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A REVIEW ON PARENTERAL CONTROLLED DRUG DELIVERY SYSTEM

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ABSTRACT

The parenteral administration route is the most effective and common form of delivery for active drug substances with poor bioavailability and the drugs with a narrow therapeutic index. Drug delivery technology that can reduce the total number of injection throughout the drug therapy period will be truly advantageous not only in terms of compliance, but also to improve the quality of the therapy and also may reduce the dosage frequency. Such reduction in frequency of drug dosing is achieved by the use of specific formulation technologies that guarantee the release of the active drug substance in a slow and predictable manner. The development of new injectable drug delivery system has received considerable attention over the past few years. A number of technological advances have been made in the area of parenteral drug delivery leading to the development of sophisticated systems that allow drug targeting and the sustained or controlled release of parenteral medicines.

INTRODUCTION: A number of technological advances have been made in the area of parenteral drug delivery, leading to the development of sophisticated systems that allow drug targeting and the sustained or controlled release of parenteral medicines [1].

Parenteral formulations, particularly intravascular ones, offer a unique opportunity for direct access to the bloodstream and rapid onset of drug action as well as target to specific organ and tissue sites [2].

This review emphasises on the study of advanced novel parenteral drug delivery system with its application in reference. We have made discussion of injectables, implants and infusion devices which are classified as follows:

PARENTERAL DRUG DELIVERY SYSTEM

INJECTABLE	IMPLANT	INFUSION DEVICES
1. Solutions	1. In-situ Depot forming system	1.Osmotic pumps
2. Colloidal dispersions	2. Solid Implants	2.Vapour pressure powder pump
(A) Liposome		3.Battery powder pumps
(B) Niosomes		
(C) Poly meric/ mixed micelles		
(D) Nanoparticles		
a) Nanosuspensions		
b) Nanoemulsion/Microemulsion		
c) Solid Lipid Nanoparticles(SLN)		
d) Nanostructured lipid carriers (NLC)		
e) Lipid drug conjugated (LDC) nanoparticles		
3. Microparticles		
(A) Microspheres		
(B) Microcapsules		
4. Resealed erythrocytes		

INJECTABLE:

1. **SOLUTIONS [3]:** Both aqueous as well as oil solutions may be used for parenteral controlled drug release. With aqueous solutions (given i.m.), the drug release may be controlled in three ways;

   - By increasing the viscosity of vehicle by use of MC, CMC, or PVP and thus, decreasing molecular diffusion and localizing the injected drug.
   - 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).
   - 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 oli, 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.

2. COLLOIDAL DISPERSIONS

A. Liposomes: Liposomes are formed by the self-assembly of phospholipid molecules in an aqueous environment. The amphiphilic phospholipid molecules form a closed bilayer sphere in an attempt to shield their hydrophobic groups from the aqueous environment while still maintaining contact with the aqueous phase via the hydrophilic head group [1].

Methods of preparation [3]:

a) Sonication
b) High pressure extrusion or homoginization
c) Detergent dialysis
d) Lipid – alcohol - water injection
e) Reverse phase evaporation
f) Dehydration – rehydration

Applications:

i. **Liposomal Anti Cancer Agent:** The use of liposomes as anticancer drug delivery systems was originally hampered by the realization that liposomes are rapidly cleared from the circulation and largely taken up by the liver macrophage[4,5]. It was observed that doxorubicin-loaded stealth liposomes circulate for prolonged periods, accumulate, and extravagate within tumors and also improve tumoricidal activity in mice [6]. In one study, it has been reported that in patients, liposomal doxorubicin accumulates within Kaposi's sarcoma lesions and produces a good therapeutic response [7]. Liposomal doxorubicin is now licensed as Caelyx for the treatment of Kaposi's sarcoma. This formulation is currently in clinical trials for ovarian cancer and could be approved shortly for use in ovarian cancer patients who have failed to respond to paclitaxel and cisplatin [8, 9].

ii. **Liposomes as Vaccine Adjuvants:** Liposomal vaccines can be made by associating microbes, soluble antigens, cytokines, or DNA with liposomes, the latter stimulating an immune response on expression of the antigenic protein [10]. Liposomes encapsulating antigens are subsequently encapsulated within alginate lysine microcapsules to control the antigen release and to improve the antibody response [11]. Liposomal vaccines may also be stored dried at refrigeration temperatures for up to 12 months and still retain their adjuvanticity [7, 12].

iii. **Liposomal Anti-Infective Agents:** Liposomal amphotericin B (Ambisome) is used for the treatment of systemic fungal infection. This is the first licensed liposomal preparation. It was observed in one study that liposomal amphotericin B, by passively targeting the liver and spleen, reduces the renal and general toxicity of the drug at normal doses [7]. Some of the actives incorporated in injectable liposomes are presented in following table.

