Delivery of proteins
(Approaches for rate-controlled parenteral delivery systems)

1

Approaches for rate-controlled delivery

- Rate control can be achieved by several different technologies similar to those used for conventional drugs.

Rate control through open loop type approach
- Continuous infusion with pumps: mechanically or osmotically driven input: constant/pulsatile/wave form
- Implants: biodegradable polymers, lipids
- Input: limited control

Rate control through closed loop approach/feed back system
- Biosensor-pump combination
- Self regulating system
- Encapsulated secretory cells

Table 9 Controlled release systems for parenteral delivery.

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Mechanical Pumps:

- Continuous infusion, open loop, available at different sizes, prices, portable or not, inside/outside the body, used in hospitals.
- As ideal pump properties, are:

1) It must deliver the drug at the prescribed rate (s) for extended period of time.
2) I must be safe.
3) It must be convenient (small size, easy, durable).

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Osmotically driven systems:

- As example, osmotic mini-pump, which is S.C implant with continuous, constant infusion over a prolonged periods of time.
- The rate determining process is the influx of water through the rigid, semi-permeable external membrane.
- Then the release depend on membrane properties and osmotic pressure differences over this membrane (osmotic agent inside the pump).

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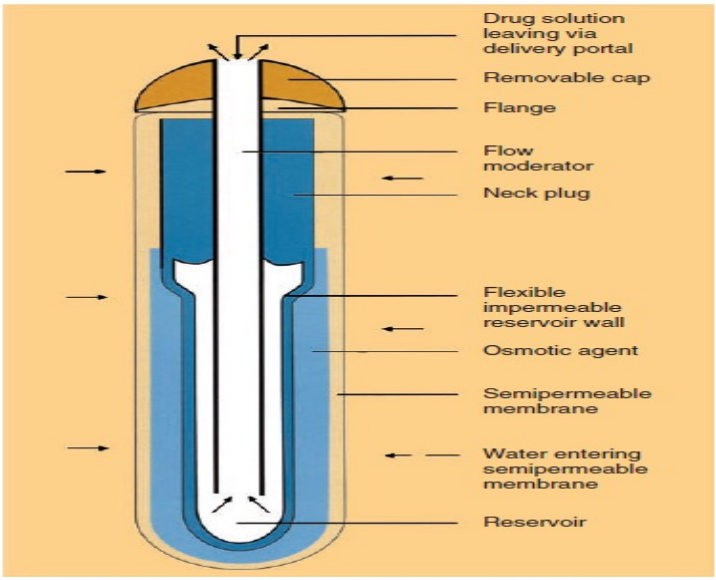

Figure 18 Cross section of functioning Alza Alzet osmotic minipump. *Source*: Adapted from Banerjee et al., 1991.

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Bio-degradable microspheres:

- Biodegradable polymers like PLGA (polylactic acid-polyglycolic acid can be used for enclosing certain types of proteins (like LHRH agonist =leuprolide) to be taken as implants with dose ranges 1-6 months.
- As requirement of this system, we need:

1) Highly potent drugs (low dose)
2) Sustained presence in the body
3) No adverse reaction at the administration site.

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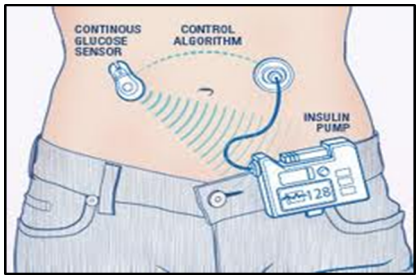
Biosensor-pump combinations:

- They consist of:

1) a biosensor.
2) an algorithm (calculate the required input rate).
3) A pump system (administer the drug at the required rate over prolonged periods of time).



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Self-regulating systems:

- The drug release is controlled by stimuli in the body.
- Two approaches for controlled drug release are being followed:

1) Competitive desorption
2) Enzyme-substrate reaction (depend on pH drop)

When glucose is converted to Gluconic acid in presence of Glucose oxidase, this induces Changes in acid-sensitive Delivery devices.

