# PharmacoLearn

**MPH201T Molecular Pharmaceutics (Nano Tech and Targeted DDS), M.Pharm Semester 2**

## Unit 1: Targeted Drug Delivery Systems

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Molecular Pharmaceutics (Nano Tech and Targeted DDS), subject code MPH201T, is a core Semester 2 subject of M.Pharm Pharmaceutics. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. This subject is about delivering a drug to the place in the body where it is needed, in the amount needed, instead of distributing it everywhere and accepting toxicity in healthy tissues. The first unit builds the concept of targeted drug delivery, the biological events a carrier must survive, and the two model problems of tumour targeting and brain specific delivery. The second unit studies the methods of targeting and the two carrier families examined in most depth, nanoparticles and liposomes, with their types, preparation and evaluation. The third unit covers microcapsules and microspheres, monoclonal antibodies as targeting agents, and the vesicular and related carriers niosomes, aquasomes, phytosomes and electrosomes. The fourth unit turns to site specific routes in their own right: pulmonary delivery by aerosols and intra nasal delivery. The last unit deals with nucleic acid based therapeutics: gene therapy, viral and nonviral gene transfer, liposomal gene delivery, and the antisense molecules and aptamers that are expected to become the drugs of the future. A student who completes this subject should be able to explain how a targeted system is designed, prepare and evaluate the main carrier systems in the laboratory, and judge which carrier suits a given drug and target.

### 1.1 The concept of drug targeting

Conventional dosage forms distribute the drug throughout the body according to the physicochemical properties of the molecule. Only a small fraction of the dose reaches the tissue that needs treatment, while the rest is taken up by healthy organs, where it causes side effects, and is cleared by the liver and kidneys. A targeted drug delivery system is designed to reverse this distribution: the drug, alone or loaded in a carrier, is transported preferentially to the target tissue, organ, cell or even an intracellular compartment, so that the concentration at the site of action rises and the exposure of the rest of the body falls.

The idea is old. Paul Ehrlich proposed the concept of a magic bullet (Zauberkugel) at the beginning of the twentieth century: a carrier that would seek out the diseased site and deliver its toxic payload only there. Targeted delivery is the practical attempt to build that bullet, usually by attaching the drug to a carrier (a nanoparticle, liposome, microsphere or antibody) whose size, surface and ligands decide where it goes.

The advantages expected from targeting are:

- **Higher efficacy at a lower dose:** more of the administered drug reaches the receptor site, so the same effect is obtained with a smaller total dose.
- **Lower toxicity:** healthy tissues are exposed to less drug, which matters most for cytotoxic anticancer drugs with a narrow therapeutic index.
- **Protection of the drug:** the carrier shields labile molecules such as peptides, enzymes and nucleic acids from enzymes and pH during transit.
- **Control of release:** the carrier can be designed to release the drug slowly, or in response to a local stimulus such as pH, temperature or an enzyme.
- **Delivery to difficult sites:** carriers can cross or bypass barriers that the free drug cannot, for example the blood brain barrier or the interior of a solid tumour.
- **Improved patient acceptance:** less frequent dosing and fewer side effects improve compliance.

Targeting is not free of problems. The carrier itself must be non toxic, non immunogenic, biodegradable or safely eliminable, stable on storage, and manufacturable at scale and at acceptable cost. The body also treats most carriers as foreign particles and removes them through the reticuloendothelial system (section 1.2), so a targeting design is always a negotiation between the carrier and the body's defences.

