PRINCIPLES AND SYSTEMS OF DRUG DELIVERY · SEMINARS 24–28

Targeted delivery and nanomedicine: from liposomes to smart systems

Educational program “Pharmacy” · 4th year · Al-Farabi Kazakh National University

Passive and active targeting

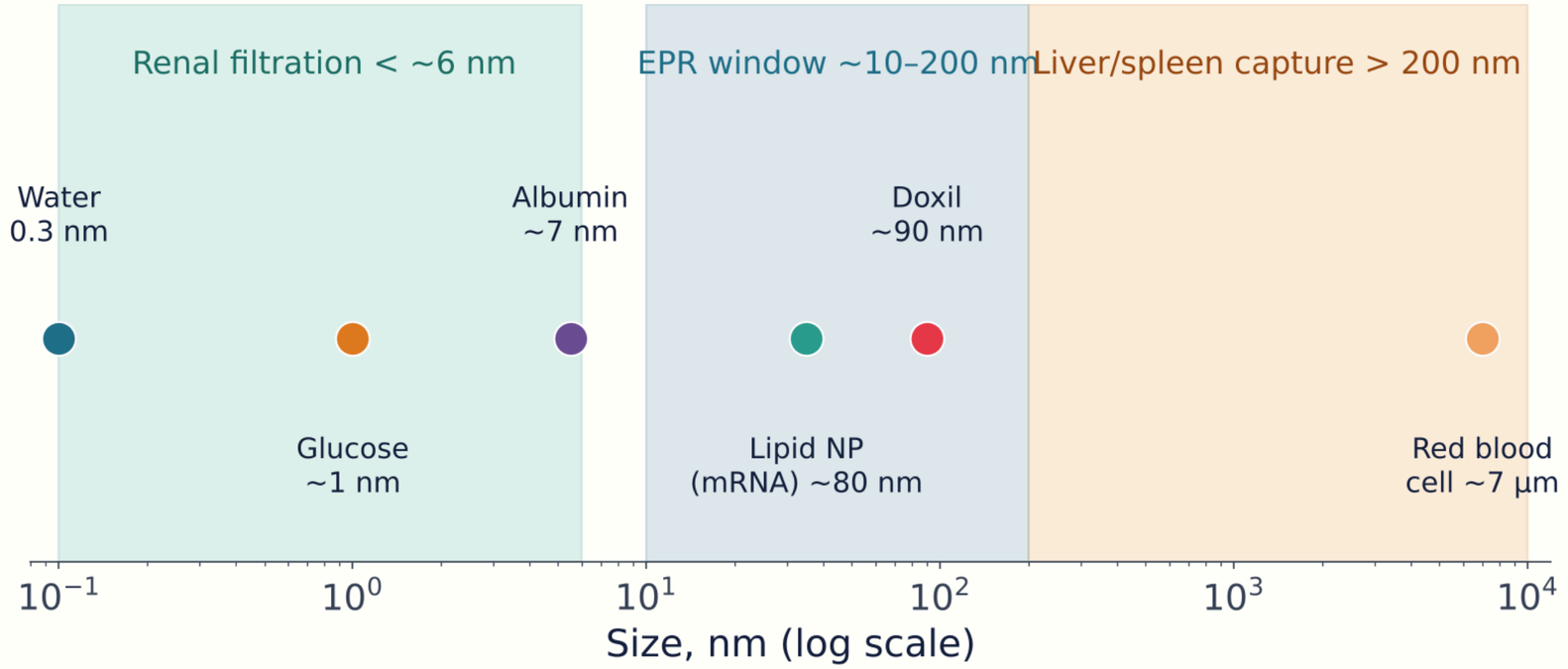
Passive: EPR effect

- Leaky tumour vessels let 10–200 nm particles out
- Poor lymphatic drainage keeps them there
- Needs long circulation (PEG)
- Strong in mice, variable in patients

Active: ligands

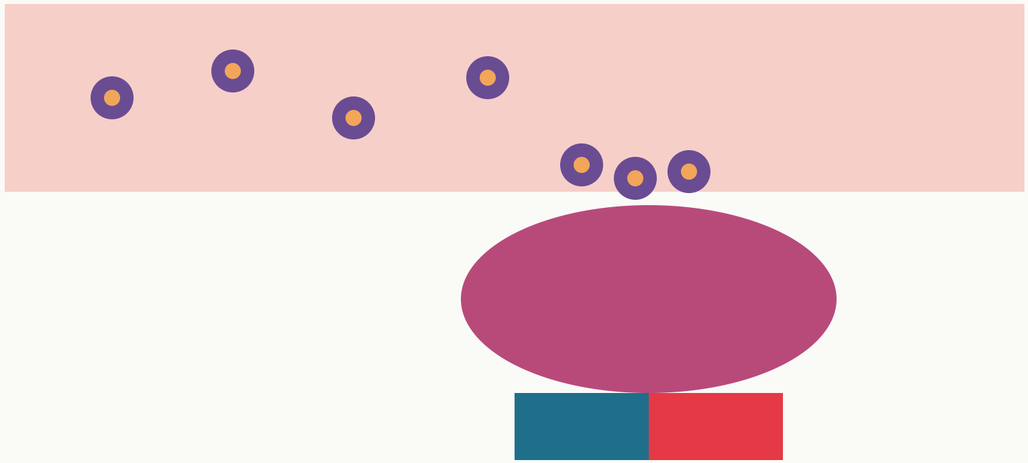
- Antibodies, peptides (RGD), folate, transferrin
- Bind receptors on target cells → uptake
- GalNAc → liver (siRNA conjugates)
- Antibody–drug conjugates: trastuzumab deruxtecan

Size decides where a particle goes



Shape, charge and surface coating change these limits, but size is the first design decision.