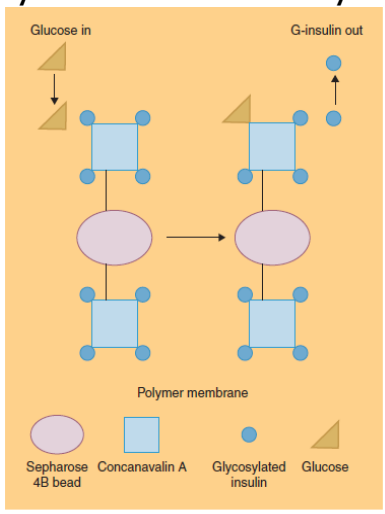
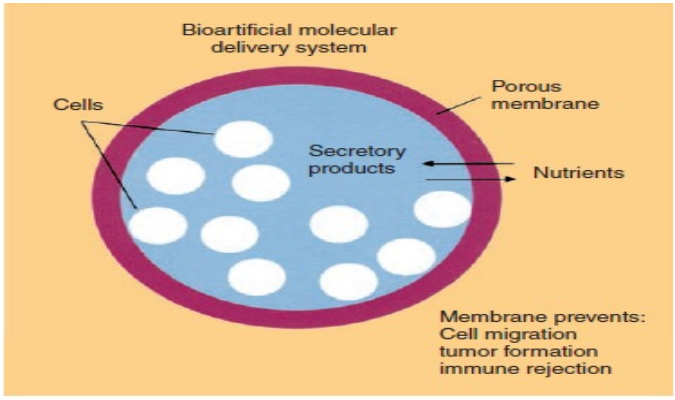


Figure 23 Schematic design of the Con A immobilized bead/G (*glycosylated*)-insulin/membrane self-regulating insulin deliv-

Microencapsulated secretory cells

- Like implantation of Langerhans cells in diabetics to restore their insulin production through biofeedback.
- They should be protected from the body environment (no rejection).



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Site-specific delivery (Targeting) of protein drugs

- It is used

1) For decrease degradation in body organ other than the site of action
2) More localization in the target organ and less non-target organs distribution

- Components of targeted drug delivery (carrier based) are:

1. An active moiety	For: therapeutic effect
2. A carrier	For: (metabolic) protection, changing the disposition of the drug
3. A homing device	For: specificity, selection of the assigned target site

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1. Drugs with high total clearance are good candidates for targeted delivery.
2. Response sites with a relatively small blood flow require carrier-mediated transport.
3. Increases in the rate of elimination of free drug from either central or response compartments tend to increase the need for targeted drug delivery; this also implies a higher input rate of the drug-carrier conjugate to maintain the therapeutic effect.
4. For maximizing the targeting effect, the release of drug from the carrier should be restricted to the response compartment.

Table 12 Pharmacokinetic considerations related to protein targeting.

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Targeting can be classified into:

1) Passive: use of the natural disposition pattern of the carrier system as in macrophages action toward certain particulate carriers circulating in the blood and then accumulate in the liver and spleen.
2) Active: change the natural disposition of the carrier by some types of homing device or homing principle to select one particular tissue or cell type.

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Factors affecting protein targeting

- The physicochemical properties of carrier (its charge, mol.wt./ size, surface hydrophobicity and presence of ligands for interaction with surface receptors.
- The nature of endothelial barrier, healthy or non (inflamed, necrotic or tumorous)

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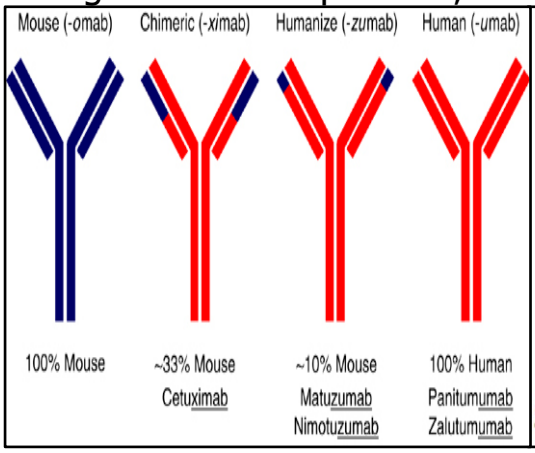
Types of carriers for targeting

- Soluble carrier systems: ex. **MAb** (monoclonal antibodies), Bispecific antibodies, immuno-conjugates
- Colloidal particulate carrier systems: Liposomes, bio-degradable nanoparticles, and microspheres



