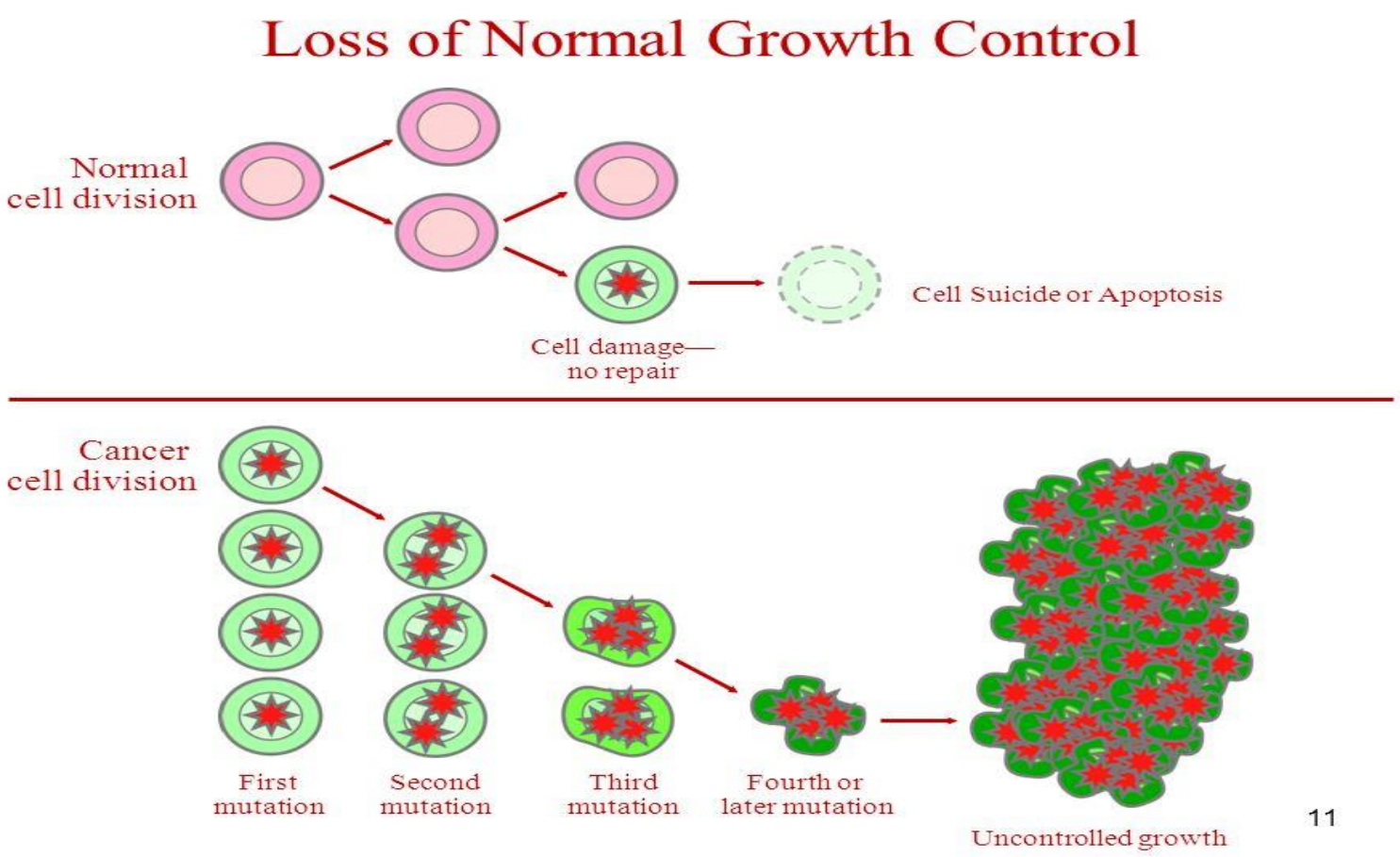
Targeted drug delivery systems

Tumor targeting and brain specific delivery

Tumor

- It is an abnormal mass of tissue which is a classic sign of inflammation.
- It is a fluid-filled lesion that may or may not be formed by an abnormal growth of neoplastic cells that appears enlarged in size.
- The term cancer refers to a new growth which has the ability to invade tissues, metastasize (spread to other organs) and which may eventually lead to the patient's death if untreated.