## 1.2 Events and biological processes involved in drug targeting

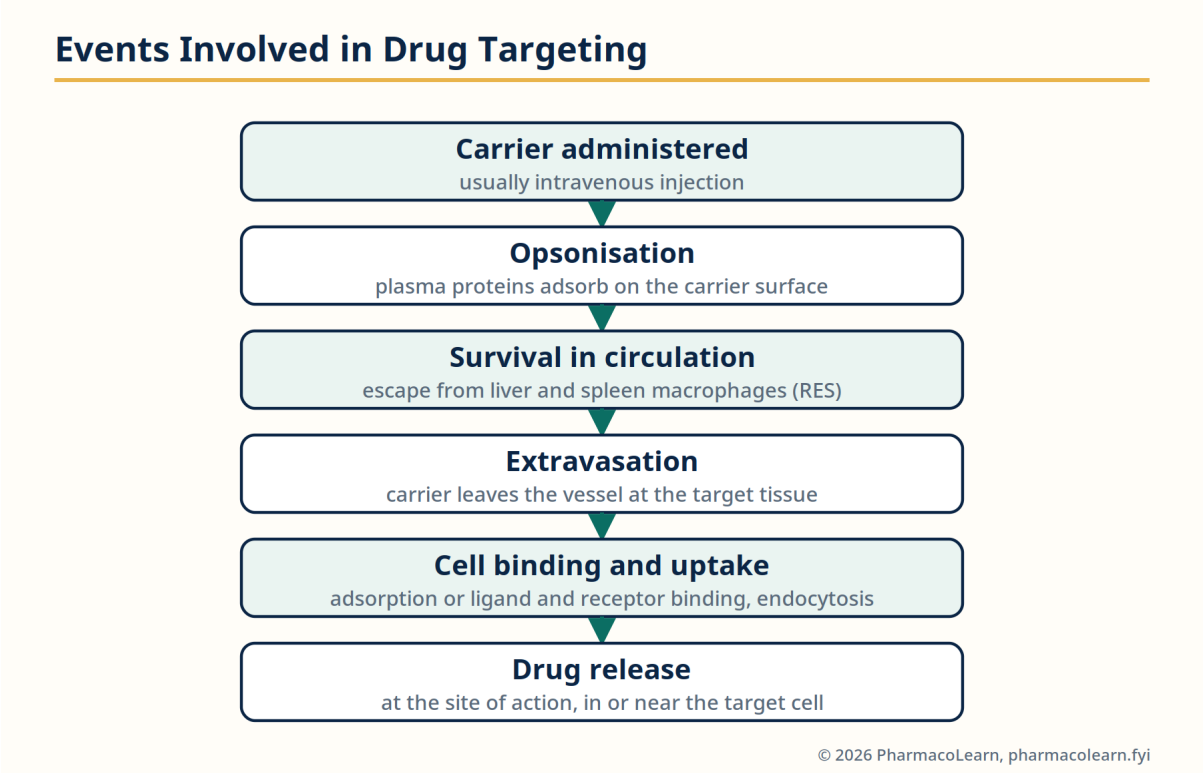


*Figure: The sequence of events a targeted carrier must pass through: it can fail at any step, and carrier design is the attempt to survive each one.*

Between injection or administration and arrival at the target, a carrier passes through a sequence of events, and it can fail at every step. Understanding this sequence is the basis of all carrier design.

```
Sequence of events in drug targeting
Carrier administered (usually intravenous)
        |
        v
Circulation: plasma proteins adsorb (opsonisation)
        |
        v
Survival against reticuloendothelial clearance
        |
        v
Extravasation: carrier leaves the blood vessel at the target tissue
        |
        v
Interstitial transport to the target cell
        |
        v
Binding to the cell surface (ligand and receptor, if active targeting)
        |
        v
Internalisation (endocytosis) and intracellular trafficking
        |
        v
Drug release at the site of action
```

The main biological processes in this sequence are:

- **Opsonisation.** As soon as a particle enters the blood, plasma proteins called opsonins (immunoglobulins, complement components such as C3b, fibronectin) adsorb onto its surface. This protein layer, often called the protein corona, marks the particle as foreign.
- **Reticuloendothelial clearance.** Opsonised particles are recognised and phagocytosed by the fixed macrophages of the reticuloendothelial system (RES), also called the mononuclear phagocyte system, mainly the Kupffer cells of the liver and the macrophages of the spleen and bone marrow. Conventional particles are cleared within minutes. This is the single biggest obstacle to targeting any site other than the liver and spleen themselves, and it is why surface modification with hydrophilic polymers such as polyethylene glycol (PEG), which reduces opsonisation, is used to make long circulating or stealth carriers.
- **Extravasation.** To reach tissue cells, the carrier must leave the blood vessel. Normal continuous endothelium allows only small molecules through, but the endothelium in inflamed tissue and solid tumours is fenestrated and leaky, and the liver and spleen sinusoids are discontinuous, so particle size decides which tissues a carrier can enter.
- **Interstitial transport.** After leaving the vessel, the carrier must diffuse through the extracellular matrix to reach the cells. High interstitial pressure inside tumours opposes this movement.
- **Cell binding and uptake.** The carrier binds to the cell, by simple adsorption in passive systems or by a ligand binding its receptor in active systems, and is then usually taken in by endocytosis (phagocytosis for large particles, pinocytosis and receptor mediated endocytosis for smaller ones).
- **Intracellular fate and release.** Endocytosed carriers enter endosomes and then lysosomes, where enzymes and low pH can destroy the drug. A successful carrier either releases the drug before this happens, escapes the endosome, or is designed so that the lysosomal enzymes themselves trigger release.