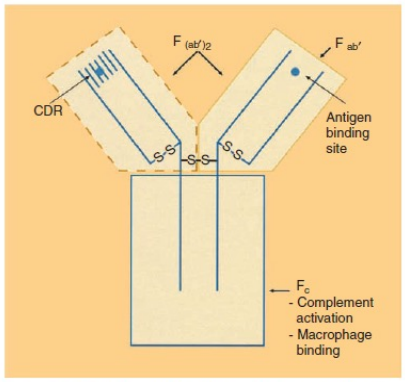
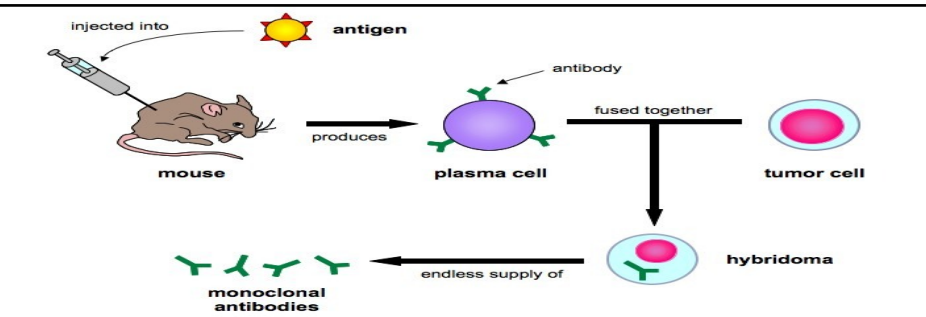
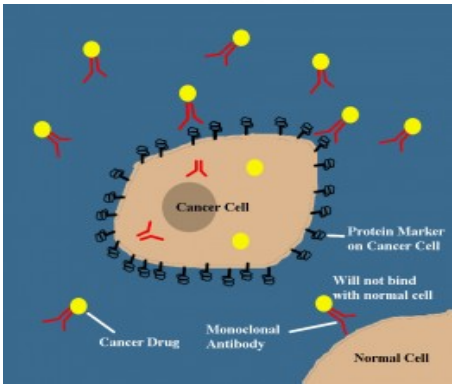
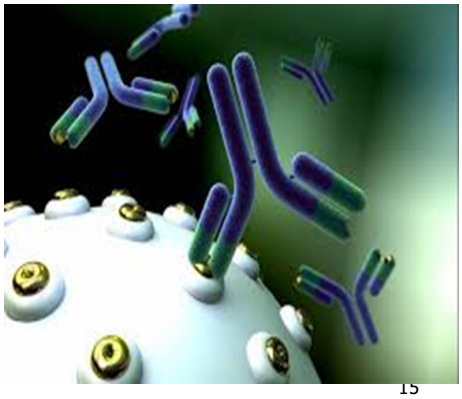


Figure 27 Highly simplified IgG1 structure. *Abbreviation:* CDR, complementarity determining region.







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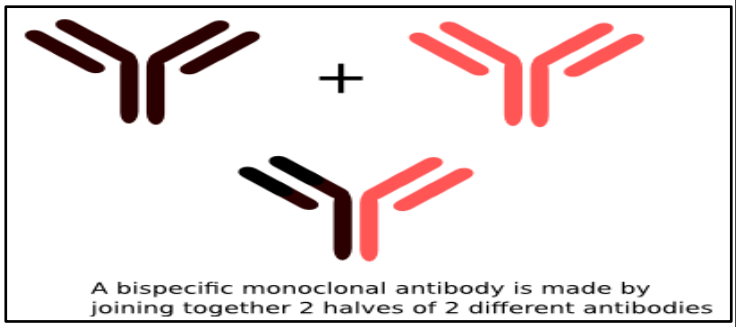
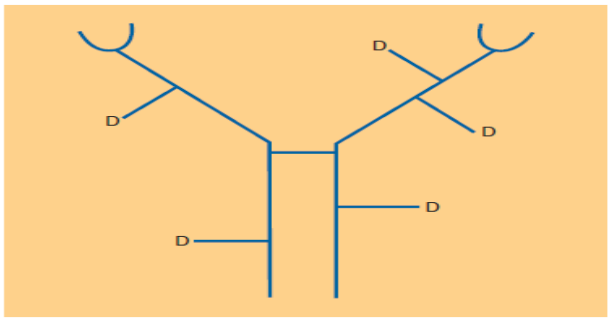
With more Therapeutic Potential, With two Binding sites



A bispecific monoclonal antibody is made by joining together 2 halves of 2 different antibodies



More activity

Figure 28 A schematic view of an immunoconjugate. *Abbreviation*: D, drug molecules covalently attached to antibody (fragments).

