly branched; uniform size; multiple surface groups for drug/ligand attachment
Carbon nanotubes (CNT)	Single-wall or multi-wall CNT	Drug attached inside/outside; electrical/thermal properties
Quantum dots	CdSe, CdS semiconductor NPs	Fluorescent probes; imaging + theranostics
Protein NPs	Albumin (Abraxane), gelatin	Biocompatible; receptor-mediated uptake; paclitaxel in albumin NP (nab-paclitaxel)

Nanospheres vs. Nanocapsules

Feature	Nanosphere (Matrix)	Nanocapsule (Reservoir)
Structure	Drug uniformly dispersed in solid polymer matrix	Drug enclosed in liquid/solid core surrounded by polymer shell
Release mechanism	Diffusion + erosion through polymer matrix	Diffusion through polymer shell + core dissolution
Drug type	Lipophilic drugs (in matrix) or hydrophilic (adsorbed)	Lipophilic drugs in oil core; hydrophilic in aqueous core
Encapsulation efficiency	Moderate	Higher for oily drugs
Examples	PLGA nanospheres, albumin nanoparticles	PCL nanocapsules, Eudragit nanocapsules

Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC)

Solid Lipid Nanoparticles (SLN)

- **Composition:** Solid lipid (Compritol, Precirol, stearic acid, beeswax) + surfactant (Poloxamer, Tween 80) + aqueous phase.
- **Structure:** Solid lipid matrix (crystalline at room temperature) with drug dispersed/dissolved in lipid core.
- **Size:** 50–1000 nm.
- **Advantages:** Biocompatible; high drug loading (especially lipophilic drugs); controlled release; no organic solvents in some preparation methods; stable on storage.
- **Disadvantages:** Drug expulsion on storage (lipid crystallization); limited drug loading for hydrophilic drugs.

- **Preparation:** Hot homogenization; cold homogenization; microemulsion technique; solvent emulsification-evaporation.

Nanostructured Lipid Carriers (NLC)

- **Composition:** Mixture of solid lipid + liquid lipid (oils) — imperfect crystal structure.
- **Advantage over SLN:** Imperfect crystalline lattice accommodates more drug → higher loading; reduces drug expulsion on storage.
- **Types:** (I) Imperfect NLC — small amounts of liquid lipid create imperfect crystals. (II) Amorphous NLC — special lipids that remain amorphous. (III) Multiple NLC — liquid lipid nanocompartments in solid lipid matrix.

Polymeric Nanoparticles — PLGA

- **Most studied biodegradable polymer for NPs:** PLGA (Poly-lactic-co-glycolic acid).
- **Biodegradation:** Hydrolytic degradation → lactic acid + glycolic acid → Krebs cycle → CO_2 + H_2O. Non-toxic products.
- **Drug release:** Initial burst (surface drug) → sustained release as polymer erodes (weeks to months). Controlled by LA:GA ratio and MW.
- **Surface modification:** PLGA-PEG for stealth; PLGA-folate, PLGA-transferrin for active targeting.
- Preparation methods:
  - Solvent evaporation (O/W emulsion): For hydrophobic drugs.
  - Double emulsion (W/O/W): For hydrophilic drugs and proteins.
  - Nanoprecipitation (Solvent displacement): Drug + PLGA in water-miscible solvent → injected into aqueous phase → instantaneous precipitation.
- **Examples:** PLGA-PTX (paclitaxel NPs), PLGA-Dox, PLGA-siRNA NPs.

Gold Nanoparticles (AuNPs)

- **Properties:** Strong optical absorption (surface plasmon resonance — SPR); biocompatible; easily functionalized; photothermal agent.
- **Shapes:** Nanospheres, nanorods, nanostars, nanocages — shape determines SPR wavelength (NIR for nanorods = ideal for tissue penetration).
- **Photothermal therapy (PTT):** AuNPs absorb near-infrared (NIR) laser light → convert to heat → selective tumor ablation without damaging surrounding tissue.
- **Drug conjugation:** Thiol-gold bonds attach drug/targeting ligand to AuNP surface.
- **Diagnostic applications:** Lateral flow assays (COVID antigen tests), SERS probes, CT contrast agents.

Dendrimers

- **Structure:** Highly branched, tree-like, monodisperse macromolecules synthesized from a central core with layers of branches (generations — G0, G1, G2...G8+).
- **Core:** Ethylenediamine or ammonia — determines shape and branching pattern.
- **Types:** PAMAM (Polyamidoamine) — most studied; PPI (Polypropyleneimine); PEG dendrimers; carbohydrate dendrimers.