Targeting is also described by orders or levels, according to how precise the destination is. In **first order targeting** the carrier reaches a whole organ or tissue compartment (for example the liver). In **second order targeting** it reaches a particular cell type within that organ (for example the hepatocyte rather than the Kupffer cell). In **third order targeting** it reaches an intracellular destination, such as the nucleus or a lysosome. The higher the order, the more sophisticated the carrier design must be.

## 1.3 Why most carriers accumulate in liver and spleen

The pattern of RES clearance explains the default biodistribution of almost every particulate carrier: the majority of an intravenous dose of conventional nanoparticles, liposomes or microspheres ends in the liver and spleen. This is a failure when the target is elsewhere, but it can be used deliberately. Liver targeting is exploited for drugs against hepatic infections and for lysosomal storage disorders, and splenic and macrophage targeting is useful against infections that hide inside macrophages, such as leishmaniasis, where liposomal amphotericin B reaches the infected macrophages of the liver and spleen directly. The lesson for design is that biodistribution is decided mainly by size, surface charge and surface hydrophilicity, and only secondarily by the drug inside the carrier.

| Property of carrier | Effect on fate in the body |
|---|---|
| Size above about 200 nm | Rapid uptake by spleen and liver macrophages |
| Strong positive or negative surface charge | More opsonisation, faster RES clearance |
| Hydrophobic surface | More protein adsorption, faster clearance |
| PEG coated (stealth) surface | Reduced opsonisation, long circulation, more time to reach the target |
| Ligand on the surface | Binding to cells carrying the matching receptor, if the carrier reaches them |

