REVIEW ON PARENTRAL DRUG DELIVERY SYSTEM: A NOVEL APPROACH

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ABSTRACT

Drug delivery is a process that includes dosage form and route of administration. It refers to procedures or approaches for transporting pharmaceutical compound in the body safely to achieve its therapeutic effect. The Parenteral drug delivery system 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 administration of drug is often critical and associated with problems such as limited number of acceptable excipients, stringent requirements of aseptic production process, safety issues, and patient noncompliance. Still this route maintains its value due to special advantages like quicker onset of action in case of emergency; target the drug quickly to desired site of action, prevention of first pass metabolism etc. The application of advanced drug delivery technology to parenteral administration lead to development of SLNs, liposomes, niosomes, lipid nano dispersions etc. to overcome limitations of conventional parenteral delivery.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. 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.

Keywords: Parenteral drug delivery system, First pass metabolism, SLNs, liposomes, niosomes, lipid nano dispersions.

Introduction

The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development. Parenteral formulations, particularly intravascular ones, offer a unique opportunity for direct entry to the bloodstream and rapid onset of drug action as well as target to specific organ and tissue sites. This review emphasis on the study of advanced novel parenteral drug delivery system with its application in reference of discussion of solid lipid nanoparticles (SLN), *In situ* forming parenteral drug delivery systems, Organogels, lipid nanodispersions (nanoemulsions and nanosuspensions),niosomes and liposomes.

ADVANTAGES OF PARENTERAL DRUG DELIVERY TECHNOLOGY [1]

- It is related to advanced drug delivery technology that can reduce the number of injections throughout drug therapy period.
- Reduction in the frequency of drug dosing is achieved, by the use of specific formulation technologies.

  3) Depots, implants are used which can work from months to year and deliver the drug locally or to the systemic circulation rate.
- Therapeutic concentration can be maintained over a longer period of time.
- Smoothen the plasma concentration time profiles by eliminating the peaks and the valleys.

ADVANCED PARENTERAL DRUG DELIVERY SYSTEM [1- 4]

1) SOLID LIPID NANOPARTICLE (SLN)

Solid lipid nanoparticles (SLN) are aqueous colloidal dispersions, composed of a biocompatible or biodegradable lipid matrix that is solid at body temperature and exhibit size range in between 100-400nm.

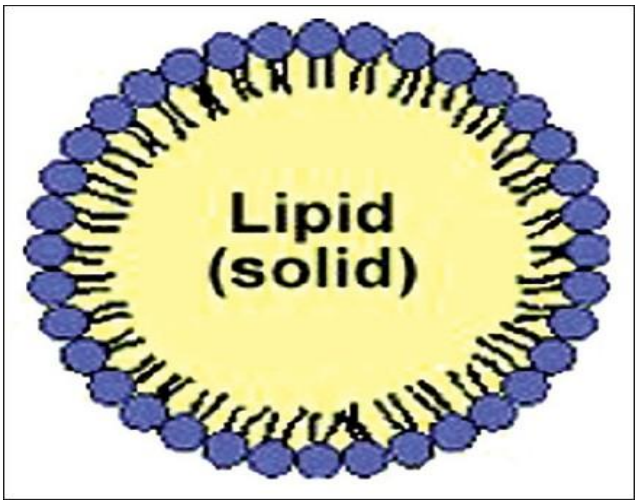

FIGURE 1: SOLID LIPID NANOPARTICLE

Overview of various actives incorporated in injectable lipid nanoparticles [2]

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 of SLNs

- Use of biodegradable physiological lipids which decreases the danger of acute and chronic toxicity and avoidance of organic solvents in production methods.
- Improved bioavailability of poorly water soluble molecules.
- Site specific delivery of drugs, enhanced drug penetration into the skin via dermal application.
  Possibility of scaling up.
- Protection of chemically labile agents from degradation in the gut and sensitive molecules from outer environment.
- SLNs have better stability compared to liposomes.
- Enhance the bioavailability of entrapped bioactive and chemical production of labile incorporated com-pound.
- High concentration of functional compound achieved.
- Lyophilization possible

Applications of SLNs

- Treatment of cancer.
- Liver targeting.

