PARENTERAL CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

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INDEX

- Introduction.
- Routes of parentral administration.
- Biopharmaceutics of SR/CR parentral products.
- Different approaches.
- Evaluation tests.

- The Parenteral administration route is the most common and efficient for delivery of active drug substances with poor bio-availability and the drugs with a narrow therapeutic index.
- Though parenteral route offers rapid onset of action in results in rapid declines of systemic drug level.
- It requires frequent injection, which ultimately leads to patient discomfort.
- For the sake of effective treatment it is often desirable to maintain systemic drug levels within the therapeutically effective concentration range for as long as treatment calls for.

ADVANTAGES:

- Wide variety of drugs can be formulated as PDDS.
- Most of the PDDS are biocompatible with vascular system
- The possible biotransformation reactions encountered by several drugs after oral administration can be minimized by this approach.
- Targeting of several drugs particularly anti-Neoplastic drugs to specific site and also to maintain desired therapeutic conc. Is achieved.
- Prolonged residence of certain drugs at a specific site can be made possible by using suitable parenteral approach.
- Biotransformation and excretion loss can be minimized so that the dose required for parenteral administration can be reduced.
- Maintaining therapeutic concentrations over a longer period of time.

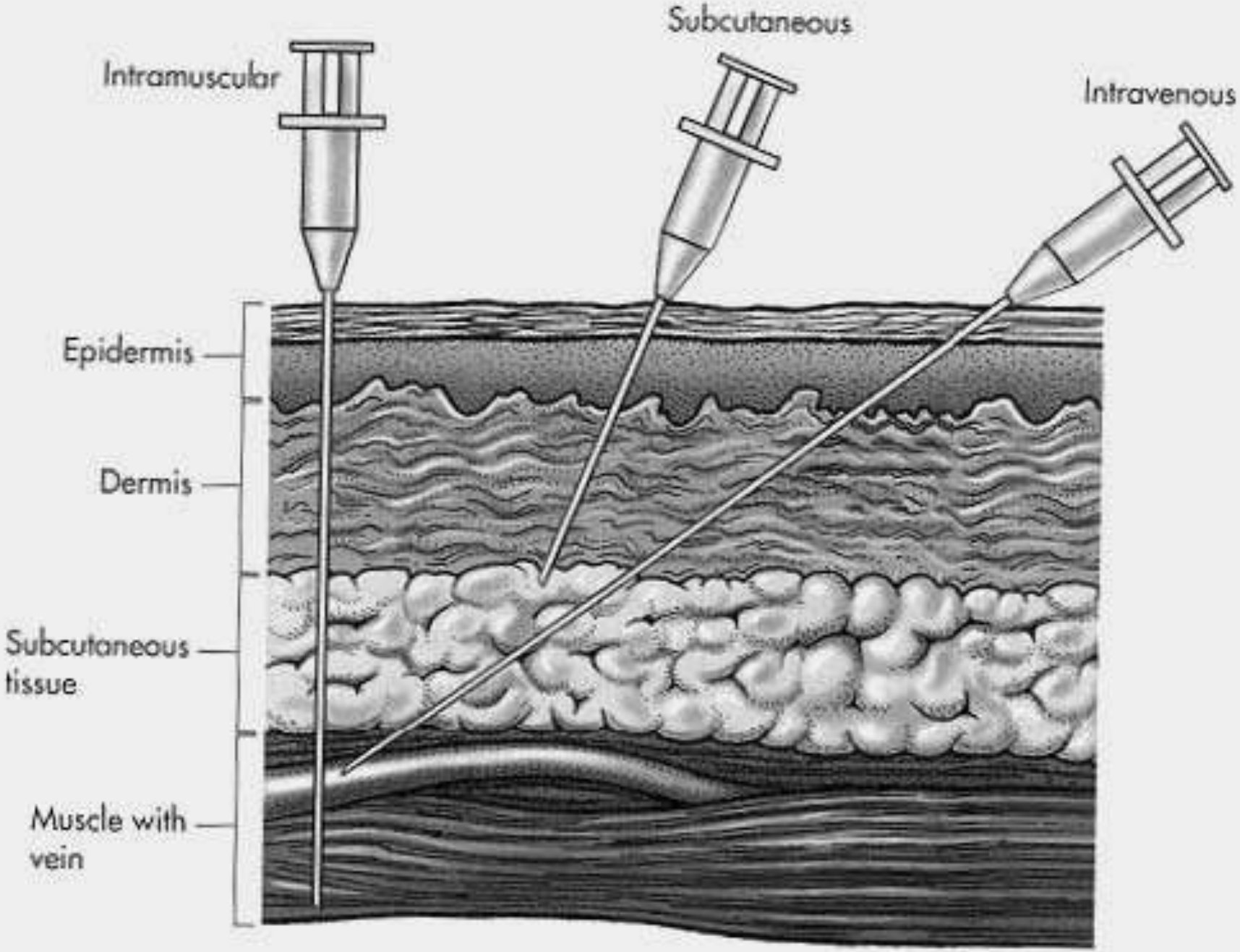
DISADVANTAGES:

