Lecture 10

Organic Pharm. Chemistry for Pharmacy Students

By

Professor Dr. Mohie Sharaf El Din

Drug targeting

- is defined as the ability of a drug molecule to accumulate in the target organ or tissue **selectively** such that the concentration of the drug at the disease site is high, while its concentration in nontarget organs and tissues is low, preferably, below certain minimal level so as to prevent any toxic effect.

- Thus, drug targeting **can**

i. overcome the non-specific toxic effect of conventional drug delivery.

ii. This may also reduce the amount of drug required dose.

- A drug can be targeted **on**

i. the level of a whole organ,

ii. on the level of certain cells specific for a given organ,

iii. or even on the sub-cellular level of specific tissue .

- The concept of drug targeting can be considered as an entity **consisting of two components** —

a. the first one should recognize and bind the target, while

b. b. the second should provide a therapeutic action in this target.

- Currently, the concept includes a coordinated behavior of three components – drug, targeting moiety and pharmaceutical carrier

- **Various pharmaceutical carriers** explored for targeting drug include polymeric micelles, liposomes, nanoparticles such as solid lipid nanoparticles, gold nanoparticles, quantum dots, etc.
- All these carriers can be made targeted in one way or another.
- The most widely-used approach involves utilizing specific targeting moieties.
- However in certain cases, physical principles or some physiological features of the target area may be utilized for a successful targeting of pharmaceuticals and pharmaceutical carriers.

Direct application

- Direct application of a drug into the affected area qualifies as a drug targeting approach as a high concentration of drug is achieved in the target area.
- Direct application may sound like a simple technique to achieve drug targeting, however developing such formulations can be complicated.
- The successful **example** of this approach includes intra-articulate administration of **methotrexate** liposomal preparations containing a phospholipid conjugate of methotrexate and dimyristoylphosphatidylethanolamine (MTX-γ-DMPE) for the treatment of arthritis .
- Ophthalmic delivery of **carteolol** loaded poly-ε-caprolactone nanoparticles for the treatment of intraocular hypertension **Carteolol (eye drops for glaucoma)**
- is **another example**

دواء يُستخدم ملعاجلة التهاب املفاصل الروماتيزمي

من الأدوية المناعية التي تستخدم لعلاج العديد من الأمراض المناعية (خاصة الروماتيزم).

Carteolol (eye drops for glaucoma

I. Passive Targeting

- Passive accumulation of drug through leaky vasculature of a diseased area has been explored by many researchers as a potential for drug targeting.
- It was found that under certain pathological states, such as tumors, infarcts, and inflammation, permeability of vascular endothelial increases and they become leaky.
- In such areas with increased vascular permeability, nanoparticles such as micelles and liposomes can accumulate and exert their therapeutic effect.
- This spontaneous or 'passive' drug delivery is also known as an '**enhanced permeability and retention**' **(EPR) effect** and is largely used for cancer targeting .
- A marketed drug formulation**, Doxil**, which is **doxorubicin** incorporated into long circulating **polyethylene glycol(PEG)** coated liposomes, is an excellent example of EPR-based targeting

- Doxil : is an antibiotic medicine containing doxycycline.

Physical Targeting

- Physical factors such as pH, or temperature have been explored for targeted drug delivery.
- The drug targeting is based on the fact that certain pathological areas differ from normal tissues in their pH and temperature.
- Various other physical attributes that can be used for physical targeting are

  A. Redox-sensitive systems,

  B. Magnetic-sensitive systems and

  C. Ultrasound-sensitive systems.

- In physical targeting, the carrier is distributed in systemic circulation and will not accumulate at the target site.
- However, the carrier will degrade in the target site, where the drug will release and accumulate .
- All of these systems are discussed in detail below.