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

A. Future Opportunities and Challenges: Drug delivery systems have greater potential for many applications, including antitumor therapy, gene therapy, acquired immune deficiency syndrome therapy, radiotherapy, in the delivery of proteins, antibiotics, virostatics, vaccines, and as vesicles to pass the blood-brain barrier. The cytotoxicity or their degradation products is a major problem, and improvements in biocompatibility obviously are a main concern of future research. Many technological challenges have to be met in developing the following techniques:

- Advanced polymeric carriers for the delivery of therapeutic peptide/proteins (bio-pharmaceutics);
- Nano-drug delivery systems that deliver large, but highly localized, quantities of drugs to specific areas to be released in controlled ways;
- Materials for nanoparticles that are biocompatible and biodegradable;
- Architectures/structures, such as biomimetic polymers, nanotubes;
- Controllable release profiles, especially for sensitive drugs;
- Technologies for self-assembly;
- Functions (active drug targeting, on-command delivery, intelligent drug release devices/bioresponsive triggered systems, self-regulated delivery systems, systems interacting with the body, smart delivery).

I. **Niosomes:** Niosomes are nonionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants of the alkyl or dialkyl polyglycerol ether class, with or without incorporation of cholesterol or other lipids.[13] A typical structure of Niosome is presented in **figure 1**. Various drugs incorporated into niosomes by different methods are shown in table.

Drugs incorporated into Niosomes by various methods:

Method of preparation	Drug incorporated
Ether injection	Sodium stibogluconate, doxorubicin
Hand shaking	Methotrexate, doxorubicin
Sonication	9-desglycinamide, 8-arginine, vasopressin, oestradiol

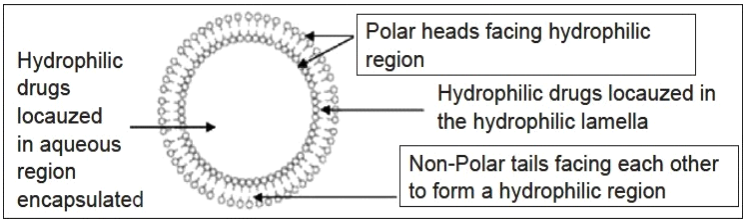

FIGURE 1: STRUCTURE OF NIOSOMES

Advantages of Niosomes [14, 15]:

- They entrap solute in a manner analogous to liposomes.
- They are osmotically active and stable.
- Handling and storage of surfactants requires no special conditions.
- They possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with a wide range of solubilities.
- They exhibit flexibility in their structural characteristics (composition, fluidity, and size) and can be designed according to desired application.
- They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
- They allow their surface for attachment of hydrophilic group and can incorporate hydrophilic moieties in bilayer to bring about changes in their in vivo behavior.
- The surfactants are biodegradable, biocompatible, and nonimmunogenic.
- They improve the therapeutic performance of the drug molecules by delaying the clearance from the circulation, protecting the drug from biological environment, and restricting effects to target cells.
- Niosomal dispersion in an aqueous phase can be emulsified in a nonaqueous phase to regulate the delivery rate of drug and administer normal vesicle in external nonaqueous phase.

Applications:

i. **Anticancer Niosomes:** Anticancer niosomes, if suitably designed, will be expected to accumulate within tumors. For example, niosomal encapsulation of methotrexate and doxorubicin increases drug delivery to the tumor and tumoricidal activity. It was reported that doxorubicin niosomes having size 200 nm with a polyoxyethylene (molecular weight 1000) surface are rapidly taken up by the liver and accumulate to a lesser extent in tumor; this technology may prove advantageous for the treatment of hepatic neoplasms [16, 17].

ii. **Niosomes at Targeted Site:** Uptake by the liver and spleen make niosomes ideal for targeting diseases manifesting in these organs [18]. One such condition is leishmaniasis, and a number of other studies have shown that niosomal formulations of sodium stibogluconate improve parasite suppression in the liver, spleen, and bone marrow. Niosomes may also be used as depot systems for short-acting peptide drugs on intramuscular administration [19].

iii. **Niosomes as Vaccine Adjuvants:** It was studied that niosomal antigens are potent stimulators of the cellular and humoral immune response. The formulation of antigens as a niosome in water-in-oil emulsion further increases the activity of antigens and hence enhances the immunological response [1, 20].

II. **Polymeric/mixed micelles [3]:** Polymeric micelles are nanosized core/shell assemblies of amphiphilic block copolymers that are suitable for the delivery of hydrophobic and amphiphilic agents. Among different micelle-forming block copolymers, those with PEO as the shell forming block and poly(l-aminoacid)s (PLAA)s and poly(ester)s as the core forming block are must popular in drug development. Hydrophobic core of polymeric micelles provides an excellent host for the incorporation and stabilization of anticancer agents that are mostly hydrophobic. Nanosize of these micelles enables them to escape the phagocytic effects of RES, enhance their circulation life and penetration in to tumour tissues.