- Patient compliance is less.
- Withdrawal of the dose is not possible.
- Self administration is not possible.
- Administration requires strict adherence to aseptic procedures, and some pain on injection.
- The manufacturing and packaging requirements, are more expensive than preparations of given by other routes.

routes of administration

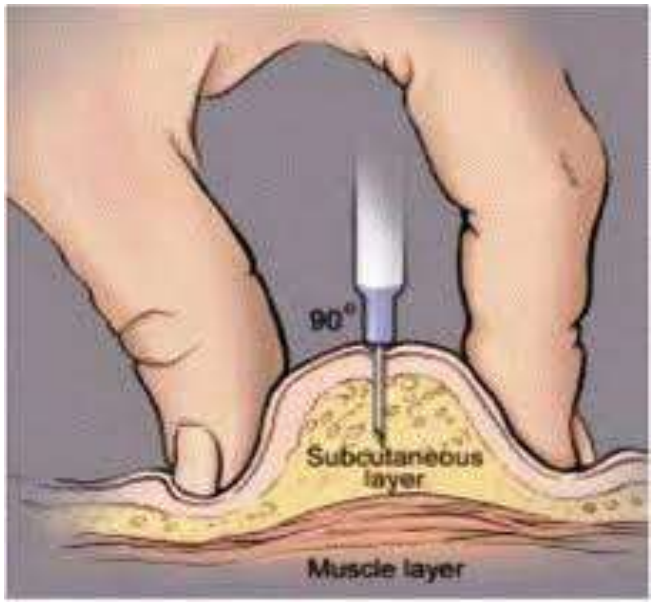
The major routes of parentral administration include :

1. Subcutaneous administration.
2. Intramuscular administration.
3. Intravenous administration.
4. Intraperitoneal administration.


Intramuscular
Subcutaneous
Intravenous
Epidermis
Dermis
Subcutaneous tissue
Muscle with vein

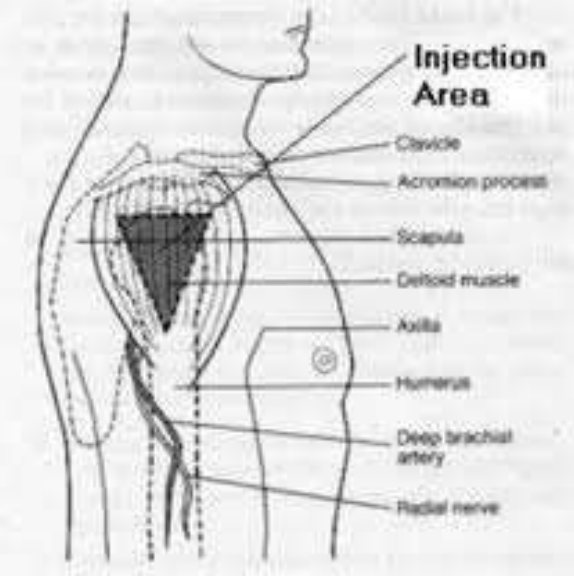
Subcutaneous route:

- Poorly perfused with blood.
- Limited to drugs that are non-irritating , water soluble and well absorbed.
- For chronically administered drugs injection site must be rotated.
- Volume restricted is 0.5 - 1.5ml.



Intramuscular route:

- Gluteal, deltoid and vastus lateralis muscles are the sites.
- Injected deep into muscle and away from nerves and arteries.
- Volume must not be more than 2ml.



Intravenous route:

- Used for SR/CR dosage forms such as Liposomes, nanoparticles, erythrocytes and polypeptides.

Drug particle size (μm)	Target site
> 1	lung
0.1 – 7	liver/spleen
< 0.1	bone marrow

Advantages :

• precise, accurate and immediate onset of action,100% bioavailability.

Disadvantages :

•risk of embolism.
•high concentrations attained rapidly leading to greater risk of adverse effects.