Growth of cancer cells



Drug targeting to tumor

- Drug targeting to tumor have been divided into categories of "passive" and "active".

- PASSIVE TARGETING: Passive targeting can differentiate between normal and tumor tissues and has the advantage of direct permeation to tumor tissue. Drug administered passively in the form of prodrug or inactive form, when exposed to tumor tissue, becomes highly active.

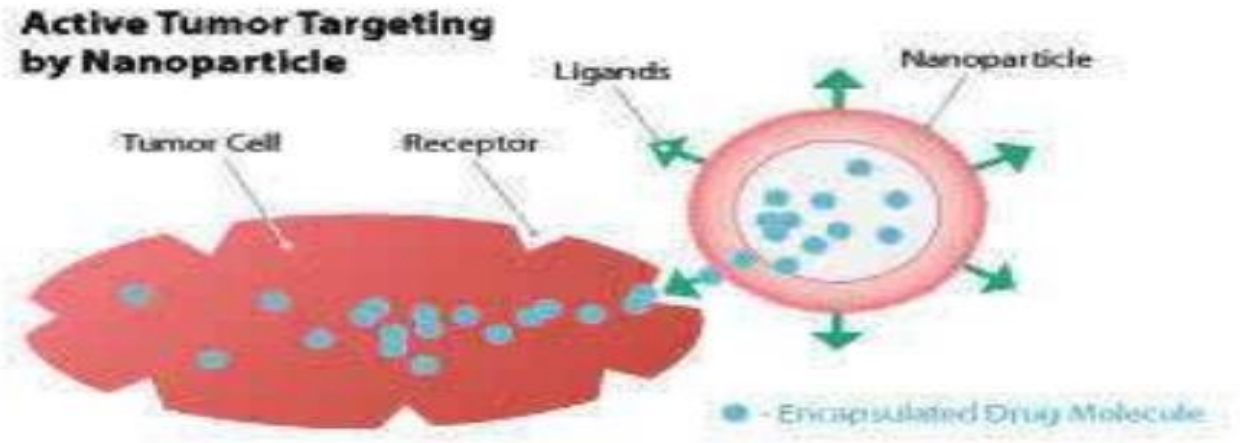
- Nanoparticles follow the biological mechanisms such as ERS (Enhanced Retention System).

- Size should be below 100 nanometers in diameter and drug accumulates around the tissue.

Active targeting

Active targeting:

- By conjugating the nanoparticles with a drug to desired target site, an active targeting may be achieved.
- Active targeting allows the increased accumulation of the drug in cancer tissue.



Targeted Therapies available in tumor treatment

Many different targeted therapies have been approved for use in cancer treatment. These are:

- Hormone therapies,
- Signal transduction inhibitors,
- Gene expression modulator,
- Apoptosis inducer,
- Angiogenesis inhibitor,
- Immuno therapies,
- Toxin delivery molecules

Treatment with targeted molecular therapy

- It is a type of personalized medical therapy designed to treat cancer by interrupting unique molecular abnormalities that drive cancer growth.
- Targeted therapies are drugs that are designed to interfere with a specific biochemical pathway that is central to the development, growth and spread of that particular cancer.

Treatment with Immunotherapy

- Immunotherapy is designed to repair, stimulate, or enhance the immune system's responses using patients' own immune systems to fight cancer. It uses the body's own immune system to:
- Target specific cancer cells, thereby potentially avoiding damage to normal cells.
- Make cancer cells easier for the immune system to recognize and destroy.
- Prevent or slow tumor growth and spread of cancer cells.

Example: vaccine therapy

Treatment with Gene therapy

- Cancer is caused by changes in our genes.

- Gene therapy is designed to modify cancer cells at the molecular level and replace a missing or bad gene with a healthy one.

- The new gene is delivered to the target cell via a 'vector,' which is usually an inactive virus or liposome, a tiny fat bubble

Antibody directed enzyme prodrug therapy

- First injection---- the monoclonal Ab is given (with enzyme attached)
- Second injection (hours later)-----a second drug (the pro drug) is given
- Activation---- the prodrug comes into contact with the enzyme and drug then able to destroy the cancer cells
- Selectivity-----enzyme Ab conjugate doesnot attach to normal cells. And drug doesnot affect them

Stimuli Responsive drug release

- The tumor microenvironment differs from the normal cells microenvironment

- Advantage of the difference in pH, temperature and presence of enzymes is used to release the drug in tumor microenvironment.