- Treatment of cardiovascular diseases.
- *Targeting the central nervous system.*
- Treatment of parasitic diseases.
- Treatment of rheumatoid arthritis.

IN SITU FORMING PARENTERAL DRUG DELIVERY SYSTEM [1, 2, 5]

Biodegradable injectable in situ forming drug delivery systems represent an attractive alternative to microspheres and implants as parenteral depot system. The controlled release of bioactive macromolecules has a number of advantages, such as:

1) Ease of administration,
2) Less complicated fabrication,
3) Less stressful manufacturing conditions for sensitive drug molecules.

Classification of injectable *in situ* forming implants[2,5]

(According to their mechanism of depot formation)

Thermoplastic pastes

Thermoplastic pastes are semisolid polymers, which injected as a melt and form a depot upon cooling to body temperature. They are characterized as having a low Melting point or Tg (glass transition temperature) in the range of 25-65˚C and an intrinsic viscosity in the range of 0.05-0.8 dl/g35, 36. Below the viscosity of 0.05 dl/g, no delayed release could be observed, where as above 0.8 dl/g the ISFD was no longer injectable using a needle. At injection temperature above 37˚C but below 65˚C these polymers behave like viscous fluids which solidify to highly viscous depots. Drugs are incorporated into the molten polymer by mixing without the application of solvents. Bioerodible thermoplastic pastes could be prepared from monomers such as D, L-lactide, glycolide, E-caprolactone, dioxanone and orthoesters. [5]

In situ cross-linked polymer systems

The formation of a cross-linked polymer network is advantageous, to control the diffusion of the hydrophilic macromolecules. Cross-linked polymer network can be found in situ by free radical reactions initiated by heat (thermosets) or absorption of photon or ionic interactions between small cation and polymer anions. [5]

In situ polymer precipitation

The concept ISFD based on polymer precipitation was first developed by Dunn and coworkers in 1990.In this method 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**.

Thermally induced gelling systems

numerous polymers show abrupt changes in solubility as a function of environmental temperature. **Macro Med** 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. Sol-gel transitions occurs around 308ºC at polymer concentrations of 15 to 23% (w/w) in aqueous solution. Biocompatibility and toxicity do not seem to be problematic[2].

ORGANOGELS [6,7]

Organogels are semi-solid systems in which an organic liquid phase is immobilized by a three-dimensional network composed of self assembled, intertwined gelator fibers. Despite their majoritarily liquid composition, these systems demonstrate the appearance and rheological behavior of solids.

ADVANTAGES OF ORGANOGELS [6]

- Ease of preparation.
- They are organic in character and also resist microbial contamination.
- Cost reduction due to less number of ingredients.
- Longer shelf life.

- Thermodynamically stable.
- Both hydrophobic and hydrophilic drugs can be incorporated.
- Organic solvents could be of natural origin eg: sunflower oil, mustard oil, etc.

METHOD OF PREPARATION

- Fluid-Filled Fiber Mechanism
- Solid Fiber Mechanism
- Hydration Method

LIPID NANO DISPERSIONS [2, 8, 9]
There are broader applications of lipid systems in parenteral drug delivery. However, with specific new chemical entities, it has been limited due to the following reasons:

- only a small number of parenteral lipid excipients are approved.
- There is increasing number of drugs that are partially or not soluble in conventional oils and other lipid solvents.
- The ongoing requirement for site-specific targeting and controlled drug release.The advanced parenteral lipid nano dispersions include **nanoemulsions** and **nanosuspensions**

NANOEMULSION [8]
Nanoemulsions or miniemulsions are transparent or translucent **oil-in-water** (o/w) or **water-in-oil** droplets with droplet diameter in the range of 100 – 1000 A (10 – 100 nm).They are also known as submicron emulsions. Nanoemulsions are kinetically stable with great stability in suspension due to their small droplet size.