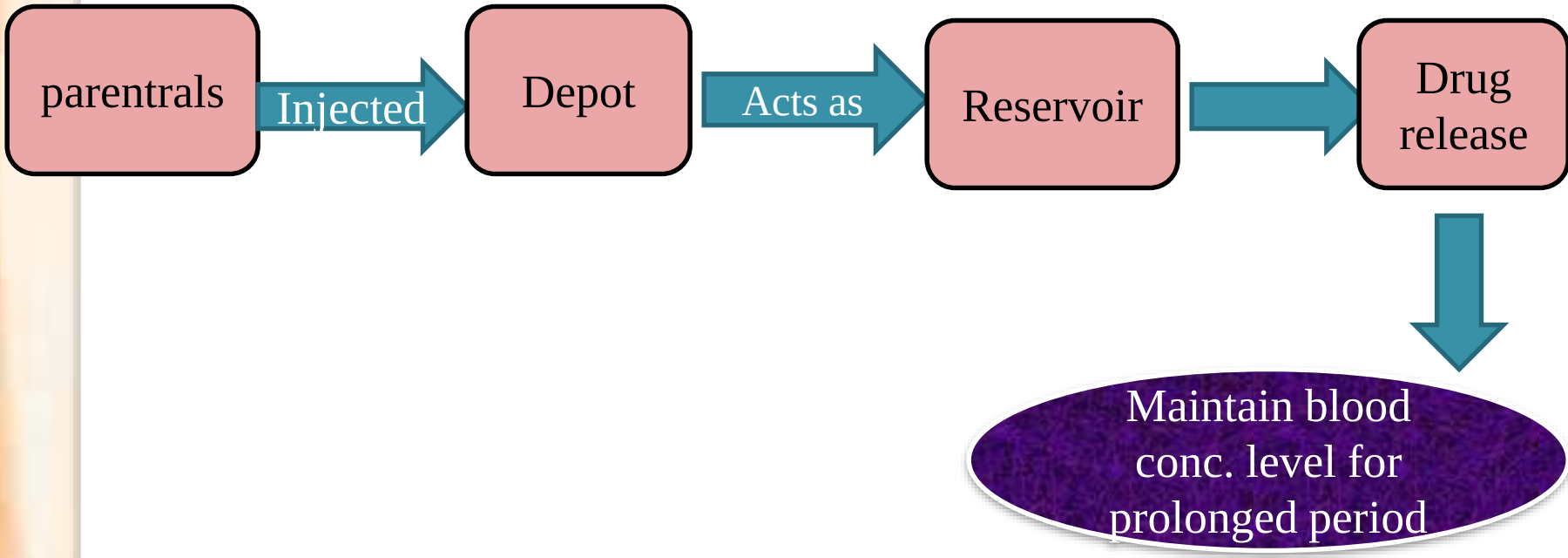
Intraperitoneal route:

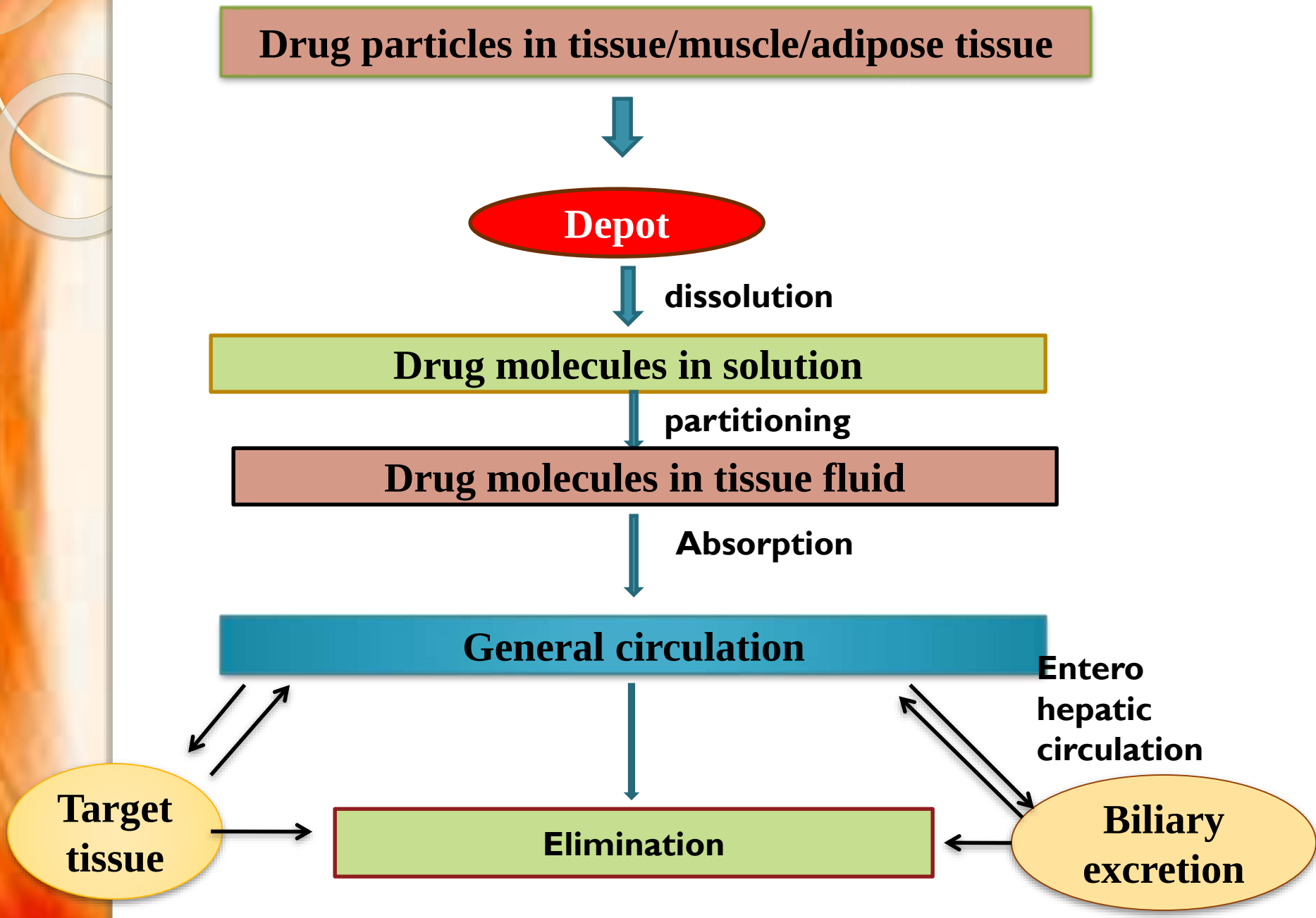
- Macromolecules administered through this route gain direct access into lymphatic system.
- Tumors are metastatized majorly by the route of lymphatic channels.
- Advantageous to target antineoplastic drugs.