- The rapid release of drug from its carrier is key to the therapeutic efficacy of dosage form

Limitations of tumor targeting

- Cancer cells can become resistant to them. Resistance can occur in two ways—
- The target itself changes through mutation so that the targeted therapy no longer interacts well with it.
- The tumor finds a new pathway to achieve tumor growth that does not depend on the target.

- SIDE EFFECTS

The most common side effects seen with targeted therapies are :

- Diarrhea and liver problems, such as hepatitis and elevated liver enzymes.
- Skin problems (rash, dry skin, nail changes, hair depigmentation)
- Problems with blood clotting and wound healing
- High blood pressure.

Future perspectives

- For cancer therapies, the ideal targeted drug delivery system is the one that delivers the drug only to the target tumor.

- As tumors may not be eradicated by just aiming at one target, it may also be necessary to simultaneously aim at multiple targets. Thus, it may be worthwhile to develop “magic shotgun” strategies that deliver multiple drugs, and/or deliver the drug to multiple targets

Brain specific drug delivery system

Aim

- To emphasize on drug delivery to brain by using various approaches.
- To study the Blood Brain barrier.
- To study different approaches to bypass the BBB and to deliver therapeutics into the brain.

INTRODUCTION

- Drug delivery to the brain is the process of passing therapeutically active molecules across the Blood Brain Barrier for the purpose of treating brain maladies.
- This is a complex process that must take into account the complex anatomy of the brain as well as the restrictions imposed by the special junctions of the Blood Brain Barrier.
- In response to the insufficiency in conventional delivery mechanisms, aggressive research efforts have recently focused on the development of new strategies to more effectively deliver drug molecules to the CNS.
- Various routes of administration as well as conjugations of drugs,

e.g. with liposomes and nanoparticles are considered.

- Some routes of direct administration to the brain are non-invasi such as transnasal route whereas others involve entry into the CNS by devices and needles such as in case of intrathecal and intracerebroventricular is considered along with sustained and controlled release delivery.
- Among the three main approaches to drug delivery to the CNS systemic administration, injection into CSF pathways, and direc injection into the brain, the greatest developments is anticipate to occur in the area of targeted delivery by systemic administration.
- Overcoming the difficulty of delivering therapeutic agents to specific regions of the brain presents a major challenge to treatment of most brain disorders. The brain (central nervous system) is protected by barriers which control the entry of compounds into the brain, thereby regulating brain homeostasi Brain is tightly segregated from the circulating blood by a uniqu membranous barrier - the Blood Brain Barrier (BBB).

BLOOD-BRAIN BARRIER

- The blood–brain barrier (BBB) is a highly selective permeability barrier that separates the circulating blood from the brain extracellular fluid (BECF) in the central nervous system (CNS).
- BBB is a unique membranous barrier that tightly segregates the brain from the circulating blood .
- The blood-brain barrier acts very effectively to protect the brain from many common bacterial infections.
- The blood-brain barrier is composed of high density cells restricting passage of substances from the bloodstream much more than endothelial cells in capillaries elsewhere in the body.

Structure of BBB

- Capillaries of brain are lined with a layer of special endothelial cells that lack fenestrations and are sealed with tight junctions
- These tight junctions called zona occludens .
- The tight junctions produced by the interaction of several transmembrane proteins such as occludin and claudin that project into and seal the paracellular pathway.
- The interaction of these junctional proteins is complex and effectively blocks an aqueous route of free diffusion for polar solutes from blood along these potential paracellular pathways and thus denies these solutes free access to brain interstitial (extracellular) fluid .

Ependymal cells lining the cerebral ventricles and glial cells are of three types

- **Astrocytes** form the structural framework for the neurons and control their biochemical environment.

Astrocytes foot processes or limbs that spread out and abutting one other, encapsulate the capillaries are closely associated with the blood vessels to form the BBB.

- **Oligodendrocytes** are responsible for the formation and maintenance of the myelin sheath, which surrounds axons and is essential for the fast transmission of action potentials by salutatory conduction.