Magnetically controlled delivery

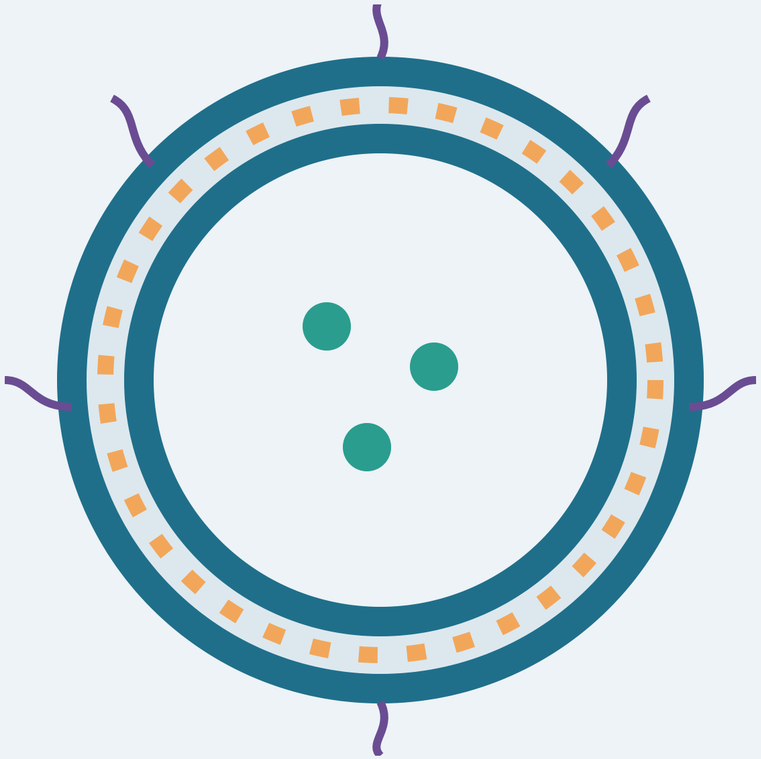


Superparamagnetic iron oxide (SPION) core, 10–100 nm, coated with dextran or PEG

External magnet concentrates particles at the target

Also: MRI contrast, hyperthermia in an alternating field (NanoTherm, EU-approved for glioblastoma)

Liposomes, niosomes and pharmacosomes



Liposome: phospholipid bilayer; **hydrophilic drug** inside, **lipophilic drug** in the bilayer, **PEG** outside

Niosome: non-ionic surfactant (Span) + cholesterol; cheaper, more stable

Pharmacosome: drug covalently bound to a lipid; self-assembles, no leakage

Types by size: SUV < 100 nm, LUV 100–1000 nm, MLV multilamellar

Methods of liposome preparation

Method	Principle	Result
Thin-film hydration	Dry lipid film hydrated with buffer (Bangham)	MLV; then sized
Sonication, extrusion	Energy or polycarbonate membranes reduce size	SUV, LUV of set size
Reverse-phase evaporation	Water-in-oil emulsion, solvent removed	LUV, high aqueous load
Ethanol injection, microfluidics	Lipid in ethanol mixed rapidly with water	Small uniform particles; LNP for mRNA
Remote (active) loading	pH or ammonium sulfate gradient pulls drug in	~100% doxorubicin loading (Doxil)

Lyophilisation with sugars (sucrose, trehalose) improves storage stability.

Characterising nanocarriers

Size, PDI

Dynamic light scattering; PDI < 0.2 = uniform

Zeta potential

Surface charge; |ζ| > 30 mV stable

Morphology

TEM, cryo-TEM: lamellarity, shape

Encapsulation

EE% = encapsulated / total drug × 100

Release

Dialysis bag, sample-and-separate methods

Stability

Size, leakage, lipid oxidation over time

Cells as drug carriers

Erythrocytes

Loaded “ghosts” by hypotonic lysis; circulate up to 120 days. Example: dexamethasone in autologous RBCs (EryDex, studied in ataxia-telangiectasia).

Exosomes

30–150 nm vesicles from cells; natural RNA and protein carriers, low immunogenicity; manufacturing is the challenge.

Stem and immune cells

Mesenchymal stem cells home to tumours and inflammation; CAR-T cells are “living drugs”.