## 1.4 Tumour targeting

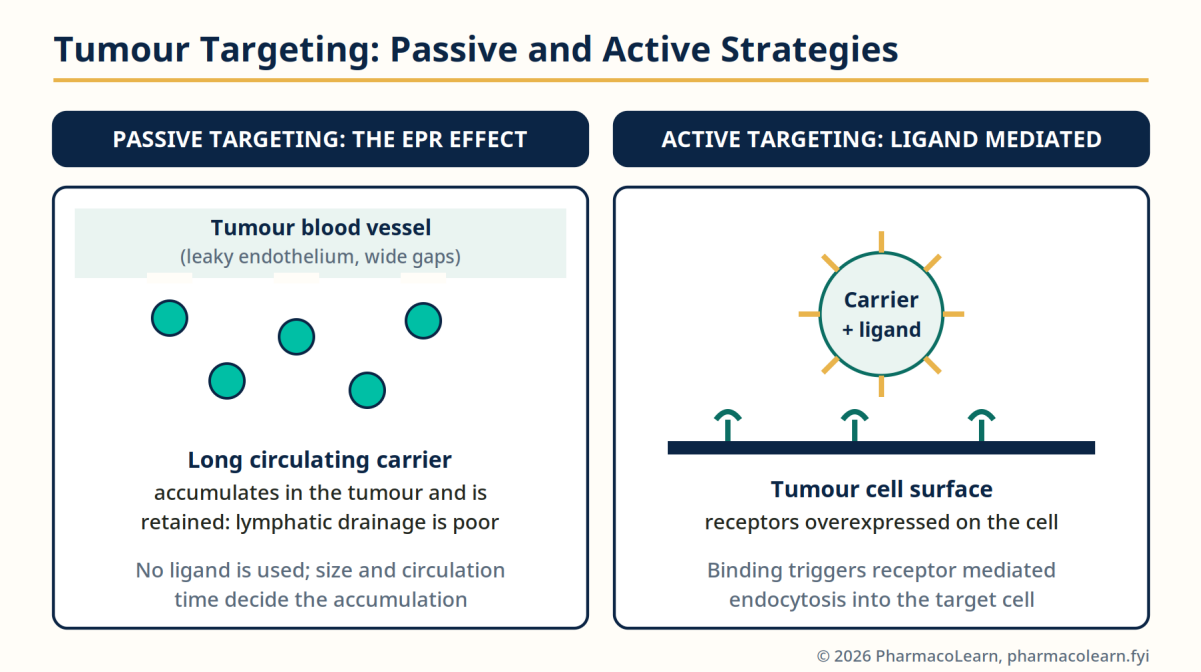


*Figure: Passive targeting accumulates long circulating carriers in tumours through the EPR effect; active targeting adds a ligand so the carrier binds and enters receptor bearing cells.*

Solid tumours are the most studied target in this subject, because anticancer drugs are potent, toxic and needed in high local concentration. Tumour targeting rests on the unusual biology of the tumour tissue:

- **Angiogenesis and leaky vasculature.** A growing tumour secretes angiogenic factors such as vascular endothelial growth factor (VEGF) and builds new blood vessels in haste. These vessels are poorly organised, with wide fenestrations and gaps in the endothelium (openings of the order of 100 to 800 nm are reported between tumour endothelial cells, much wider than in normal vessels), and an incomplete basement membrane.
- **Poor lymphatic drainage.** Tumours lack a functional lymphatic system, so material that enters the tumour interstitium is not drained away efficiently and is retained.
- **Enhanced permeability and retention (EPR) effect.** The combination of leaky vessels and poor drainage, described by Maeda and co-workers, means that macromolecules and nanoparticles in a suitable size range (roughly 10 to 200 nm) extravasate preferentially into tumours and accumulate there to concentrations many times higher than in normal tissue. This is the basis of passive tumour targeting.
- **A distinctive microenvironment.** Tumour tissue is often slightly acidic, hypoxic in its core, and rich in certain enzymes, which can be used as triggers for stimulus responsive release.

Two strategies are used. In **passive targeting**, no ligand is used; the carrier is made long circulating (for example PEGylated) and of a size that exploits the EPR effect, so accumulation follows from the tumour's own anatomy. The first approved nanodrug, Doxil (PEGylated liposomal doxorubicin, approved in 1995), works in exactly this way and reduces the cardiac toxicity of free doxorubicin. In **active targeting**, a ligand such as an antibody, a peptide, folic acid or transferrin is attached to the carrier surface so that it binds a receptor overexpressed on tumour cells (for example HER2, folate receptor or transferrin receptor) and is internalised by receptor mediated endocytosis. Active targeting mainly improves cell uptake after the carrier has already arrived in the tumour; it does not by itself bring more carrier out of the blood stream, which is why it is combined with a long circulating design. A third approach, **stimulus responsive targeting**, uses

carriers that release the drug when they meet the tumour's low pH, raised temperature or specific enzymes.

Limitations must be stated honestly: the EPR effect varies between tumour types and between patients, tumour interstitial pressure is high and opposes carrier entry, and necrotic tumour cores are poorly perfused. Even so, tumour targeting remains the model application in which nearly every carrier in Units 2 and 3 is tested.