S. No	Route Of Administration	Site Of Injection	Injection Volume &Needle Size	Examples
1.	Intra muscular(I.M)	gluteal, deltoid and Vastus lateralis muscles	NMT 2ml 22 size	For less soluble drugs Butorphanol tartrate,contraceptives
2.	Subcutaneous (S.C)	Adipose tissue	0.5-1.5 ml 24-25size	non-irritating, water-soluble drugs eg:insulin,vaccines, vit B12
3.	(Intravenous (I.V) Less common for C.R)	Veins	</=100ml 18-22size	liposomes, nanoparticle, erythrocytes, and polypeptides
4.	Intra peritoneal (I.P)	Lymphatic system	1ml 23 size	Antineoplastic agents into the lymphatic system.

biopharmaceutics

MECHANISM:


parentrals
Injected
Depot
Acts as
Reservoir
Drug release
Maintain blood conc. level for prolonged period


Drug particles in tissue/muscle/adipose tissue
Depot
dissolution
Drug molecules in solution
partitioning
Drug molecules in tissue fluid
Absorption
General circulation
Entero hepatic circulation
Target tissue
Elimination
Biliary excretion

formulation

Formulation ingredients:

Excipients	Functions	IV	SC/IM
Surfectant	Particle stabilization	+	+
Buffer	pH adjustment and control	+	+
Polysaccharides	Viscosity enhancement	-	+
Sugars	Tonicity adjuster and/or lyoprotectants	+	+
Additional polymers	Bioadhesives, matrices for sustained release	-	+
Preservatives	Preservatives for multidose products	-	+
Chelating agents	Scavenging of metal ions (depend on drug stability)	+	+

IV - intravenous; SC - subcutaneous; IM - intramuscular

different approaches

CLASSIFICATION OF PCDDS

A. Aqueous solutions →

1. Highly viscous solutions
2. Complex solutions

B. Oily solutions

C. Suspensions →

1. Aqueous suspensions
   - Viscosity builders
   - Microspheres
   - Microcapsules
   - Magnetic microspheres
2. Oily suspensions

D. Emulsions

E. Biocompatible carriers →

1. Resealed erythrocytes
2. Liposomes
3. Niosomes
4. Nanoparticles
5. Prodrugs
6. Implants
7. Infuse aids

AQUEOUS SOLUTIONS:

1. HIGH VISCOSITY PRODUCTS

- By increasing the viscosity of the vehicle, the diffusion coefficient of the drug is reduced hence the drug transfer is delayed.

- Methylcellulose, Sodium CMC, PVP are some viscosifying agents.

- Incorporation of gelling agents like aluminum monostearate into oil solutions causes the reduction in absorptive area and the rate of drug transfer is better controlled.

- Diffusivity plays a major role in the release of the drug from viscous reservoir.

- Low mol.wt compounds have high diffusivity.

- Drugs with mol.wt > 750 daltons fails to undergo diffusion.

2. COMPLEX FORMATION

- Principle involved is similar to that of plasma protein binding and tissue binding in prolonged drug action.

- Polyvinylpyrrolidone, methylcellulose, sodium CMC are the macromolecules used for complex formation.

- Delay in the drug absorption occurs if the drug molecules undergo complexation with macromolecules.

- rate of drug release from the complex is expressed as

$$d[c]/dt = -k\, f\, [c]$$

where, k = release rate constant.
f = fraction of drug that is freely available.
c = total conc. of drug in dosage form.

- Another mechanism for delaying the drug release is using caffeine micromolecules which lower the solubility of the drug and achieve the sustained release.

Ex: Acetaminophen forms 1:1 complexes with theophylline and caffeine.

- Long chain molecules having micro molecules can also be used to extend drug release

Ex:

1. Tannic acid forms complex with insulin to give zinc insulin tannate.
2. cyanacobalamine forms complex with tannic acid to give cyanacobalamine zinc tannate.

OILY SOLUTIONS:

- Cotton seed oil, linseed oil etc., are some of the oils used as vehicles.

- Drugs that are soluble in oils are preferred mostly in the formulation of oily solutions.

- Drugs inherent partition coefficient play a major role in the release of the drug

- Utricaria, Allergic dermatitis, lipoidal utricaria are some of the problems encountered and hence usage is minimized.

SUSPENSIONS:

1. AQUEOUS SUSPENSIONS

- Suspension gives a longer duration of action than an aqueous solution when given iv/sc.
- Here the drug is in finely divided soluble state, it has to undergo dissolution and then the action is achieved.
- The dissolution rate of drug can be described by modified Noyes-Whitney equation

$$\frac{dc}{dt} = \frac{DAC}{h}$$

where D = diffusion coefficient of the drug
A = surface area
C = conc. of the drug
h = viscosity of external phase.

❖ Precautions to be followed in the formulation of parentral aqueous suspension:

i. solid particulate component should be restricted to 0.5 – 5% w/v.
ii. size of particulate matter should be 0.1 – 10μ in size.