III. Nanoparticles

a) **Nanosuspension [21,22]:** A nanosuspension is a submicron colloidal dispersion of drug particles that are produced by suitable methods and stabilized by surfactants. A pharmaceutical nanosuspension can be defined as the nano-sized drug particle which is finely dispersed in an aqueous vehicle for either oral and topical use or parenteral and pulmonary administration. In general, the particle size in nanosuspension is always less than 1µm (usually lies between 200nm to 600nm).

- They should be sterile, pyrogen free, stable, resuspendable, syringable, injectable, isotonic & non-irritating.
- Because of above requirements injectable suspensions are one of the most difficult dosage forms to develop in term of their stability, manufacture & usage.
- The parenteral suspension may be formulated as already to use injection or require a reconstitution step prior to use.
- They are usually administered by either subcutaneous (s.c.) or intramuscularNever suspension delivery systems containing drug in microparticulate or nanoparticfe can be injected by intravenously or intraarterially.
- These suspensions usually contain between 0.5% and 5.0% solid & should have particle size less than 5 micrometer for I.M. or S.C. administration.
- Certain antibiotic preparation (For example procaine Penicillin G) may contain up to 30 % solids.

Preparation of Nanosuspension: Nanosuspension is generally prepared by two methods that are “Bottom up technology” and” Top down technology”. “Bottom up technology “follows precipitation method where the drug is dissolved in a solvent, which is then added to a non-solvent which precipitates crystals. Precipitation technique uses simple and low cost equipments.

The basic challenge of this technique is that during the precipitation procedure the growing of the drug crystals needs to be controlled by addition of surfactant to avoid formation of microparticles. The limitation of this technique lies in the fact that the drug needs to be soluble in at least one solvent and this solvent needs to be miscible with the nonsolvent. Moreover precipitation technique is not applicable to drugs, which are simultaneously poorly soluble in aqueous and nonaqueous media.

Some nanosuspensions of Carbamazepine, Cyclosporin, Griseofulvin, and Retinoic acid have already been developed by precipitation method. The "Top down technology" follows the method of disintegration which is preferred over the conventional precipitation technology. Technologies like Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in nonaqueous media (Nanopure), combination of Precipitation and High-Pressure Homogenization (Nanoedege) and others like Emulsion Solvent diffusion method and Microemulsion as templates are various examples of "Top down technology".

i. Media milling
ii. Emulsion method
iii. Nanojet technology
iv. Nanoedge technology
v. High pressure Homogenization
vi. Microemulsion template
vii. Dry co-grinding
viii. Supercritical fluid method

Application of Nanosuspension as Parenteral Administration: Nanosuspension can be delivered either intra-articular or intravenous route. But in case of parenteral administration, solute should be remained in solubilized form or particle or globule size below 5 µm to avoid capillary blockage. Some current approaches have come resolve the drawbacks of poorly soluble drug for parenteral delivery. These are salt formation, solubilization using co-solvent, miceller solution, complexation with cyclodextrin and vesicular system (liposome and transferosome). In recent time, vesicular systems like liposome have been accepted for parenteral delivery but they have some limitation in terms of physical instability, high manufacturing cost and difficulties in scale-up. However nanosuspension has still been considered as a useful dosage form which employs better efficacy for parenteral administered drugs. More for example, paclitaxel nanosuspension has been found better responses in treating tumour than taxol.

b. Nanoemulsion/Microemulsion [23]: Nanoemulsion / Microemulsion are liquid dispersions of water and oil that are made homogenous, transparent (or translucent) and thermodynamically stable by the addition of relatively large amounts of a surfactant and a co-surfactant and having diameter of the droplets in the range of 100 – 1000 A (10 – 100 nm) shown in **figure 2**.

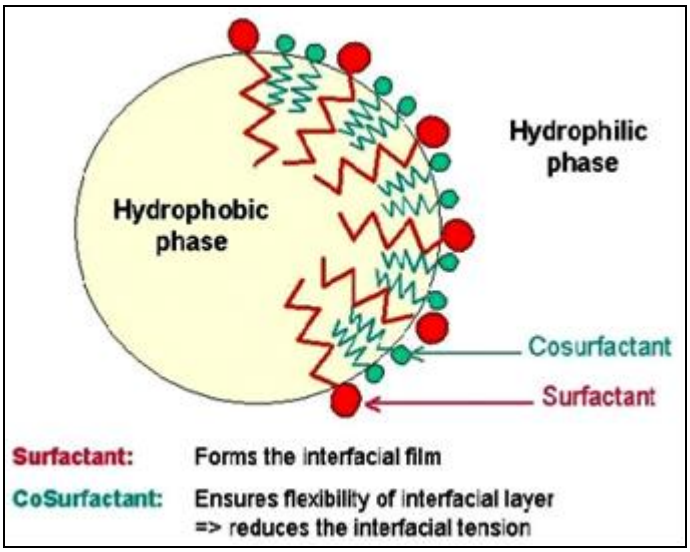

FIGURE 2: STRUCTURE OF DROPLET FORMED IN EMULSION

Components of Nanoemulsion: Main three components of Nanoemulsions are as follows:

1) Oil - like Myristic acid isopropyl ester, Glyceryl Tricaprylate (Tricaprylin), Glyceryl Tricaorylate/Caprate
2) Surfactant/Co-surfactant
3) Aqueous phase- Water for injection

Different types of surfactant are shown in **figure 3**.