### 1.5 Brain specific delivery

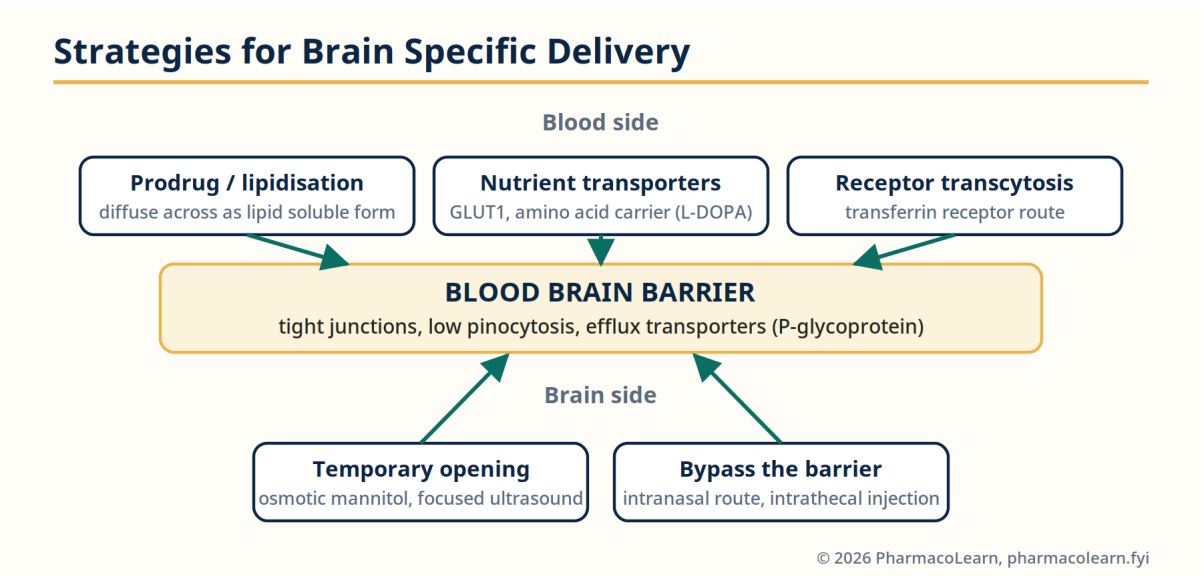


*Figure: The blood brain barrier and the five families of strategy used to cross it or bypass it.*

The brain is protected by the blood brain barrier (BBB), a continuous layer of endothelial cells joined by tight junctions, supported by pericytes and astrocyte end feet, with very low pinocytotic activity and with efflux transporters such as P-glycoprotein that pump foreign molecules back into the blood. The barrier keeps out almost all large molecules and the great majority of small molecules too, which protects the brain but also makes brain tumours, infections and neurodegenerative diseases very difficult to treat with drugs given by ordinary routes.

The main strategies for brain specific delivery are:

- **Lipidisation and prodrugs.** Making the molecule more lipid soluble, or masking polar groups in a prodrug that is converted after crossing, improves passive diffusion across the endothelium. The classic example is heroin (diamorphine), the lipid soluble prodrug of morphine, which crosses far faster than morphine itself.
- **Carrier mediated transport.** The BBB carries nutrient transporters, for example the glucose transporter GLUT1 and the large neutral amino acid transporter. L-DOPA is the standard example of a drug that crosses on the amino acid transporter and is then converted to dopamine inside the brain.
- **Receptor mediated transcytosis.** Receptors such as the transferrin receptor and the insulin receptor carry their ligands across the endothelium by transcytosis. Attaching a drug or a carrier to transferrin, or to an antibody against the transferrin receptor, hijacks this route; this is one of the main approaches for delivering nanoparticles and biologics to the brain.
- **Adsorptive mediated transcytosis.** Cationic molecules and cationised proteins bind the negatively charged endothelial surface and are carried across; the route is effective but not brain specific.

- **Temporary disruption of the barrier.** Osmotic opening with hypertonic mannitol, or focused ultrasound with microbubbles, opens the tight junctions for a short time so that drugs can enter; the risk is that unwanted substances enter too.
- **Bypassing the barrier.** Intranasal delivery along the olfactory and trigeminal pathways (Unit 4), intrathecal injection and direct implants avoid the BBB altogether.
- **Nanocarriers.** Lipid nanoparticles and polymeric nanoparticles, especially when surface modified with ligands such as transferrin or with polysorbate coatings that adsorb apolipoproteins from plasma, show improved brain uptake in experimental work and are an active research direction.

The design lesson of this unit is that a targeted system is defined by three things together: the biology of the target, the properties of the carrier, and the events in between. Units 2 and 3 now take up the carriers one by one.

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