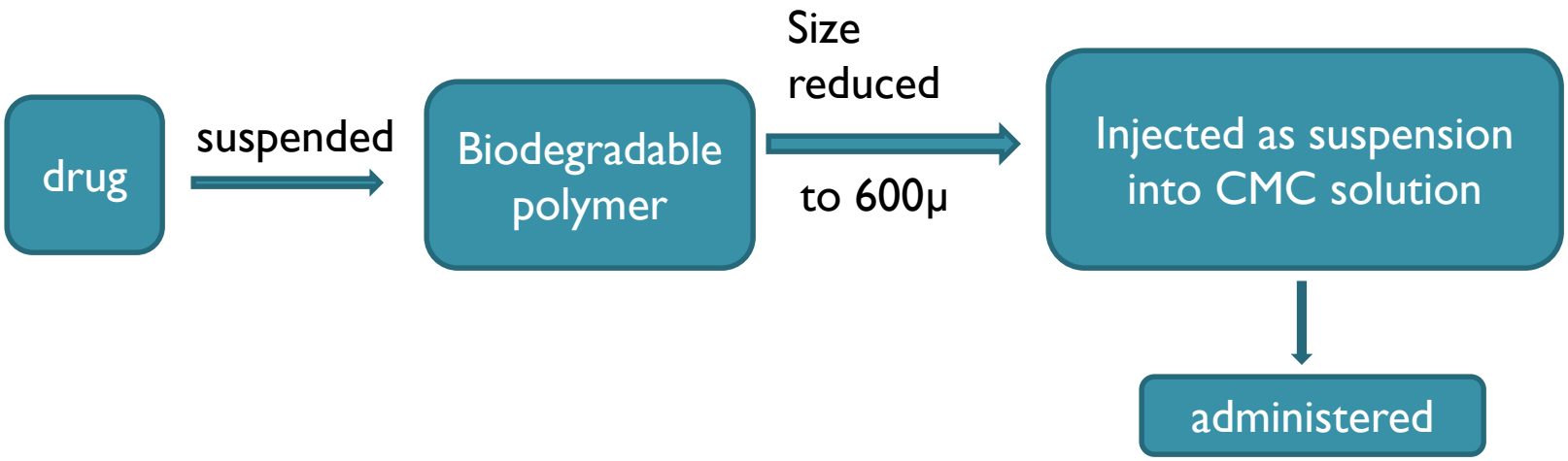
1. USE OF VISCOSITY BUILDER

- Used to increase the vehicle viscosity and reduce the diffusion coefficient of the drug.

- Methyl cellulose, sodium CMC, polyvinylpyrrolidone are some of the viscosity builders.

2. MICROSPHERES :

- Spherical shaped particles containing the drug in solid or liquid state enclosed or embedded into polymeric matrix system.



- Polymers used are polygalactin, polylactic acid, etc.,

❖ Drug release mechanism:

➢If it is matrix.
➢If it is continuous polymer sheet.

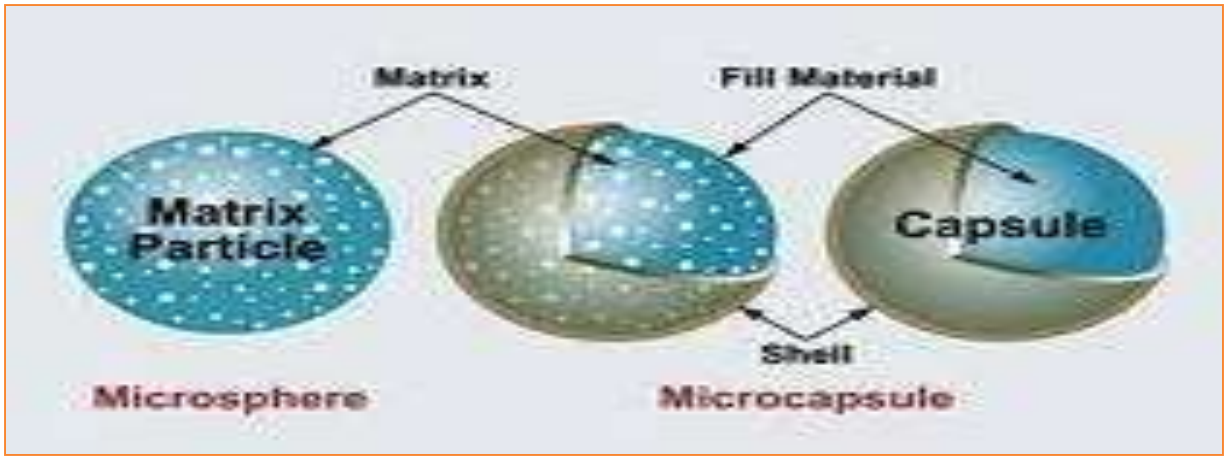
3. MICROCAPSULES :

- Microcapsules are spherical particles containing drug concentrated in the core.

- Microencapsulation method is used to encase particles of gases, liquids or solids.