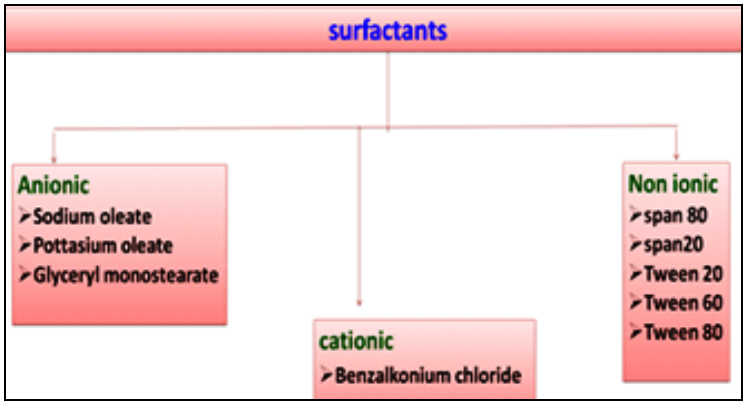

FIGURE 3: CLASSIFICATION OF SURFACTANTS

Methods of Preparation:

1) High-Pressure Homogenisation
2) Microfluidization

Application:

I. Microemulsions can also be used as intravenous delivery systems for the fat soluble vitamins and lipids in parenteral nutrition.
II. Microemulsions are generally not dilutable with aqueous fluids, such as certain bodily fluids and buffer solutions.
III. Microemulsions are also sensitive to temperature and are not stable outside of room temperature conditions.
IV. O/W microemulsions were characterized by their small particle size and their wide range of temperature stability, typically from about -20^{o}-50^{o}C. They could be administered by intravenous, intraarterial, intrathecal, intraperitoneal, intraocular, intraarticular, intramuscular or subcutaneous injection.

c. Solid Lipid Nanoparticles [24]: Melt-emulsified nanoparticles based on lipids (or waxes) are solid at room temperature and generally prepared by hot high pressure homogenization.The concept of lipid nanoparticles for injectable delivery was developed from submicron sized parenteral fat o/w emulsion used for parenteral nutrition viz. Intralipid in 1960s. This gave birth to the idea of encapsulating lipophilic drugs into oil droplets. The only drawback associated with these submicron emulsions was the low viscosity of the droplets, causing fast release and susceptibility of the incorporated actives towards degradation by the aqueous continuous phase.

In 1990s, researchers (Mueller and coworkers and Gasco and coworkers) started exploring the potential of nanoparticles-based solid lipids or SLNs in the drug delivery. SLN are colloidal particles composed of a biocompatible/biodegradable lipid matrix that is solid at body temperature and exhibit size range in between 100 and 400 nm. A typical structure of SLN is presented in **Figure 4**. Various drug molecules have been incorporated in injectable SLN for treatment of different diseases are shown in the table given below;

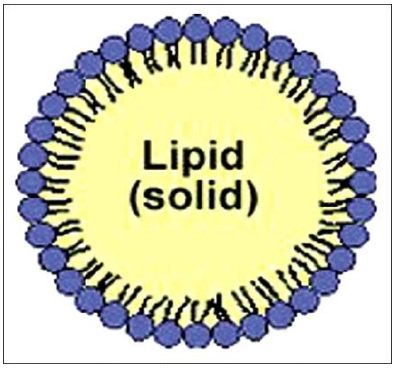

FIGURE 4: SOLID LIPID NANOPARTICLE

Overview of various actives incorporated in injectables lipid nanoparticles

Drug	Disease	Route of administration
5-FU	Cancer	Intravenous (IV)
Actarict	Rheumatoid arthritis	Intravenous
Bromocriptine	Anti parkinsonism	Intraperitoneum (IP)
Clozapine	Antipsychotic	Intradeodenum (ID)
Etoposide	Cancer	IV/SC/IP
Paclitaxel	Cancer	Intravenous
Tobramycin	Antibiotic	IV/ID

SC – subcutaneous

Advantages:

- Particulate nature
- Amenability to encapsulate hydrophilic and hydrophobic drugs
- Ability to sustain the release of incorporated drug
- Ability to prevent chemical, photochemical, or oxidative degradation of drug
- Ability to immobilize drug in the solid matrix
- Ease of scale-up and manufacture
- Low cost of solid lipids as compared with phospholipids and biodegradable polymers

Application of Lipid Nanoparticles for Parenteral Drug Delivery:

I. **Treatment of Cancer:** SLN have been shown to improve the efficacy and residence time of the cytotoxic drugs, with concomitant reduction in the side-effects associated with them.[8, 9] The salient features of SLN which make them a suitable carrier for antitumor drug delivery are their ability to encapsulate antitumor agents of diverse physiochemical properties, improved stability of the drug, less in vitro toxicity, enhanced drug efficacy, and improved pharmacokinetics.

