## UNIT-IV

## PARENTERAL CONTROLLED RELEASE SYSTEMS

One of the major **advantages** of parenterals controlled drug delivery systems is that the duration of action can be extended for days or months and sometimes upto a year. The prime *drawback* is that, once administered, the drug cannot be easily removed if an undesirable action is precipitated or if the drug is no longer needed. Most of such systems are administered by subcutaneous and intramuscular routes and few by intravenous and intraperitoneal routes. Subcutaneous route is limited to well absorbed water-soluble drugs like insulin and dose volume is limited to 0.5 to 1.5 ml. Deep intramuscular route is suitable for polymeric systems or slightly soluble drugs, the volume size restricted to 2 ml. Intravenous route is useful for administration of Liposomes, nanoparticles, erythrocytes and polypeptides. An important criteria for this route is drug particle size. A disadvantage of i.v. route is that the system may be taken up by the reticuloendothelial system but the same can be put to use in targeting drugs to such a system. Intraperitoneal route is important in targeting of antineoplastics into the lymphatic system.

The vehicle, polymers and other substances used in the formulation of parenterals controlled-release dosage forms should be sterile, pyrogen free, nonirritating, biocompatible and biodegradable into nontoxic compounds within an appropriate time, preferably close to the duration of drug action.

There are several approaches to achieve controlled drug delivery via parenterals route, the release being controlled by dissolution, diffusion, dissociation, partitioning or bioerosion. The systems can be broadly classified as:

**A. Injectables:**
1. Solutions
2. Dispersions
3. Microspheres and Microcapsules
4. Nanoparticles and Niosomes
5. Liposomes
6. Resealed Erythrocytes

**B. Implants**

**C. Infusion Devices:**
1. Osmotic Pumps
2. Vapor Pressure Powered Pumps
3. Battery Powered Pumps

**Solutions**
Both aqueous as well as oil solutions may be used for controlled drug release. With *aqueous solutions* (given intramuscularly), the drug release may be controlled in three ways:

i. By increasing the viscosity of vehicle by use of MC, CMC or PVP and thus, decreasing molecular diffusion and localizing the injected drug.
ii. By forming a complex with macromolecules like MC, CMC or PVP from which the drug dissociates at a controlled rate (only free drug will get absorbed).

iii. By forming complexes that control drug release not by dissociation but by reducing the solubility of parent drug e.g. protamine zinc insulin and cyanocobalamin zinc tannate.
*Oil solutions* control the release by partitioning the drug out of the oil in the surrounding aqueous biofluids. Vegetable oils like arachis oil, cottonseed oil, etc. are used for such a purpose. The method is applicable only to those drugs which are oil soluble and have optimum partition coefficient.

**Dispersions**
Dispersed systems like emulsions and suspensions can be administered by i.m., s.c. or i.v. routes. Among *emulsions*, the o/w systems have not been used successfully since absorption of drug incorporated in the oil phase is rapid due to large interfacial area and rapid partitioning. Similarly, few w/o emulsions of water-soluble drugs have been tried for controlled-release. **Multiple emulsions** of w/o/w and o/w/o types (more correctly, double **emulsions**) are becoming popular since an additional reservoir is presented to the drug for partitioning which can effectively retard its release rate.

Control of drug release from *suspensions* is easier and predictable. Drug dissolution and subsequent diffusion are the main rate controlling steps. Release of water-soluble drugs can be retarded by presenting it as oil suspension and *vice versa* for oil soluble drugs.

Factors to be considered in the formulation of such a system include –

i. Solid content : should be ideally in the range 0.5 to 5.0%
ii. Particle size : this factor is very important since larger the particle size, slower the dissolution; however, larger particles have their own disadvantages like causing irritation at the injection site (size should therefore be below 10 microns), poor syringeability and injectability and rapid sedimentation. The latter problem can be overcome by use of viscosity builders which also retard drug diffusion.

*Aqueous suspensions* can be given by i.m. or s.c. routes. Generally crystalline and stable polymorphic forms of the drug are chosen rather than amorphous forms to delay release. Solubility can be further reduced by salt or complex formation e.g. crystalline zinc insulin shows more prolonged action than amorphous zinc insulin complex. *Oil suspensions*, generally given i.m., prolong drug action much more in comparison to oil solution and aqueous suspension since drug release involves two rates- limiting steps viz. dissolution of drug particles, and partitioning of the dissolved drug from oil to the aqueous biofluids.