- **Microglias** are blood derived mononuclear macrophages. The tight junctions between endothelial cells results in a very high trans-endothelial electrical resistance of 1500-2000 Ω.cm2 compared to 3-33 Ω.cm2 of other tissues which reduces the aqueous based paracellular diffusion that is observed in other organs.

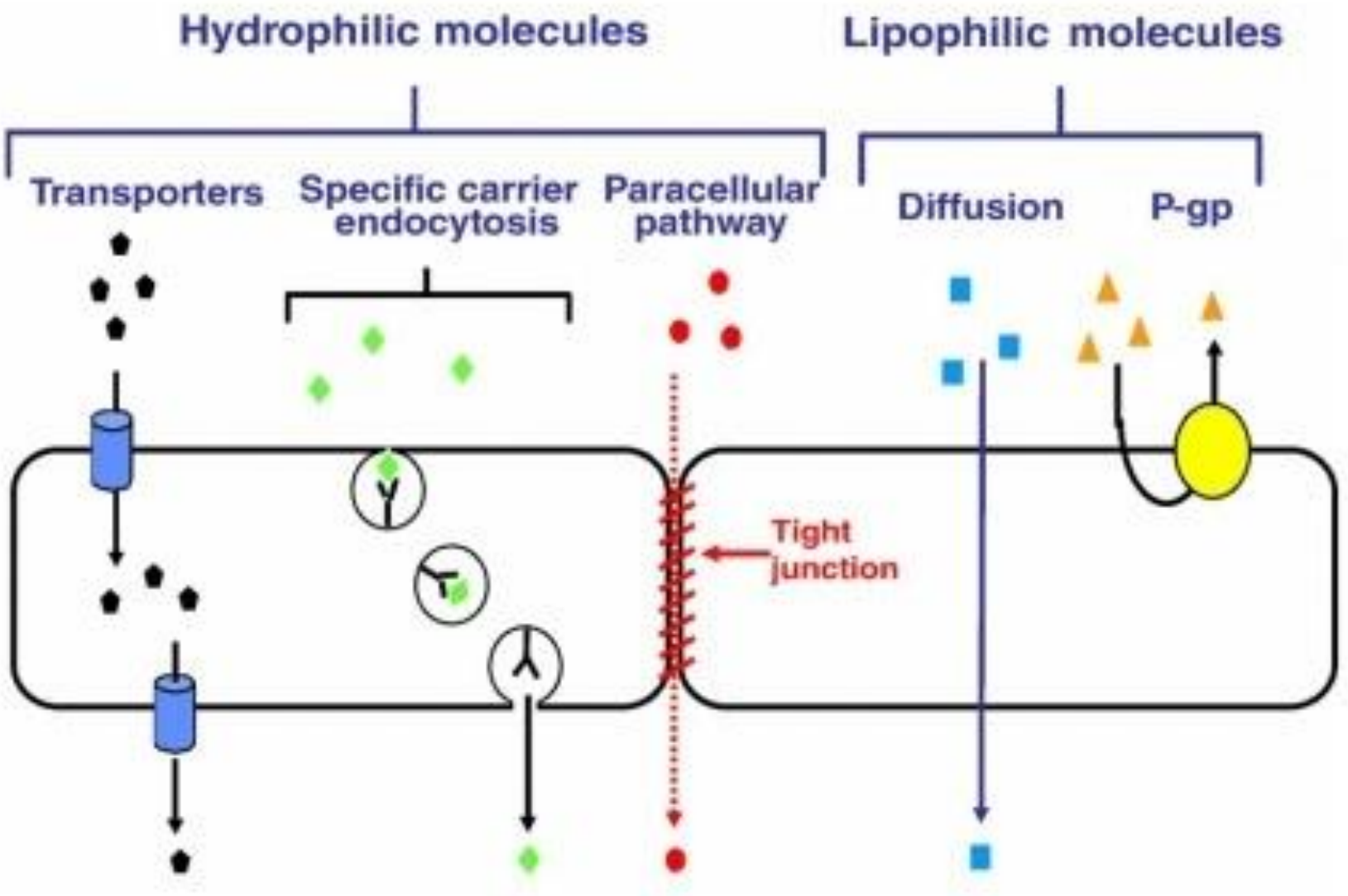
- Small hydrophilic molecules such as amino acids, glucose, and other molecules necessary for the survival of brain cells use transporters expressed at the luminal (blood) and basolateral (brain) side of the endothelial cells.