II. **Transfection:** Cationic SLN have been shown to be efficacious in transfecting COS-1 cells in vitro. These 100 nm SLN were able to bind deoxyribonucleic acid (DNA) to form a stable complex of 300 to 800 nm size. The transfection efficacy was determined using COS-1 cells.

III. **Liver Targeting:** Particulate carriers (including SLN) usually accumulate in the liver by passive targeting on parenteral administration. However, passive targeting leads to entrapment of the drug in the Kupffer cells and not in the hepatocytes, which is the major target for the treatment of hepatic diseases such as cancers. Hence, for liver targeting, SLN containing galactosylated or mannosylated lipids are employed.

IV. **Targeting the Central Nervous System:** Various drugs ranging from antipsychotics, antiparkinson, antieschemic to antibiotics have been encapsulated in lipid nanoparticles with the aim to either modify the biodistribution or for brain targeting. Recently, potential of surface-modified SLN has been demonstrated in the treatment of brain diseases such as cerebral malaria. Gupta et al. fabricated transferrin-conjugated SLN and studied their ability to target quinine hydrochloride to brain by studying biodistribution.

V. **Treatment of Cardiovascular Diseases:** Tanshinone IIA, a lipophilic natural drug product, has the ability to dilate coronary arteries and increase myocardial contractility. Liu and coworkers studied the ability of SLN to improve the delivery of Tanshinone II A by in vitro and in vivo studies.

VI. **Treatment of Parasitic Diseases:** Antiparasitic agents represent a class of drugs which had been neglected as a model for drug delivery systems for a long time. As compared with other therapeutic agents, relatively fewer reports are published on the delivery of antiparasitic agents. Transferrin-conjugated SLN of quinine dihydrochloride, an antimalarial drug, were prepared to target it to the brain for the management of cerebral malaria.

VII. **Treatment of Rheumatoid Arthritis:** Actarit SLN were prepared with the aim of passive targeting. These SLN were shown to enhance the therapeutic efficacy with concomitant reduction in the various adverse effects such as nephrotoxicity and gastrointestinal disorders.

VIII. **Treatment of other Diseases:** Cholesteryl butyrate SLN as a prodrug carrier was used for anti-inflammatory therapy of ulcerative colitis.

IX. **Toxicity of Lipid Nanoparticles:** For the successful regulatory clearance of SLN for parenteral delivery, it is essential to establish their biocompatibility with blood components and other tissues. Thus, SLN can be used as intravenous carriers because of their prolonged circulation time and high toxicological acceptance.

d. Nanostructured lipid carriers (NLC) [3]: NLC are oil loaded Solid- Lipid Nanoparticles. NLC offers several advantages over SLN such as,

- Greater degree of drug loading.
- Reduced burst release of drug.
- Better control of drug release.

e. Lipid Drug Conjugate (LDC) Nanoparticles [3]: Covalent bonding or salt formation of a hydrophilic drug with lipid is done to:

- Enhance *in vivo* stability
- Improve membrane permeability.
- Control drug release.

MICROPARTICLES:

A. **Microspheres [3]:** 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 form which release occurs by a first order process. The polymers used are biocompatible and biodegradable e.g. PLA, PLGA, 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 inttrvenously administered microsphere by the RES and promot drug targeting to tumours with good perfusion, magnetic microspheres were developed. They are prepared from albumin and magnetite(Fe_2O_3) 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. Magnetic microspheres have specifically been used to target anticancer drug such as doxorubicin to tumours and as diagnostics/contrast agent for magnetic resonances imaging(MRI)

Disadvantages of microspheres for controlled release parenterals include-

- Difficulty of removal from the site.
- Low drug loading (maximum of 50%).
- Possible drug degradation within the microspheres.
- Changes in drug crystallinity or polymorphic form during microsphere processing.

B. **Microcapsules [3]:** 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 antineoplastic have been successfully administered parenterally by use of controlled release microcapsules.The methods used for preparing microcapsules(for parenterally or per-os delivery) can be classified into two categories:

1. **Type A processes:** These are defined as those in which capsule formation occurs entirely in a liquid filled stirred tank or tubular reactor e.g.;

   - Complex coacervation
   - Polymer polymer incompatibility
   - In situ polymerization
   - Solvent evaporation or in liquid drying
   - Submerged nozzle extrusion

2. **Type B processes:** are processes in which capsule formation occurs because a coating is sprayed or deposited in some manner onto the surface of a liquid or solid core material dispersed in a gas phase or vaccum e.g.;

   - Spray drying
   - Fluidized bed coating
   - Centrifugal extrusion
   - Extrusion or spraying into a desolvation bath
   - Rotational suspension separation(spinning disk).