a. pH-sensitive Systems

- The pH of the pathological tissue is lower than the normal tissue, e.g. at the site of inflammation pH drops from 7.4 to pH 6.5.
- The same is observed in the case of infarcts . Also, the pH is lower in the tumor mass (pH 6.5) than the surrounding tissue (pH 7.4).
- The microenvironment of a tumor is acidic because insufficient oxygen in tumors leads to hypoxia and causes production of lactic acid.
- This behavior is utilized for the preparation of pH-responsive drug or gene delivery systems, which can exploit the biochemical properties at the diseased site for targeted delivery

- Various nanocarriers use the approach of pH difference to target the drug at a tumor site. Anticancer drugs can be conjugated to pH sensitive polymers.
- This is done by conjugating the acid sensitive spacers between the drug and polymer, enabling the release of the drug either in relatively acidic extracellular fluids, or after endocytosis in endosomes or lysosomes of tumor cells

- Uses of nanocarriers such as liposomes and polymeric micelles have also been described that include the components with acid-labile bonds .
- Long circulating PEGylated pH sensitive liposomes were prepared by Roux et al. using the combination of PEG and pH-sensitive terminally alkylated copolymer of N-isopropylacrylamide and methacrylic on the same liposome.
- pH-sensitive liposome attached with target specific ligands (folate and Tf) for cytosolic delivery has also been developed

b. Temperature-sensitive Systems

- Temperature-sensitive nanocarrier targeting is based on the fact that many pathological conditions demonstrate distinct hyperthermia.
- Meyer et al. showed the viability of the temperature-sensitive approach by demonstrating a significantly greater accumulation of the intravenously administered **liposomes** and other nanocarriers in the tumor upon heating to 42°C in human ovarian carcinoma xenograft model .

- Temperature-sensitive **polymeric micelles** can be prepared by using thermosensitive polymers which displays a lower critical solution temperature (LCST) in aqueous solution.
- LCST is the temperature below which the polymers are water soluble and above which they become water-insoluble.
- An **example** of **thermosensitive polymers** includes Poly(N-alkylacrylamide)s Poly(NIPAM) and its block copolymers, Poly(methyl vinyl ether) (PMVE) etc.

- **Liposomes** can also be made temperature-sensitive via the incorporation of polymers which display a lower critical solution temperature (LCST), slightly above the physiological temperature.
- Because these polymers are soluble below LCST and precipitate when the temperature increases above the LCST, they can damage the liposomal membrane during precipitation and allow for drug release.
- Poly(N-isopropylacrylamide) (NIPAM) can be used for such liposome preparations.
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- For example, Han et al. investigated the release of doxorubicin (Dox) from liposomes composed of poly(N-isopropylacrylamide- co-acrylamide) (NIPAAm-AAM) and PEG.
- The release of doxorubicin was increased around the transition temperature of the polymer.
- In addition, modified liposomes were found to be stable in the serum compared with unmodified liposomes suggesting that NIPAAm-AAM/PEG modified liposomes are suitable for targeted-drug delivery

C. Redox Potential Sensitive Systems

- The use of high redox potential difference, which exists between the reducing intracellular space and oxidizing extracellular space, can also be utilized for the formulation of stimuli-sensitive systems.
- To make use of redox potential, the chemistry of the disulfide bond is employed. In these systems, the active molecule, drug or DNA, are loaded into nanocarriers whose structure is maintained by a disulfide bond.
- As soon as those bonds are reduced to thiol groups due to the presence of high glutathione inside the cells, the integrity of the carrier is compromised and the drug is released .

- Cavallaro et al. have used polymers that are positively charged and thiol groups incorporated into the polymer structure to complex DNA (via positive charge) and to form polymeric network (via disulfide bridges formed from groups).
- When reduced, disulfide bridges convert back to thiols, polymeric carrier disintegrates and DNA release is facilitated .
- Kirpotin et al. reported other redox-sensitive liposomes with long circulating property made up of detachable disulfide linked PEG polymer coating.

d. Magnetic-sensitive Systems

- The concept of magnetic drug targeting was first introduced by Widder et al. in 1979.
- The concept is based upon conjugation of a drug molecule with magnetic particles and guiding these magnetic particles towards the intended pathology site under the influence of an external magnetic field .
- In magnetic-sensitive systems, iron oxide nanoparticles, namely **magnemite** or **magnetite**, with particle size 4–10 nm are used.
- They are referred to as superparamagnetic iron oxide nanoparticles (SPIONs) based on their superparamagnetic properties and small size.