- Larger and/or hydrophilic essential molecules such as hormones, transferrin for iron, insulin, and lipoproteins use specific receptors that are highly expressed on the luminal side of the endothelial cells. These receptors function in the endocytosis and transcytosis of compounds across the BBB.

- Small lipophilic molecules can diffuse passively across the BBB into the brain but will be exposed to efflux pumps (Pglycoprotein [P-gp].

Diseases related to BBB

- Meningitis
- Brain abscess
- Epilepsy
- Multiple sclerosis
- Neuromyelitis optica
- Late-stage neurological
- trypanosomiasis (Sleeping sickness)
- Progressive multifocal leukoencephalopathy (PML)
- Alzheimer's Disease, etc.



Functions of BBB

- The BBB acts very effectively to protect the brain from many common bacterial infections.
- Infections of the brain that do occur are often very serious and difficult to treat.
- Antibodies are too large to cross the blood–brain barrier, and only certain antibiotics are able to pass.
- The blood–brain barrier becomes more permeable during inflammation.
- This allows some antibiotics and phagocytes to move across the BBB. However, this also allows bacteria and viruses to infiltrate the BBB.
- An exception to the bacterial exclusion is the diseases caused by spirochetes, such as Borrelia, which causes Lyme disease, and Treponema pallidum, which causes syphilis. These harmful bacteria seem to breach the blood–brain barrier by physically tunneling through the blood vessel walls.

APPROACHES

- To bypass the BBB and to deliver therapeutics into the brain, three different approaches are currently used —

- invasive approach
- pharmacological approach
- physiological approach

Invasive Approach

- It includes
  - intracerebro ventricles infusion
  - Convection enchanced delivery
  - Polymer or microchip systems (implants)

1.Intra-cerebro-ventricular (ICV) infusion

- One strategy for bypassing the BBB .
- injection or intraventricular infusion of drugs directly into the CSF.
- Drugs can be infused intraventricularly using an Ommaya reservoir, a plastic reservoir implanted subcutaneously in the scalp and connected to the ventricles
- Drug solutions can be subcutaneously injected into the implanted reservoir and delivered to the ventricles by manual compression of the reservoir through the scalp.
- Eg; Glycopeptide and aminoglycoside antibiotics used in meningitis

Convection-enhanced delivery (CED)

- The general principle of CED involves the stereotactically guided insertion of a small-caliber catheter into the brain parenchyma.
- Through this catheter, infusate is actively pumped into the brain parenchyma and penetrates in the interstitial space. The infusion is continued for several days and the catheters are removed at the bedside.
- CED has been shown in laboratory experiments to deliver high molecular weight proteins 2 cm from the injection site in the brain parenchyma after as little as 2 h of continuous infusion
- Limitations: Some areas of the brain are difficult to saturate fully with infusate, particularly — infiltrated tissues surrounding a cavity.

3.Intra-cerebral injection or use of implants

- Both the bolus injection of chemotherapy agents and the placement of a biodegradable, chemotherapeutic impregnated, wafer into a tumour resection cavity, rely on the principle of diffusion to drive the drug into the infiltrated brain..

4.Disruption of the BBB Osmotic disruption:

- Disruption of the BBB can open access of the brain to components in the blood by making the tight junction between the endothelial cells of the brain capillaries leaky. Different techniques are used to disrupt the tight junctions:
- The osmotic shock causes endothelial cells to shrink, thereby disrupting the tight junctions. Intracarotid administration of a hypertonic mannitol solution with subsequent administration of drugs can increase drug concentration in brain and tumour tissue to reach therapeutic concentration.

- MRI-guided focused ultrasound BBB disruption technique: Ultrasound has been shown to be capable of BBB disruption. The combination of microbubbles . This technique has been shown to increase the distribution of Herceptin in brain tissue by 50% in a mice model

- Application of bradykinin-analogue: There is evidence of the opening of the tight junctions to occur by activation of bradykinin B2 receptors through a calcium-mediated mechanism.