3. **Resealed Erythrocytes [3]:** Drug loading into body's own erythrocytes when used to serve as controlled delivery systems shown in figure-5 has several advantages:

   - Fully biodegradable, biocompatible, and non immunogenic.
   - Longer life span in circulation.
   - Drug protected from enzymatic inactivation.
   - Ability to target the organs of the RES.

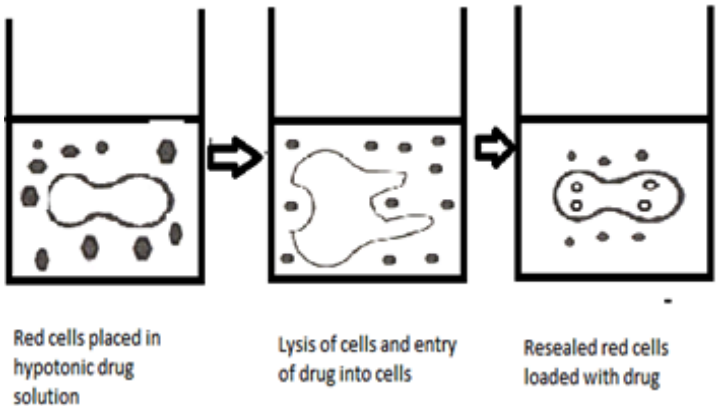

FIGURE 5: SCHEMATIC PRESENTATION OF RESEALED ERYTHROCYTES

Drug loading can be done by immersing yhe cell in buffered hypotonic solution of drug which causes them to rupture and release haemoglobin and trap the medicament. On restoration of isotonicity and incubation at 37^{o}C, the cells reseal and are ready for use Upon reinjection, the drug loaded erythrocytes serve as slow circulating depots.

Damaged erythrocytes are removed by the liver and spleen. These organs can thus be specifically targeted by drug loaded erythrocytes and is used in the therapy such as enzyme replacement,treating liver tumours, eradication of parasites, etc.

IMPLANT [24]: Lafarge first introduced the concept of implantable therapeutic system for long term, continuous drug administration in 1861 with the development of a subcutaneous implantable drug pellet. The technique was used to administered crystalline hormone in form of solids steroids pellets. Implant represent novel approach in the use of solid dosage forms as parentral product. Implants are insert under the skin by cutting and stitching it alter insertion of' the sterile tablet which is cylindrical, rod and ovoid shaped and more than 8 mm in length. The sterile tablets consisting of the highly purified drug, compressed without excipients. If, intended for subcutaneous implantation in the body.

1. *In-situ* Forming Implant (*In-situ* Depot forming system):

Classification of injectable *in situ* forming implants:

a. **Thermoplastic pastes:** Semi-solid polymers can be injected when melted and form a depot upon cooling to body temperature. The requirements for such In SituForming Devices (ISFD) include low melting or glass transition temperatures in the range of 25 to 658°C and an intrinsic viscosity in the range of 0.05 to 0.8 dl/g. Thermoplastic pastes allow local drug delivery at sites of surgical interventions for the delivery of antibiotic or cytotoxic agents. Alternatively, they can be used to generate a subcutaneous drug reservoir from which diffusion occurs into the systemic circulation.

b. **Thermally induced Gelling Systems:** Numerous polymers show abrupt changes in solubility as a function of environmental temperature. MacroMed distributes OncoGelw, which contains paclitaxel at a concentration of 6 mg/g ReGelw for intratumoral injection, followed by a continuous drug release over a period of 6 weeks. The clear advantage is the ability to solubilize the water-insoluble drug substances, such as paclitaxel, which allows a prolonged release for more than 50 days.

   ReGelw also exhibited sustained release kinetics for protein drugs. Release data were published by Gentner *et al*. Sol-gel transitions occur around 308^{o}C at polymer concentrations of 15 to 23% (w/w) in aqueous solution. Biocompatibility and toxicity do not seem to be problematic. Stability of proteins in the aqueous polymer solutions, the shelf life of the formulations, and *in vivo* release data for proteins are under investigation.

c. ***In situ* polymer precipitation:** A water-insoluble and biodegradable polymer is dissolved in a biocompatible organic solvent to which a drug is added, forming a solution or suspension after mixing. When this formulation is injected into the body, the water-miscible organic solvent dissipates and water penetrates into the organic phase. This leads to phase separation and precipitation of the polymer, forming a depot at the site of injection.

   This method has been developed by ARTIX Laboratories and is designated as the Atrigel technology. Various parameters of different systems are shown in following table.