- **Drug loading:** (1) Encapsulation in interior voids (hydrophobic drugs). (2) Surface conjugation via covalent bonds (prodrug approach). (3) Electrostatic complexation (DNA/siRNA with cationic PAMAM).
- **Advantages:** Monodisperse; precise MW; multivalent surface for targeting; high drug payload per molecule.
- **Disadvantages:** Complex synthesis; cationic PAMAM cytotoxic at high doses; high cost.
- **Applications:** Cancer targeting, gene delivery, boron neutron capture therapy (BNCT), antimicrobial delivery.

Applications of Nanoparticles

Application	NP Type	Example / Details
Cancer drug delivery	PLGA NPs, SLN, Albumin NPs	Abraxane (nab-paclitaxel, albumin NPs) — approved for breast cancer, NSCLC, pancreatic cancer
Gene delivery (siRNA/DNA)	Cationic lipid NPs, PLGA NPs	mRNA-LNP vaccines (Pfizer, Moderna COVID-19); siRNA-LNP (Onpattro — patisiran for hereditary TTR amyloidosis)
Brain drug delivery	Transferrin-targeted NPs, AuNPs	Cross BBB via receptor-mediated transcytosis; for brain tumors, Alzheimer's
Photothermal cancer therapy	Gold nanorods	NIR laser-triggered tumor ablation; localized heating > 45°C kills cancer cells
MRI contrast imaging	SPION (Fe_3O_4, Fe_2O_3)	Negative MRI contrast agent; liver/lymph node imaging; magnetically guided drug delivery
Antimicrobial delivery	AgNPs, chitosan NPs	Silver NPs: broad-spectrum antimicrobial; wound dressings; burn care
Vaccine delivery	Lipid NPs, PLGA NPs	Enhanced antigen presentation; depot effect; immune activation
Oral drug delivery	Chitosan NPs, SLN	Protect drugs from GI enzymes; enhance intestinal absorption of proteins
Topical/transdermal	SLN, NLC	Controlled release in skin; enhance drug permeation; cosmeceuticals (retinol, vitamins)
Theranostics	Quantum dots, SPION	Combined therapy + imaging in single nanoplatform

MONOCLONAL ANTIBODIES (mAbs)

Monoclonal Antibodies (mAbs)

Monoclonal antibodies (mAbs) are highly specific antibodies produced from a single B-cell clone, giving them uniform specificity for a single antigenic epitope (target). Developed using hybridoma technology (Köhler and Milstein, 1975), mAbs represent the most successful class of biopharmaceuticals — with over 100 mAbs approved for clinical use in cancer, autoimmune diseases, infectious diseases, and cardiovascular disorders.

📌 **Key Point:** Monoclonal Antibody = Identical antibody molecules, all with the same antigen specificity, produced by a single B-cell clone (hybridoma technology). Used as targeted therapeutics, cancer immunotherapy agents, and drug delivery vectors.