- Another interesting approach of SPIONs in tumor targeting is to increase the local temperatures by an alternating magnetic field. The method is based on tumor accumulation of SPION and the exposure of the tumor to an alternating magnetic field, whereby the tumor is eliminated by heat developed by oscillating SPION.
- The temperature increase achieved by this depends on the size, shape and accumulation of the nanoparticles in the intended site and on the applied alternating magnetic field.

- **E. Ultrasound-sensitive Systems**
- The concept of ultrasound-sensitive drug delivery systems is based upon accumulation of nanocarrier in the required area where they can be made leaky by the local application of an external ultrasound. Once the structure is disrupted, nanocarriers can liberate incorporated drugs or genes .
- **Polymeric micelles** incorporated with doxorubicin have been prepared. They demonstrated the release after ultrasonication was applied .
- A similar approach was used by Tiukinhoy-Laing et al. for the local release of thrombolytic enzymes, plasminogen activator, from **echogenic liposomes** in the area of clot formation. In this case, specific binding of plasminogen activator with fibrin additionally facilitated drug accumulation in the target zone providing a promising multifunctionality: contrast properties, targeting ability and thrombolytic drug release .

II. Active Targeting

- Active targeting is a non-invasive approach, in which the drug is transported to the target organ or tissue using site-specific ligands.
- The pairing of drug carriers, such as liposome, particulate nanocarrier etc., with a ligand leads to the specific targeting to selected cells. **Targeting ligands can be broadly classified as proteins** (mainly antibodies and their fragments such as TAT), **nucleic acids** (aptamers), or other receptor ligands (peptides, vitamins, and carbohydrates)

- One of the earliest approaches of **active drug targeting** is a direct coupling of a drug to a targeting moiety. **Immunotoxins** is an example of this approach .
- In addition, particulate or reservoir type drug carriers can be used to load the drug which provides the advantage of high loading capacity, eliminated need for covalent conjugation of the drug, protection of the entrapped drug from enzymatic inactivation by formulation, along with the possibility to control size, permeability and plasmic longevity (PEGylated).

- Targeting cancer with a monoclonal antibody (mAb) was described by Milstein in 1983 . Afterwards, the feasibility of using an antibody as a ligand for targeting has been demonstrated with many molecules.
- For example, **mAb rituximab** (Rituxan) was used for treatment of patients with non-Hodgkin's lymphoma (a type of cancer that originates in lymphocytes**), Trastuzumab** (Herceptin), an anti-HER2 mAb that binds to ErbB2 receptors for the treatment of breast cancer, and many more .

Challenges in Developing Targeted Drug Delivery Systems

- They have not been extensively characterized in a clinical setting i.e., pharmacokinetics, biodistribution, and toxicity.
- Each system is unique and must be evaluated as a new formulation.
- Development of suitable screening methodologies for determining optimal characteristics of nanocarriers is still not clear. Therefore, successful targeting strategies must be determined experimentally on a case-by-case basis, which is laborious.

- **Major developmental concerns** have to be resolved such as formulation stability, particle size uniformity, control of drug release rate and large scale manufacture of sterile preparations before these formulations can become therapeutically relevant.
- The overall cost is very high and furthermore, the development process is time consuming due to its unique requirements.
- The relevance of a**n in vitro tests** activity, selectivity, uptake, and toxicity of targeted systems to the animal or human is still an area of research and great amount of work is needed before clinical application of such systems.