Various parameters of different Systems:

	Thermoplastic paste	Thermogelling system	Polymer precipitation
Injection	Semisolid paste	Aqueous solution	Organic solution
Depot formation	Solidification	Sol-gel transition	Phase separation
Drug loading	Dry powder	Aqueous solution	Organic solution
Protien stability	High	Medium	Medium
Drug burst	Low	Medium	High
Release	Surface erosion	Pore diffusion/bulk erosion	Pore diffusion/bulk erosion
Local tolerance	High	High	Low
Injection pain	Low	Low	High

d. ***In situ*** **cross-linked polymer systems:** Gelsite polymer is a natural acidic polysaccharide that is extracted and purified from the aloe plant. The polymer,in an aqueous solution, forms a gel in the presence of calcium when injected subcutaneously or intramuscularly,thus entrapping a water soluble drug in the solution and providing sustained release.

e. ***In situ*** **microparticle implants**: A novel in situ microparticle implant system consist of an internal phase(Drug containing polymer solution or suspension) and a continuous phase(aqueous solution with a surfactant, oil phase with viscosity enhancer and emulsifier). Two phases are separately stored in dual chambered syringes and mixed through a connector before administration.

Solid Implants [3]: Implant arecylindrical, monolithic devices of mm or cm dimensions, implanted by a minor surgical incision or injected through a large boreneedle into the s.c or i.m tissue. 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 in implant may be dissolved, dispersed or embedded ina matrix of polymer or waxes/lipids that control release by dissolution and/or diffusion, bioerosion, biodegradation or an activation process such as osmosis or hydrolysis.

The system is generally prepred as implantable flexible/rigid moulded or extruded rods,spherical pellets or compressed tablets. Polymer used are silicone elastomers, polymath crylates, poly-caprolactone, polylactide/glycolide, etc., while waxes include glycerlymonosterate. Drugs generally presented in such system are steroids like contraceptives (megestrol acetate, norgestrone, etc.) morphine antagonists like naltrexone for opioid dependent addicts, etc.

Novel Technologies in Implants [25]

1. **ZOLADEX (Goseraline Acetate Implant):** Zoladex is a sterile, biodegradable product containing goseralin acetate designed for sub cutaneous injection, continuous release for 28 days. Zoladex is also available as zoladex-3 months. The base consists of a matrix of D,L- lactic & glycolic acid copolymer. It is indicated for no. of disorders, including palliative treatment of advanced carcinoma of prostrate. It is also used in the treatment of advanced breast cancer. It should be stored at room temp. & should not exceed 25^{o}C.

2. **GLIADEL® Wafer Implant:** GLIADEL® Wafers are small, dime-sized, half-inch white discs biodegradable polymer wafers that are designed to deliver BCNU or carmustine directly into the surgical cavity created when a brain tumor is surgically removed.Immediately after a neurosurgeon operates to remove the high-grade malignant glioma, up to eight wafers are implanted along the walls and floor of the cavity that the tumor once occupied. Each wafer contains a precise amount of carmustine that dissolves slowly, delivering carmustine to the surrounding cells. GLIADEL® Wafer therapy is used in conjunction with surgery and adjuvant radiation to treat certain kinds of brain tumors called high-grade malignant gliomas.

3. **DURIN™ Biodegradable Implants:** The DURIN biodegradable implant technology is based on the use of biodegradable polyesters as excipients for implantable drug formulations. This family of materials, which is used extensively in medical devices and drug delivery applications, includes the polymers and copolymers prepared from glycolide, DL-lactide, L-lactide, and ε-caprolactone. The overall form of the implant is typically a small rod or pellet that can be placed by means of a needle or trochar. The composition of the rod or pellet can be monolithic, where the drug is uniformly dispersed throughout the excipient. Alternatively, reservoir-type designs are also possible in which the rod or pellet is composed of a drug-rich core surrounded by a rate-controlling membrane e.g. Naltrexone, a narcotic antagonist, from a reservoir type DURIN implant.

4. **ATRIGEL® In Situ Implant System:** The ATRIGEL system is a proprietary delivery system that can be used for both Parenteral and site-specific drug delivery. It contains a biodegradable polymer dissolved in a biocompatible carrier. When the liquid polymer system is placed in the body using conventional needles and syringes, it solidifies upon contact with aqueous body fluids to form a solid implant. If a drug is incorporated into the polymer solution, it becomes entrapped within the polymer matrix as it solidifies, and is slowly released as the polymer biodegrades.The solvents employed in the ATRIGEL system to dissolve the polymers range from the more hydrophilic solvents, such as N-methyl-2-pyrrolidone (NMP), polyethylene glycol, tetraglycol, and glycol furol, to the more hydrophobic solvents, such as triacetin, ethyl acetate, and benzyl benzoate. NMP is most frequently used because of its solvating ability and its safety/toxicology profile.