- Polymers used are nylon, dipolylactic acid, albumin, etc.,

Microspheres and Microcapsules



Microspheres

Drugs: Narcotic antagonists
Antineoplastic agents

Polymers: Polygalactin,
Polylacticacid

Release mechanism:
Diffusion controlled

Microcapsules

Drugs: Antineoplasticagents,
Steroid hormones

Polymers: Nylon,
Dipolylactic acid
Crosslinked starch

Release mechanism: Both dissolution &diffusion

4. MAGNETIC MICROSPHERES

Uses :

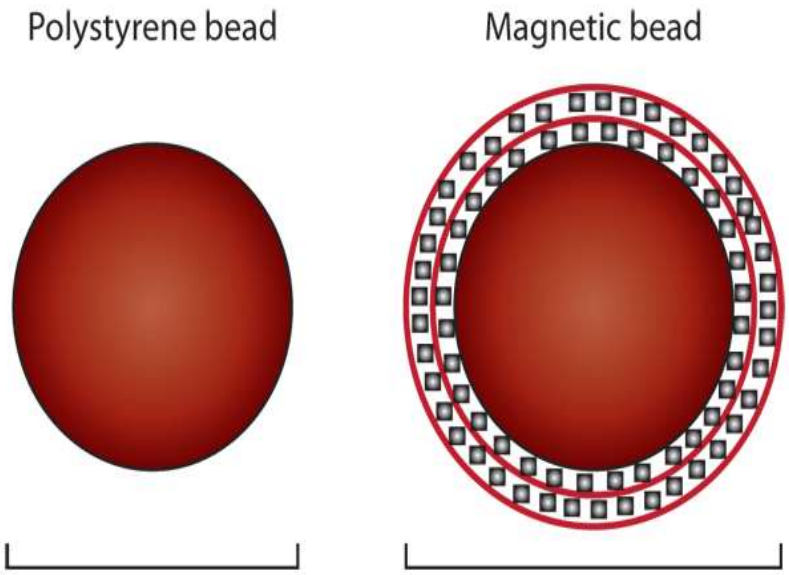
- To increase target specificity
- Used to entrap wide variety of drugs
- Prepared from albumin and magnetite
- Particle size- 1 µm

Route: **i.v**

Advantages :

nontoxic and non reactive

Eg: Doxorubicin



List of marketed microspheres

Drug	Commercial name	Company
Risperidone	Risperdal® consta®	Janseen®/Alkermes, Inc
Naltrexone	Vivitrol®	Alkermes
Octreotide	Sandostatin®LAR	Novartis
Minocycline	Arestin®	Orapharma

2. OILY SUSPENSIONS:

- Vehicle used is oil phase.

- These are prepared by dissolving drug in aq. phase 1st and then dispersed into oil phase.

Drug release mechanism:

- Involves combined mechanism of oily solution and suspension.

- First the drug is partitioned from aq. Phase to oily phase and diffusion occurs from oily phase.

EMULSIONS

- Emulsions may be classified into:

  o/w type emulsions.

  w/o type emulsions.

  Multiple emulsions(o/w/o, w/o/w)

  Micro emulsions.

1. o/w type emulsions.

- o/w type of emulsions are mostly used for parenterals.
- Prepared by dissolving drug in the oil phase and then dispersed into aq. Phase with the help of emulsifying agent.

Mechanism:

•Partition of drug from oil phase to aqueous phase.

2. w/o type emulsions:

- Prepared by dissolving drug in the aq.phase and then dispersed into oil Phase with the help of emulsifying agent.

Mechanism:

- Partition of drug from aqueous phase to oil phase.

3. o/w/o type emulsions:

Mechanism:

- partitioning of the drug from the oil phase into aq. Phase and from the aq. Phase into oil phase and finally diffusion of the drug takes place.

4. w/o/w type emulsions

BIO COMPATIBLE CARRIERS :

NIOSOMES :

- Niosomes are nonionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants of the alkyl or dialkylpolyglycerol ether class, with or without incorporation of cholesterol or other lipids.

Applications:

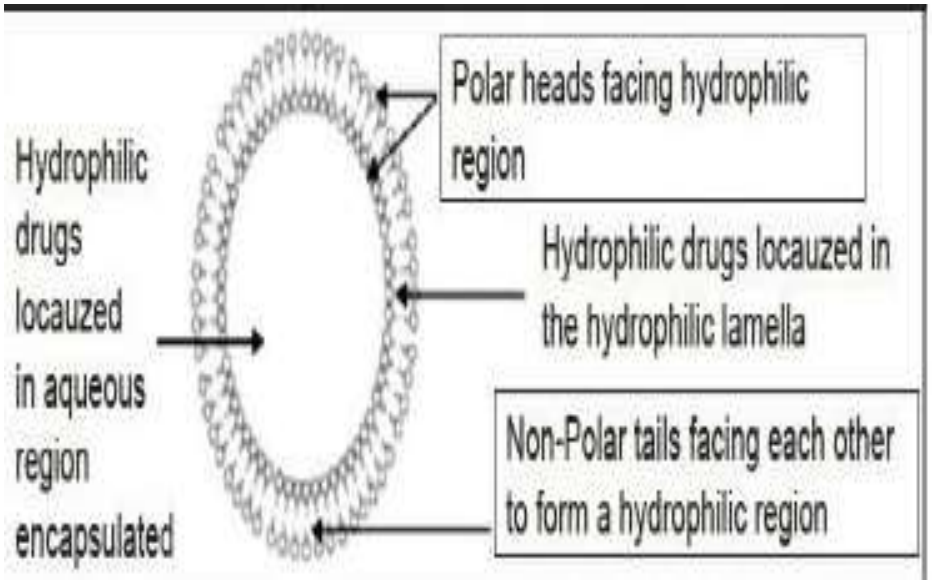
- Anticancer
- Target sites (spleen ,liver)

Drug loading techniques:

1) Passive trapping.
2) Active trapping.