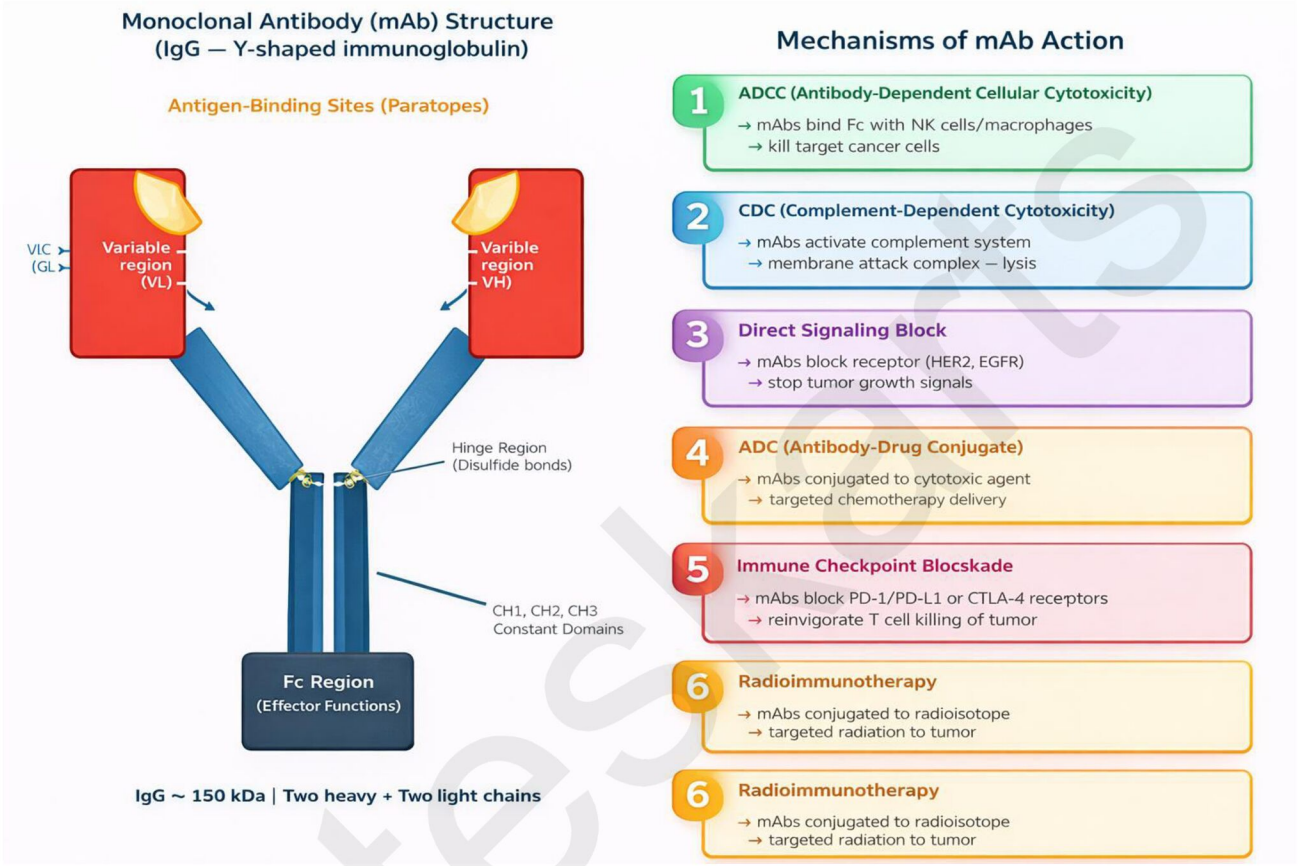

Figure 8: Monoclonal Antibody (mAb) Structure and Six Mechanisms of Therapeutic Action

Structure of Monoclonal Antibodies

The predominant therapeutic mAb format is IgG (Immunoglobulin G) — a Y-shaped glycoprotein of ~150 kDa.

Region	Component	Function
Fab (Fragment antigen-binding)	2 identical Fab arms; each has VH + VL (variable domains)	Antigen recognition and binding; determines specificity
Fc (Fragment crystallizable)	2 heavy chain constant domains (CH2, CH3)	Effector functions (ADCC, CDC); FcRn binding (half-life); complement activation

VH (Variable Heavy domain)	N-terminal domain of heavy chain; CDRs 1-3	Contains CDRs — paratope that contacts antigen epitope
VL (Variable Light domain)	N-terminal domain of light chain; CDRs 1-3	Pairs with VH to form antigen-binding site
CDRs (Complementarity Determining Regions)	3 CDR loops in VH + 3 in VL = 6 CDR loops per Fab	Direct contact with antigen — determine specificity and affinity
Hinge region	Flexible proline-rich region between CH1 and CH2	Flexibility; disulfide bonds; protease sensitivity
N-linked glycan (Fc)	Biantennary complex-type glycan at Asn297 of CH2	Affects ADCC, CDC, pharmacokinetics, immunogenicity

Nomenclature and Generation of Therapeutic mAbs

Suffix	Type	% Human Sequence	Example
-momab	Murine (mouse) mAb	0% human	Ibritumomab (Zevalin)
-ximab	Chimeric mAb	~65% human (human Fc + mouse Fab)	Rituximab (Rituxan), Cetuximab (Erbitux), Infliximab
-zumab	Humanized mAb	~95% human (human framework; mouse CDRs only)	Trastuzumab (Herceptin), Bevacizumab (Avastin), Nivolumab
-umab	Fully human mAb	100% human	Adalimumab (Humira), Pembrolizumab (Keytruda), Ipilimumab
-bartinib / ADC	Antibody-Drug Conjugate	mAb + cytotoxic payload	Kadcyla (T-DM1), Enhertu (T-DXd), Adcetris (brentuximab)