5. **Infusion Devices [3]:** 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:

I. Osmotic pressure activated drug delivery systems

II. Vapour pressure activated drug delivery systems

III. Battery powered drug delivery systems

I. **Osmotic pressure activated Drug Delivery Systems:**

A. **ALZET osmotic pumps:** The ALZET pumps are capsuler in shape and made in variety of sizes and provide zero order delivery of drug. The pump is made of three layers as shown in **figure 6**.

1) The innermost drug reservoir contained in a collapsible impermeable polyester bag (which is often to the exterior via a single portal).

2) An intermediate sleeve of dry osmotic energy source (sodium chloride).

3) The outermost rigid, rate controlling SPM fabricated from substituted cellulosic polymers.

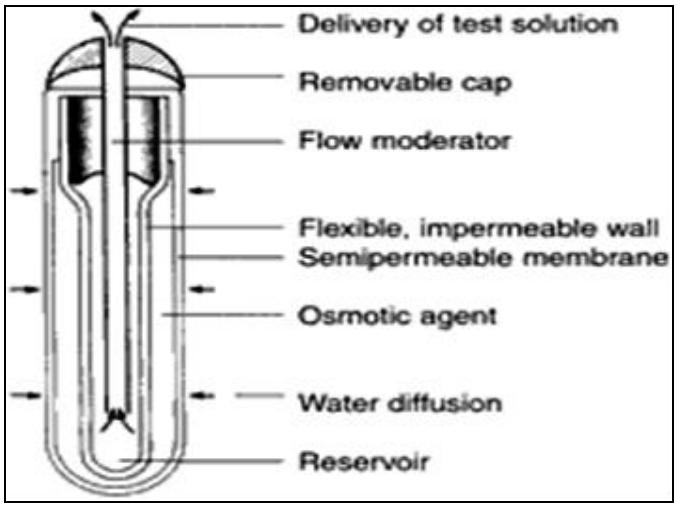

FIGURE 6: ALZET OSMOTIC PUMP

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 SPM at a controlled rate that dissolves the osmagent creating an osmotic pressure differential across the membrane. The osmotic sleeve thus expands and sinces the outer wall is rigid, it squeezes the inner flexible drug reservoir and the drug solution is expelled ina 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 bysucha device.

B. **DUROS infusion implant:** The DUROS osmotic implant is a non biodegradable, miniature titanium cylinder intended to enable systemic or tissue specific therapy for small molecule drugs, peptides, proteins, DNA and other bioactive macromolecules. The implant, which is inserted subcutaneously and retrieved at the end of the treatment duration,is designed to precisely and continuously deliver drugs for periods ranging from one month to more than a yeare.g. leuprolide acetate implant. In a DUROS system, a protein or peptide is formulated into a stable solution or suspension which is protected by the water resistant, non erodible, sterilized drug reservoir.

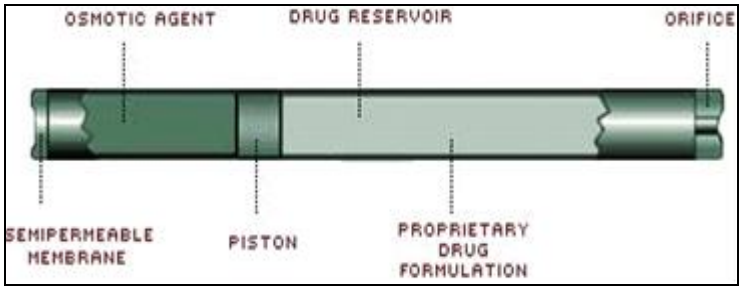

FIGURE 7: DUROS INFUSION IMPLANT

The outer titanium alloy cylinder is capped bya SPM at one end and by an exit port at the other end. Whithin the cylinder are an osmotic engine, apiston and the drug reservoir. When the DUROS system is implanted in the human body, water from surrounding tissue enters one end of the cylinder through the SPM, causing the osmotic engine to swell. This osmotic engine displaces a piston, which, in turn,causes the drug formulation tobe released from a port at other end of the system.

II. **Vapor Pressure powered Pump (Infusaid):** This device 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 chambers containing the drug solution, which is separated by a freely movable flexible bellow from the 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.

III. **Battery powered Pumps:** Two types of battery powered implantable programmable pumps used successfully to deliver insulin are peristaltic pumps and solenoid driven reciprocating pumps both with electronic controls. The system can be programmed to deliver drug at desired rate. Their design is such that the drug moves towards the exit and there is no backflow of the infusate.

CONCLUSION: Drug delivery technologies (discussed above) are used to control the delivery of drug by parenteral administration. Parenteral drug delivery systems have grown to become important technology platforms which are used by pharmaceutical companies in the recent years. So, it is important to study parenteral drug delivery system, as it provides rapid treatment objective to save valuable life of human being.

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