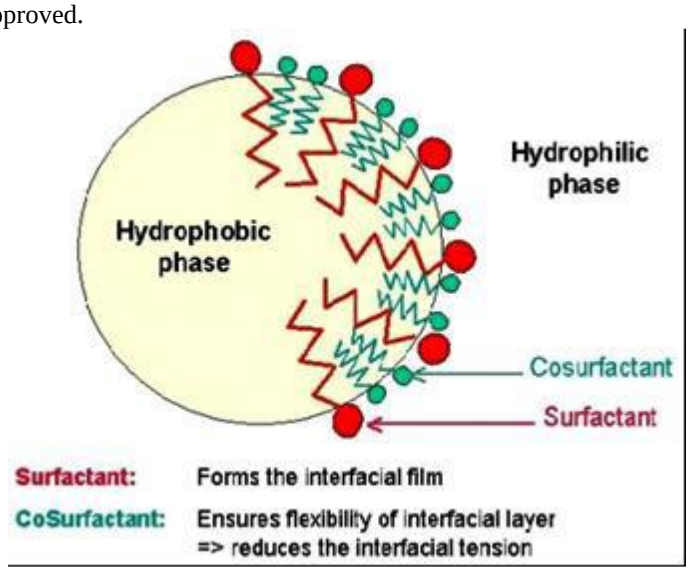

FIGURE 2: STRUCTURE OF DROPLET FORMED IN EMULSION

Methods of Preparation

- High-Pressure Homogenization
- Microfluidization

Advantages of nanoemulsions

- Higher surface area
- Free energy without the inherent creaming, flocculation, coalescence, and sedimentation.

Application of nanoemulsions

- Microemulsions can also be used as intravenous delivery systems for the fat soluble vitamins and lipids in parenteral nutrition.
- Microemulsions are generally not dilutable with aqueous fluids, such as certain bodily fluids and buffer solutions.

- Microemulsions are also sensitive to temperature and are not stable outside of room temperature conditions.

NANOSUSPENSIONS [8]

Nanosuspensions of drugs are submicron colloidal dispersions of drug particles which are stabilized by surfactants. In general, the particle size in nanosuspensions is always less than 1µm (usually lies between 200nm to 600nm).

Method of Preparation of nanosuspensions

1) Bottom up technology
2) Top down technology

Advantages of nanosuspensions

- Used to formulate drugs that are insoluble in both water and oil.
- In the case of high melting point compounds, solubilization in any solvent is difficult; nanosuspensions can be used to maintain these drugs in a preferred crystalline state of sufficiently small size for intravenous administration.

COLLOIDAL DISPERSIONS

NIOSOMES [10-12]

Niosomes are nonionic surfactant vesicles which are biodegradable, relatively nontoxic, more stable and inexpensive, an alternative to liposomes. These are obtained on hydration of synthetic nonionic surfactants of the alkyl or dialkyl polyglycerol ether class, with or without incorporation of cholesterol or other lipids. Based on the vesicle size, niosomes can be divided into three groups.

These are small unilamellar vesicles (SUV, size=0.025-0.05 µm), multilamellar vesicles (MLV, size=>0.05 µm), and large unilamellar vesicles (LUV, size=>0.10 µm).

Method of Preparation of Niosomes

1) Hand shaking method (Thin film hydration technique)
2) Micro fluidization
3) Reverse Phase Evaporation Technique (REV)
4) Ether injection method
5) Trans membrane pH gradient (inside acidic) Drug Uptake Process
6) The "Bubble" Method
7) Sonication
8) Formation of niosomes from proniosomes

Advantages of Niosomes

1) They are osmotically active and stable.
2) Handling and storage of surfactants requires no special conditions.
3) 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.
4) They exhibit flexibility in their structural characteristics (composition, fluidity, and size) and can be designed according to desired application.
5) They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
6) 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.
7) The surfactants are biodegradable, biocompatible, and non immunogenic.
8) 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.
9) 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.