Preparation of niosomes

1. Ether injection method.
2. Hand shaking method.
3. Sonication.



LIPOSOMES :

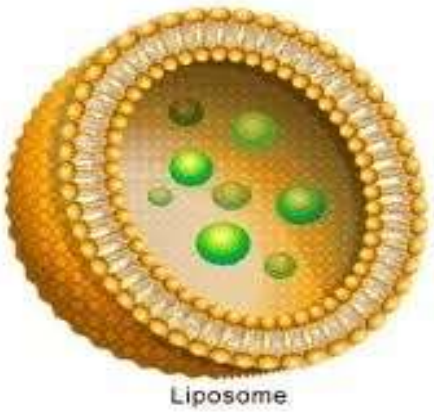
- Vesicles of lipid bilayer enclosing an aqueous compartment.

Routes of administration: I.T, S.C, I.M.

Advantages: versatile , nontoxic

Disadvantages: high production cost, leakage of drug, short half life and low solubility

Brand	Generic	Route	Indication
Ambisome	Amphotericin B	Intravenous	Antifungal
Depocyte	Cytarabine	Intrathecal	Antineoplasti
DaunoXome	Daunorubicin	Intravenous	Antineoplasti
Doxil	Doxorubicin	Intravenous	Antineoplasti

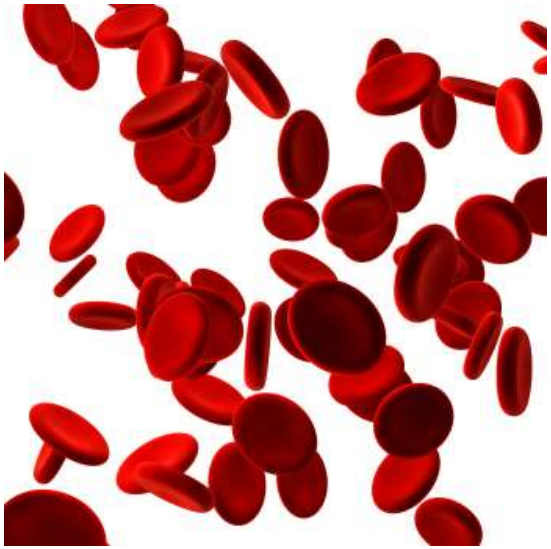

Liposome

RESEALED ERYTHROCYTES :

- Drug is loaded in body's own erythrocytes for controlled release.

➢ Advantages:

- Biocompatible and bio degradable.
- Can load large amounts of drug.
- targeting the drug to the organs.
- No drug exposure to non target cell



➢ Release patterns:

1. Phagocytosis
2. Diffusion through membrane

➢ Applications:

- Treatment of lysosomal diseases like gaucher disease
- Treatment of liver tumors

IMPLANTS :

➢ Implants are the devices which when administered into layers of skin by incision/microsurgery expected to release the drug over prolonged period of time

route of administration : S.C

Drug release: diffusion or dissolution or both mechanisms

Polymers generally employed:

- Polydimethyl siloxane
- Polycaprolactone
- Polylactic acid
- Polyglycolic acid

Biodegradable polymers

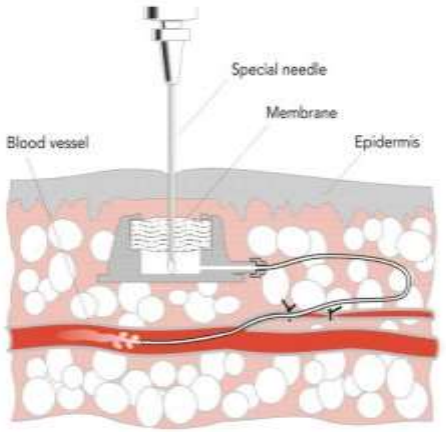


Figure 9-14 Implanted infusion port

NORPLANT

- Polymer: Silicone
- Eg: a subdermal implant to deliver levonorgestrel.