Seminar 26 · Villa et al., Adv Drug Deliv Rev 2016;106:88–103; Herrmann, Wood & Fuhrmann, Nat Nanotechnol 2021;16:748–759

Theranostics: see it, then treat it

Platform	Diagnosis	Therapy
Iron oxide NPs	MRI contrast	Magnetic hyperthermia, drug carrier
Gold nanoparticles	CT, photoacoustic imaging	Photothermal therapy
Quantum dots	Fluorescence imaging	Research only (cadmium toxicity)
Radioligand pairs	^{68}Ga-PSMA PET	^{177}Lu-PSMA (Pluvicto)

Clinical theranostics today is mostly radiopharmaceutical: the same ligand carries an imaging or a therapeutic isotope.

Nanotoxicity: what makes a particle harmful

Oxidative stress

Large reactive surface produces ROS → inflammation, DNA damage

Membrane damage

Cationic particles disrupt membranes, haemolysis

Immune reactions

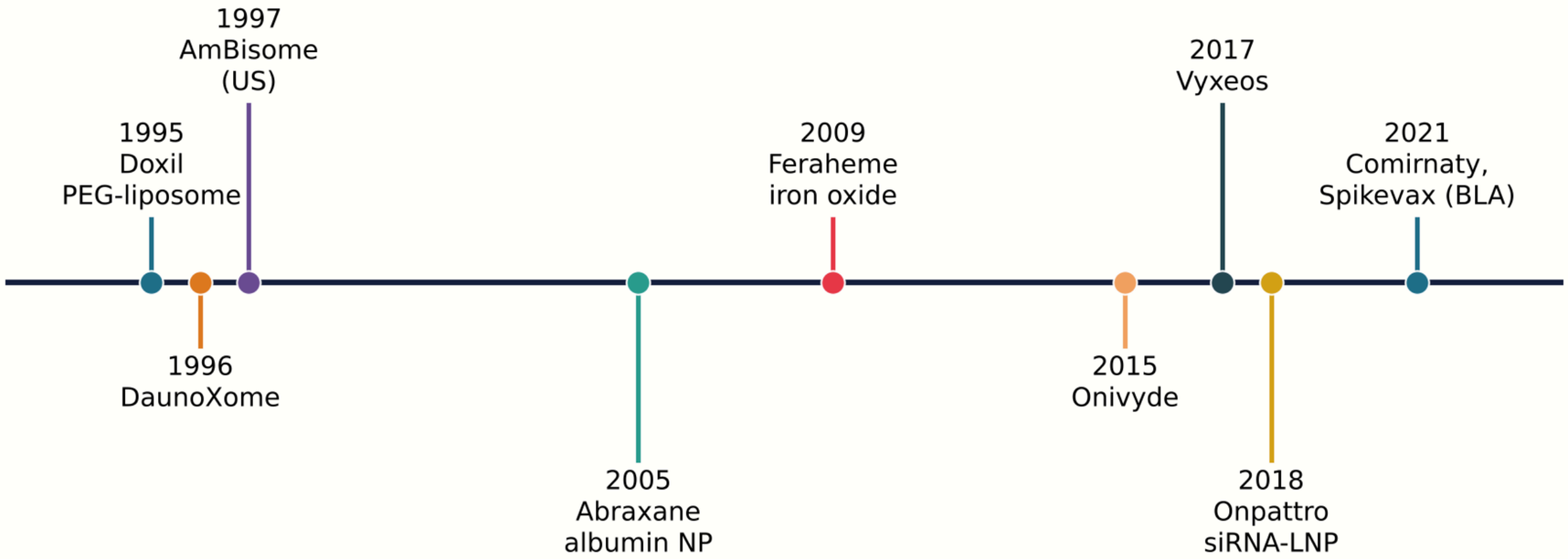
Complement activation (CARPA), anti-PEG antibodies

Persistence

Non-degradable particles accumulate in liver and spleen; long fibres

Toxicity depends on size, shape, charge, surface and dose — not only on the chemical element.

Nanomedicines that reached patients



Regulation: EMA reflection papers on nanomedicines; FDA guidance on drug products containing nanomaterials (2022); “non-biological complex drugs” need special generic rules.

Smart (stimuli-responsive) systems

Stimulus	Responsive material	Example
pH	Acid-labile bonds, Eudragit	Release in tumour or endosome
Temperature	Thermosensitive lipids, PNIPAM	ThermoDox with local heating
Enzymes	Peptide linkers (MMP, cathepsin)	Antibody–drug conjugate linkers
Glucose	Glucose oxidase, phenylboronic acid	Self-regulating insulin (research)
Light, magnetic field, ultrasound	Gold, SPION, microbubbles	Remote-controlled release

Future: closed-loop and personalised systems that sense and dose automatically.

Questions for discussion

1. Why does the EPR effect work better in mice than in patients?
2. Where in a liposome would you load doxorubicin, and where amphotericin B?
3. 10 mg drug added, 3 mg free after separation. Calculate EE%.
4. Name one advantage and one challenge of exosomes as carriers.
5. Why is the PSMA PET/^{177}Lu pair called theranostic?
6. Why are cationic nanoparticles more toxic?

References

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