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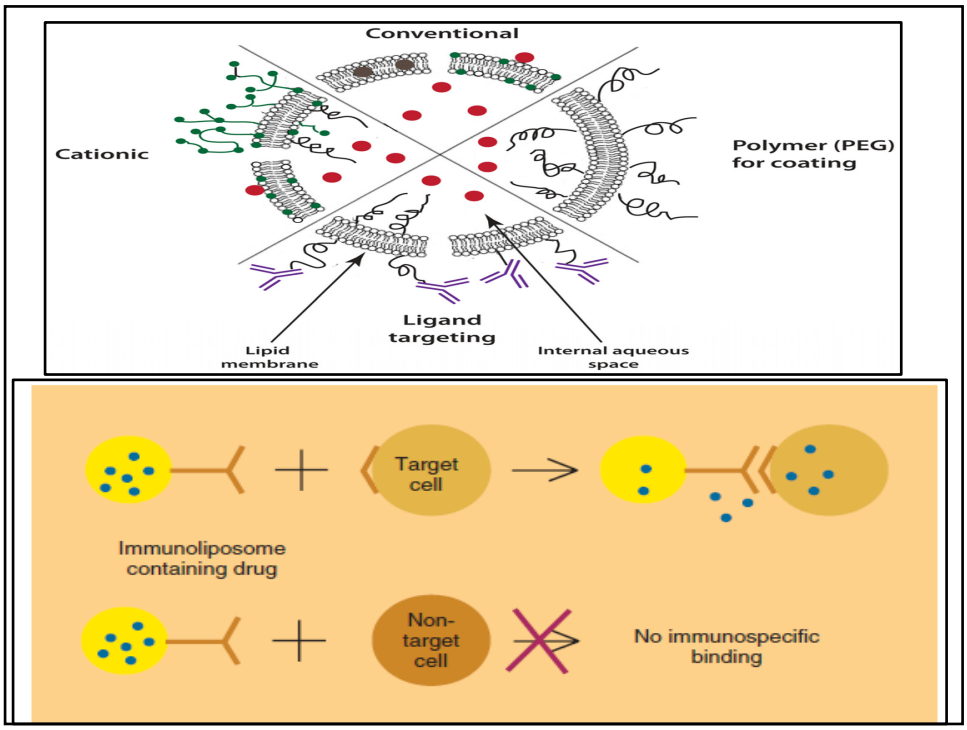

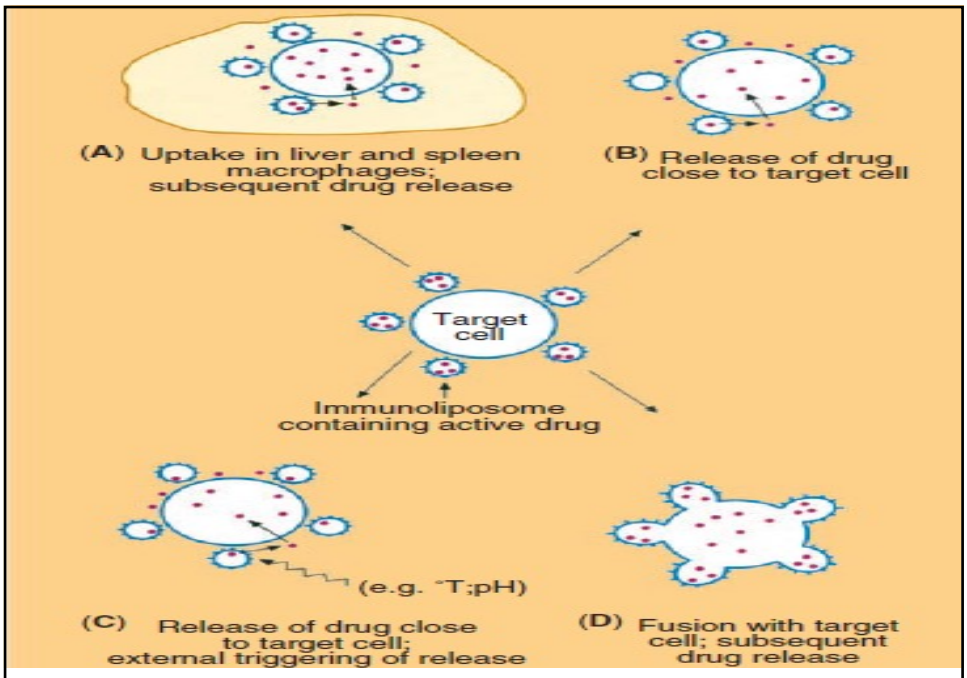

Pathways of drug release in immuno-liposomes 18