Production of Monoclonal Antibodies — Hybridoma Technology

- Step 1 — Immunization: Mouse immunized with target antigen → B-cells produce specific antibodies.
- Step 2 — Cell fusion: Mouse spleen B-cells fused with immortal myeloma cells using PEG or Sendai virus → Hybridoma cells (B-cell specificity + myeloma immortality).
- Step 3 — Selection: Hybridomas selected in HAT (Hypoxanthine-Aminopterin-Thymidine) medium — unfused myeloma cells die; unfused B-cells die naturally.
- Step 4 — Screening and cloning: Wells screened for antibody production; positive clones selected; single cell cloning (limiting dilution) → monoclonal hybridoma.
- Step 5 — Production: Large-scale bioreactor culture or ascites production → antibody harvested, purified (Protein A/G chromatography).
- Step 6 — Humanization (for therapeutic use): CDR grafting onto human IgG framework → humanized mAb → reduces immunogenicity.

Mechanisms of Action of Therapeutic mAbs

ADCC — Antibody-Dependent Cellular Cytotoxicity

- mAb binds to target antigen on cancer cell surface.
- Fc region binds FcγRIII (CD16) on NK cells, macrophages, neutrophils.
- NK cells activated → release perforin and granzymes → kill cancer cell.
- **Example:** Rituximab (anti-CD20) — ADCC against B-cell lymphoma.

CDC — Complement-Dependent Cytotoxicity

- mAb Fc region activates complement cascade (C1q binding).
- Classical complement pathway activated → C3b opsonization → Membrane Attack Complex (MAC) — C5b-9.
- MAC inserts into cancer cell membrane → osmotic lysis of cancer cell.
- **Example:** Rituximab, Ofatumumab (anti-CD20) — CDC in B-cell lymphoma/leukemia.

Direct Signaling Blockade

- mAb binds to growth factor receptor → blocks ligand binding → inhibits downstream signaling.
- Results in inhibition of tumor cell proliferation, survival, and angiogenesis.
- **Examples:** Trastuzumab (anti-HER2) — blocks HER2 dimerization in breast cancer; Bevacizumab (anti-VEGF) — blocks angiogenesis; Cetuximab (anti-EGFR).

ADC — Antibody-Drug Conjugate

- mAb conjugated via chemical linker to potent cytotoxic drug (payload).
- ADC binds to antigen on cancer cell → internalized by endocytosis → lysosomal degradation releases free payload → kills cancer cell.
- Linker types: Cleavable (pH-sensitive, protease-cleavable, disulfide) or Non-cleavable.
- Key components: mAb (targeting) + Linker (controls release) + Payload (cytotoxic drug — auristatin, maytansine, duocarmycin, calicheamicin).

ADC Product	mAb Target	Payload	Indication
Kadcyla (T-DM1)	Trastuzumab (HER2)	DM1 (maytansine)	HER2+ breast cancer
Enhertu (T-DXd)	Trastuzumab (HER2)	Deruxtecan (topoisomerase I inhibitor)	HER2+ breast, gastric, lung cancers
Adcetris (Brentuximab vedotin)	Anti-CD30	MMAE (auristatin)	Hodgkin lymphoma, ALCL
Besylomab (Mylotarg)	Anti-CD33	Calicheamicin	AML (acute myeloid leukemia)

Polivy (Polatuzumab vedotin)	Anti-CD79b	MMAE	DLBCL
Trodelvy (Sacituzumab govitecan)	Anti-TROP-2	SN-38 (topoisomerase I)	TNBC, urothelial cancer

Immune Checkpoint Blockade (Immunotherapy)

- Cancer cells exploit inhibitory immune checkpoints (PD-1/PD-L1, CTLA-4) to suppress T-cell anti-tumor activity.
- mAbs block these checkpoints → T-cells reactivated → kill cancer cells.

Checkpoint	mAb	Brand Name	Cancer Type
PD-1	Pembrolizumab	Keytruda	Melanoma, NSCLC, CRC, multiple tumors (pan-tumor approval)
PD-1	Nivolumab	Opdivo	NSCLC, melanoma, RCC, HNSCC, bladder, HCC
PD-L1	Atezolizumab	Tecentriq	NSCLC, urothelial, TNBC, HCC
PD-L1	Durvalumab	Imfinzi	NSCLC, urothelial, biliary tract cancer
PD-L1	Avelumab	Bavencio	Merkel cell carcinoma, urothelial cancer
CTLA-4	Ipilimumab	Yervoy	Melanoma (1st checkpoint inhibitor), RCC, NSCLC
PD-1+CTLA-4	Nivolumab + Ipilimumab	Opdivo + Yervoy	Combination immunotherapy — melanoma, NSCLC, RCC

Radioimmunotherapy (RIT)

- mAb conjugated to a radioisotope (^{90}Y, ^{131}I, ^{225}Ac) → delivers radiation directly to tumor.
- Bystander effect: Radiation kills neighboring tumor cells not directly bound by mAb.