PROGESTRASERT

- Reservoir type system
- Drug reservoir: progesterone
- Polymer: Ethylene vinyl acetate copolymer

OCUSERT

- Membrane controlled system
- Drug reservoir: Pilocarpine alginate
- Treatment : glaucoma.
- Polymer: ethylene vinyl acetate co polymer

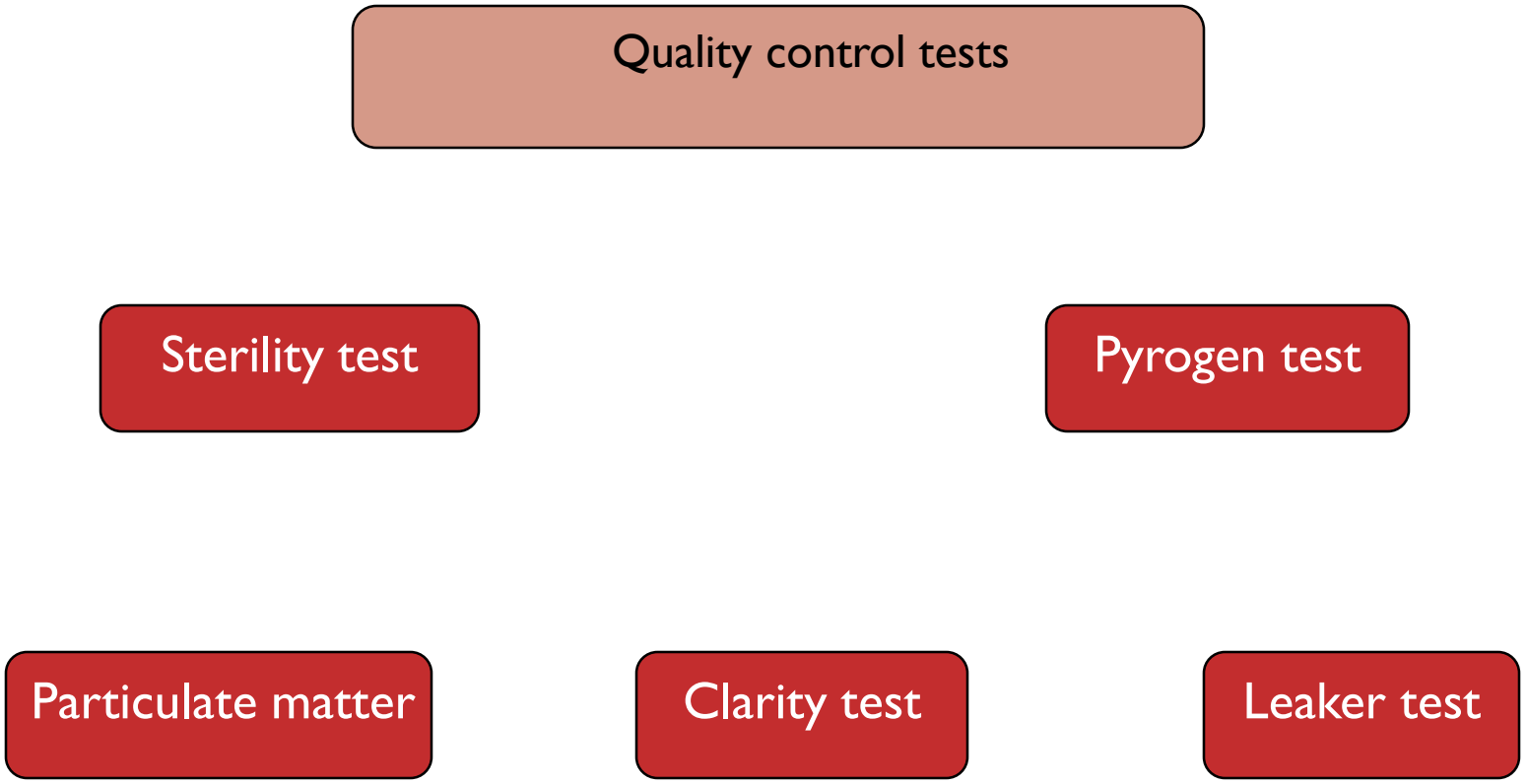
PRODRUGS :

- Prodrug approach is useful to improve bioavailability.
- If poor B.A is due to unfavorable partitioning it can be improved by forming a more lipophilic prodrug.

  Eg: Oxazolidines.
- If poor B.A is due to poor dissolution then it can be improved by forming a more hydrophilic prodrug.

  Eg: Phenytoin.

QUALITY CONTROL TESTS OF PARENTERALS



LEAKER TEST :

- Intended to detect incompletely sealed ampoules.
- Ampoules are hermetically sealed containers meant for single use.
- Presence of any capillary pores or tiny cracks may contaminate the product and spoil the appearance of the product.
- Ampoule is completely submerged in a deeply colored dye solution(0.5 – 10% methylene blue).
- Bottles are tested for the presence of vacuum by striking the base with hand to produce "water hammer" sound

CLARITY TEST :

- A clean solution having a high polish conveys that the product is of exceptional quality and purity.
- Should be free from particulate visible matter.
- Presence of any particulate visible matter the product should be discarded.
- Acc. To USP for a large volume parenteral :

✓ Limit of 50 particles of 10 μm and larger

✓ 5 particles of 25 μm and larger per millimeter.

PYROGEN TEST :

- Presence of pyrogenic substances is determined by a qualitative biologic test based on fever response of rabbits.
- If a pyrogenic substance is injected into the vein of the rabbit, an elevation in the temp. occurs with in 3hours.
- Elevation in the temp. can be determined by rectal thermometers.
- Recently developed test is LAL test which is 5 – 10 times more sensitive than rabbit test.


Thank You!