Limitations of invasive approach

- All these approaches are relatively costly, require anaesthesia and hospitalization, and are non-patient friendly. These techniques may enhance tumour dissemination after successful disruption of the BBB. Neurons may be damaged permanently from unwanted blood components entering the brain.

Pharmacological Approach

- The pharmacological approach to crossing the BBB is based on the observation that some molecules freely enter the brain, e.g. alcohol, nicotine and benzodiazepine.

- This ability to passively cross the BBB depends on the molecular size being less than 500 D, charge (low hydrogen bonding capabilities) and lipophilicity (the more lipophilic, the better the transport).

- This approach consists of modifying, through medicinal chemistry, a molecule that is known to be active against a CNS target to enable it to penetrate the BBB

- Modification of drugs through a reduction in the relative number of polar groups increases the transfer of a drug across the BBB. Lipid carriers have been used for transport, and there are successful examples of both these approaches.

- Limitations: The modifications necessary to cross the BBB often result in loss of the desired CNS activity. Increasing the lipophilicity of a molecule to improve transport can also result in making it a substrate for the efflux pump Pglycoprotein (P-gp).

Physiological approach

Among all the approaches used for increasing brain delivery of therapeutics, the most accepted method is the use of the physiological approach which takes advantage of the transcytosis capacity of specific receptors expressed at the BBB. The low density lipoprotein receptor related protein (LRP) is the most adapted for such use with the engineered peptide compound (EPiC) platform incorporating the Angiopeptide in new the most advanced with promising data in the clinic.
Eg. Receptor-mediated transcytosis

Other Non-invasive Approaches

- Lipophilic Analogs
- Prodrugs
- Receptor/Vector Mediated Drug Delivery
- Carrier Mediated Drug Delivery
- Intra nasal DDS

Lipophilic Analogues

- CNS penetration is favored by low molecular weight, lack of ionization at physiological pH, and lipophilicity. Delivery of poorly lipid-soluble compounds to the brain requires some way of getting past the BBB.

- There are several possible strategies, such as transient osmotic opening of the BBB, exploiting natural chemical transporters, highdose chemotherapy, or even biodegradable implants.

Prodrugs

- Prodrugs are pharmacologically inactive compounds.
- chemical change is usually designed to improve some deficient physicochemical property--(solubility and mem. permeability)
- Examples: levodopa, GABA, Niflumic acid, valproate or vigabatrin

Colloidal drug carriers

- Its an promising approach

- Colloidal carriers include
  - Emulsions
  - Liposome's
  - nanoparticles

- Coating with surfactants like

e g: polyoxypropylene, polyethylene glycol, polyoxyethylene

Nano particles

These are submicron drug carrier systems that are made from a broad number of materials such as

- polyalkylcyano acrylates(PCAS)
- Polyacetates
- Polysaccharides& co-polymers

Polysorbate coated nanoparticles can mimic LDL to cross the BBB

MAJOR NEEDS IN BRAIN DRUG TARGETING

- Need to target therapeutics to specific brain regions or cell types.
- Need to improve understanding of BBB transport systems.
- Need for in vivo evaluation of brain drug pharmacokinetics.
- Need to identify new brain drug targeting systems. • Need to speed development and application of molecular imaging probes and targeted contrast agents.

CONCLUSION

- The treatment of brain diseases is particularly challenging because the delivery of drug molecules to the brain is often precluded by a variety of physiological, metabolic and biochemical obstacles that collectively comprise the BBB.

- Drug delivery directly to the brain interstitium has recently been markedly enhanced through the rational design of polymer-based drug delivery systems.

- Substantial progress will only come about, however, if continued vigorous research efforts to develop more therapeutic and less toxic drug molecules are paralleled by the aggressive pursuit of more effective mechanisms for delivering those drugs to their brain targets

Questions

- State briefly on targeted drug delivery system. What are their limitation and explain briefly different approaches available for targeting of drugs to brain

(5m- 2 times)

- Explain the concept of targeted drug delivery sytem. Describe active drug targeting in detail. (5M)

- Explain the advantage of drug targeting with examples (10M)

Reference

- S.P Vyas and R.K Khar controlled drug delivery system
- Encyclopedia of controlled delivery system
- Drug delivery to the brain from wikipedia.

Thank you