Product	mAb	Isotope	Indication
Zevalin (Ibritumomab tiuxetan)	Anti-CD20 (mouse IgG1)	^{90}Y (yttrium-90)	Relapsed/refractory B-cell NHL
Bexxar (Tositumomab-^{131}I)	Anti-CD20	^{131}I	B-cell NHL (withdrawn from market 2014)
Lutathera (Lutetium DOTATATE)	Somatostatin receptor ligand	^{177}Lu	Neuroendocrine tumors (PRRT — peptide RRT)

Advantages of Monoclonal Antibodies

Advantage	Explanation
Exquisite specificity	mAbs bind single specific epitope — highly selective targeting vs. small molecules that have off-target effects.
Long half-life	IgG mAbs have t½ 14–21 days (FcRn-mediated recycling) — infrequent dosing (weekly, bi-weekly, or monthly).
Multiple mechanisms	Can be engineered for ADCC, CDC, signal blockade, ADC, checkpoint inhibition simultaneously.
High potency as ADCs	Conjugating potent payloads (auristatin, DM1) delivers cytotoxic concentration directly to cancer cell.
Reversibility	Immune-related adverse events can be managed; treatment can be stopped.
Combination therapy	mAbs can be combined with chemotherapy, other mAbs, radiation — synergistic effects.
Proven clinical success	Over 100 FDA-approved mAbs — best-selling drugs globally (Adalimumab, Pembrolizumab, etc.)
Reduced systemic toxicity	Selective binding to tumor antigens reduces damage to normal tissues vs. conventional chemotherapy.

Disadvantages of Monoclonal Antibodies

Disadvantage	Explanation
High production cost	Produced in mammalian cell cultures (CHO cells) — expensive fermentation, purification.
Immunogenicity	Murine mAbs trigger HAMA (Human Anti-Mouse Antibody) response — limits efficacy; risk of severe reactions.
Large molecule — poor tumor penetration	~150 kDa IgG penetrates solid tumor poorly vs. small molecules; only cells near blood vessels targeted.
Parenteral administration only	Oral bioavailability = 0% — all therapeutic mAbs given IV or SC.
Requires cold chain	mAbs require 2–8°C storage throughout supply chain — costly logistics.
Antigen heterogeneity	Not all cancer cells express same antigen — incomplete tumor eradication.
Immune-related adverse events (irAE)	Checkpoint inhibitors cause autoimmune colitis, pneumonitis, thyroiditis, hepatitis.
Resistance	Cancer cells downregulate target antigen; alternative survival pathways activated.

FDA-Approved Monoclonal Antibodies

Brand (Generic)	Target	Type	Indication

Herceptin (Trastuzumab)	HER2/neu	Humanized IgG1	HER2+ breast & gastric cancer
Avastin (Bevacizumab)	VEGF-A	Humanized IgG1	CRC, NSCLC, GBM, RCC (anti-angiogenic)
Rituxan (Rituximab)	CD20	Chimeric IgG1	B-cell NHL, CLL, RA, pemphigus
Keytruda (Pembrolizumab)	PD-1	Humanized IgG4	Melanoma, NSCLC, MSI-H cancers, multiple tumors
Opdivo (Nivolumab)	PD-1	Fully human IgG4	Melanoma, NSCLC, RCC, HCC, HNSCC
Humira (Adalimumab)	TNF-α	Fully human IgG1	RA, Crohn's disease, psoriasis, ankylosing spondylitis
Erbitux (Cetuximab)	EGFR	Chimeric IgG1	CRC (RAS wild-type), HNSCC
Yervoy (Ipilimumab)	CTLA-4	Fully human IgG1	Melanoma (1st checkpoint inhibitor, 2011)
Tecentriq (Atezolizumab)	PD-L1	Humanized IgG1	NSCLC, urothelial, TNBC
Kadcyla (T-DM1)	HER2 (ADC)	Humanized IgG1-DM1	HER2+ breast cancer (ADC)
Enhertu (T-DXd)	HER2 (ADC)	Humanized IgG1-DXd	HER2+/low breast, gastric, lung cancer
Cosentyx (Secukinumab)	IL-17A	Fully human IgG1κ	Plaque psoriasis, psoriatic arthritis, AS

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