**Microspheres and Microcapsules**

**Microspheres** are free flowing powders consisting of spherical particles of size ideally less than 125 microns that can be suspended in a suitable aqueous vehicle and injected by an 18 or 20 number needle. Each particle is basically a matrix of drug dispersed in a polymer from which release occurs by a first-order process. The polymers used are biocompatible and biodegradable e.g. polylactic acid, polylactide coglycolide, etc. Drug release is controlled by dissolution/degradation of matrix. Small matrices release drug at a faster rate and thus, by using particles of different sizes, various degrees of controlled release can be achieved. The system is ideally suited for controlled-release of peptide/protein drugs such as LHRH which have short half-lives and otherwise need to be injected once or more, daily, as conventional parenteral formulations. In comparison to peptides, proteins are difficult to formulate because of their higher molecular weight, lower solubility and the need to preserve their

conformational structure during manufacture. In order to overcome uptake of intravenously administered microspheres by the reticuloendothelial system and promote drug targeting to tumors with good perfusion, **magnetic microspheres** were developed. They are prepared from albumin and magnetite (Fe2O3) and have a size of 1.0 micron to permit intravascular injection. The system is infused into an artery that perfuses the target site and a magnet is placed over the area to localize it in that region. A 100 times higher concentration of doxorubicin was attained at the target site by such an approach with just half the i.v. dose.

**Microcapsules** differ from microspheres in that the drug is centrally located within the polymeric shell of finite thickness and release may be controlled by dissolution, diffusion or both. Quality microcapsules with thick walls generally release their medicaments at a zero-order rate. Steroids, peptides and antineoplastics have been successfully administered parenterally by use of controlled-release microcapsules.

**Nanoparticles and Niosomes**

**Nanoparticles** are also called as **nanospheres** or **nanocapsules** depending upon whether the drug is in a polymer matrix or encapsulated in a shell. They differ from microspheres in having submicron particles in the nanometer size range—10 to 1000 nm. The polymers used are the usual biodegradable ones. The main advantage of this system is that it can be stored for upto 1 year and can be used for selective targeting via reticuloendothelial system to liver and to cells that are active phagocytically.

Like nanoparticles, **niosomes** are inexpensive alternatives to liposomes. They are closed vesicles formed in aqueous media from nonionic surfactants with or without the presence of cholesterol or other lipids.

**Liposomes**

The term **liposomes** (meaning *lipid body*) was derived on the basis of names of subcellular particles like lysosome and ribosome. It is defined as a spherule/vesicle of lipid bilayers enclosing an aqueous compartment. The lipid most commonly used is phospholipid. Sphingolipids, glycolipids and sterols have also been used to prepare liposomes. Their size ranges from 25 to 5000 nm. Depending upon their structure, liposomes are classified as:

i. MLV (*multilamellar vesicles*) : These liposomes are made of series of concentric bilayers of lipids enclosing a small internal volume.

ii. OLV (*oligolamellar vesicles*) : These are made of 2 to 10 bilayers of lipids surrounding a large internal volume.

iii. ULV (*unilamellar vesicles*) : These are made of single bilayer of lipids. They may be SUV (*small unilamellar vesicles*) of size 20 to 40 nm, MUV (*medium unilamellar vesicles*) of size 40 to 80 nm, LUV (*large unilamellar vesicles*) of size 100 to 1000 nm or GUV (*giant unilamellar vesicles*) of size greater than 1000 nm.

A large variety of drugs (antineoplastics, antibiotics), peptides/proteins (including antibodies) and viruses and bacteria can be incorporated into liposomes. Water-soluble drugs are trapped in the aqueous compartment while lipophilic ones are incorporated in the lipid phase of liposomes. Because of their availability in various sizes, ability to incorporate both water as

well as oil soluble drugs, their inertness and their ability to protect labile drugs, liposomes are versatile carriers for parenteral drug delivery systems.

Intramuscularly and subcutaneously injected liposomes deliver drug at a controlled rate while intravenous administration selectively targets them to reticuloendothelial system and phagocytic cells. A simple method by which liposomes can be produced involves drying an organic solvent solution of lipids onto the wall of a flask/beaker followed by hydration and dispersion of lipid by addition of buffer and mixing.

**Resealed Erythrocytes**

Drug loading in body's own erythrocytes when used to serve as controlled delivery systems have several **advantages**. They are fully biodegradable and biocompatible, nonimmunogenic, can circulate intravascularly for days (act as circulatory drug depots) and allow large amounts of drug to be carried. The drug need not be chemically modified and is protected from immunological detection and enzymatic inactivation. Drug loading can be done by immersing the cells in buffered hypotonic solution of drug which causes them to rupture and release hemoglobin and trap the medicament. On restoration of isotonicity and incubation at 37o C, the cells reseal and are ready for use. Damaged erythrocytes are removed by the liver and spleen. These organs can thus be specifically targeted by drug loaded erythrocytes.

**Implants**

An *ideal* implantable parenteral system should possess following properties—

1. *Environmentally stable* : should not breakdown under the influence of heat, light, air and moisture.
2. *Biostable* : should not undergo physicochemical degradation when in contact with biofluids (or drugs).
3. *Biocompatible* : should neither stimulate immune responses (otherwise the implant will be rejected) nor thrombosis and fibrosis formation.
4. *Nontoxic and noncarcinogenic* : its degradation products or leached additives must be completely safe.
5. Should have a minimum surface area, smooth texture and structural characteristics similar to the tissue in which it is to be implanted to avoid irritation.
6. Should be *removable* when required.
7. Should release the medicament at a constant predetermined rate for a predetermined period of time.

Some of the important **advantages** of implants over injectable controlled-release formulations are—

1. More effective and more prolonged action (for over a year).
2. A significantly small dose is sufficient.

A major **disadvantage** of such systems is that a microsurgery is required for implantation of device. Some devices can be easily implanted by use of a specially designed implanter syringe. The devices are generally implanted subcutaneously or intramuscularly. Subcutaneous tissue is an ideal location because of its easy access to implantation, poor perfusion, slow drug absorption and low reactivity towards foreign materials. The drug may be dissolved, dispersed or embedded in a matrix of polymers that control release by dissolution, diffusion or both, bioerosion, biodegradation or an activation process such as osmosis or hydrolysis. The system is generally prepared as implantable flexible/rigid moulded or extruded rods, spherical pellets or compressed tablets. Polymers used are silicone

elastomers, polymethacrylates, polycaprolactone, polylactide/glycolide, etc. Drugs generally presented in such systems are steroids like contraceptives (megestrol acetate, norgestrone, etc.), morphine antagonists like naltrexone for opiod-dependent addicts, etc.

**Infusion Devices**

These are also implantable devices but are versatile in the sense that they are intrinsically powered to release the medicament at a zero-order rate and the drug reservoir can be replenished from time to time. Depending upon the mechanism by which these implantable pumps are powered to release the contents, they are classified into following types:

1. Osmotic pressure activated drug delivery systems
2. Vapor pressure activated drug delivery systems
3. Battery powered drug delivery systems

**Osmotic Pumps (Alzet)**

These pumps are capsular in shape and made in a variety of sizes. The pump is made of three concentric layers—the innermost drug reservoir contained in a collapsible impermeable polyester bag (which is open to the exterior via a single portal) followed by a sleeve of dry osmotic energy source (sodium chloride) and the outermost rigid, rate-controlling semipermeable membrane fabricated from substituted cellulosic polymers. A rigid polymeric plug is used to form a leakproof seal between the drug reservoir and the semipermeable housing. An additional component, the flow modulator, comprising of a cap and a tube made of stainless steel is inserted into the body of osmotic pump after filling. After implantation, water from the surrounding tissue fluids is imbibed through the semipermeable membrane at a controlled rate that dissolves the osmogen creating an osmotic pressure differential across the membrane. The osmotic sleeve thus expands and since the outer wall is rigid, it squeezes the inner flexible drug reservoir and drug solution is expelled in a constant volume per unit time fashion. The drug delivery continues until the reservoir is completely collapsed. Ionized drugs, macromolecules, steroids and peptides (insulin) can be delivered by such a device.

**Rate Controlling Factors:**

Porosity of semipermeable membrane
Osmotic pressure difference across the membrane

**Vapour Pressure Powered Pump (Infusaid)**

This device is based on the principle that at a given temperature, a liquid in equilibrium with its vapour phase exerts a constant pressure that is independent of enclosing volume. The disc shaped device consists of two chambers—an infusate chamber containing the drug soluton which is separated by a freely movable flexible bellow from the vapour chamber containing inexhaustible vaporizable fluid such as fluorocarbons. After implantation, the volatile liquid vaporizes at the body temperature and creates a vapour pressure that compresses the bellows and expels the infusate through a series of flow regulators at a constant rate. Insulin for diabetics and morphine for terminally ill cancer patients have been successfully delivered by such a device.

**Battery Powered Pumps**

Two types of battery powered implantable programmable pumps used successfully to deliver insulin are—peristaltic pump and solenoid driven reciprocating pump, both with electronic controls. The systems can be programmed to deliver drug at desired rates. Their design is such that the drug moves towards the exit and there is no backflow of the infusate.