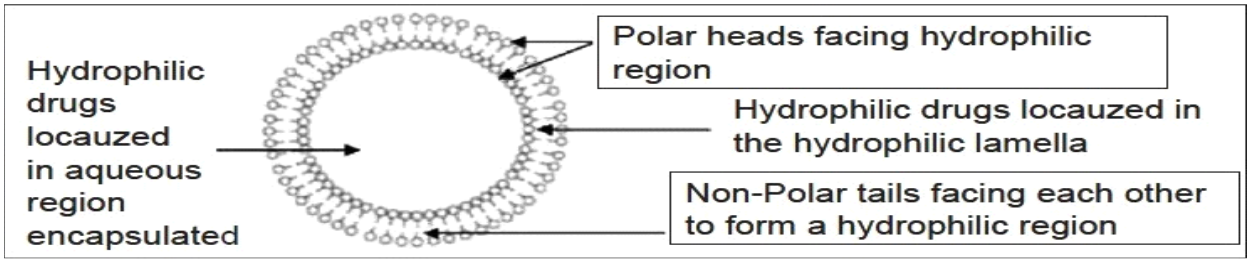

FIGURE 3: STRUCTURE OF NIOSOMES

Applications of Niosomes

- Anticancer niosomes .Eg. Niosomal encapsulation of methotrexate and doxorubicin increases drug delivery to the tumor and tumoricidal activity.
- Niosomes may also be used as depot systems for short acting peptide drugs on intramuscular administration.

3) Niosomes as vaccine adjuvant:-The formulation of antigens as a niosomes in water-in-oil emulsion increases the activity of antigens and hence enhances the immunological response.

Various drugs incorporated into niosomes by different methods are shown in given.

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

LIPOSOMES [13-15]

Liposomes are small artificial vesicles of spherical shape that can be created from cholesterol and natural nontoxic phospholipids. Due to their size and hydrophobic and hydrophilic character (besides biocompatibility), liposomes are promising systems for drug delivery. They are extensively used as a vehicle for an administration of nutrients and pharmaceutical drugs.

The liposome size can vary from very small (0.025 μm) to large (2.5 μm) vesicles. Moreover, liposomes may have one or bilayer membranes. On the basis of their size and number of bilayers, liposomes can also be classified into one of two categories: (1) multilamellar vesicles (MLV) and (2) unilamellar vesicles. Unilamellar vesicles can also be classified into two categories: (1) large unilamellar vesicles (LUV) and (2) small unilamellar vesicles (SUV).

Methods of preparation of Liposomes

- Sonication
- High pressure extrusion or homogenization
- Detergent dialysis
- Lipid – alcohol - water injection
- Reverse phase evaporation
- Dehydration – rehydration

Advantages of Liposomes

- Liposomes increased efficacy and therapeutic index of drug (actinomycin-D).
- Liposome increased stability via encapsulation.
- Liposomes are non-toxic, flexible, biocompatible, completely biodegradable, and non immunogenic for systemic and non-systemic administrations.
- Liposomes reduce the toxicity of the encapsulated agent (amphotericin B, Taxol).
- Liposomes help reduce the exposure of sensitive tissues to toxic drugs.
- Site avoidance effect.
- Flexibility to couple with site-specific ligands to achieve active targeting.

Applications of Liposomes

- Gene delivery.
- As drug delivery carriers.
- In tumour therapy.
- In multi drug resistance.

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

Conclusion

The above article gives best knowledge regarding the advancement in parenteral drug delivery system, especially in novel drug delivery system.Parentral drug delivery systems provides efficacious products with significant advantages over other existing delivery systems.

The above article also gives detailed information regarding the advancement in parenteral drug delivery system.It also gives detailed information about various novel parenteral drug delivery system like SLN, Liposomes, Niosomes etc. Parenteral drug delivery systems have grown to become important technology platforms which are used by pharmaceutical companies in the recent years due to its rapid production of newer products of better safety and enhanced efficacy.

References

1. Sengupta Sayoni, Review on parentral drug delivery system: a novel approach, JAPRB, 1(2) 2013, 60-63.
2. Patel Rakesh, Patel P Kaushal, Advances in novel parentral drug delivery systems, AJP, 4(3) 2010, 193-199.
3. Akanksha Garud, Deepti Singh, Navneet Garud, Solid Lipid Nanoparticles (SLN): Method, Characterization and Applications, REVIEW ARTICLE OPEN ACCESS,2012 licensee Saki Publishing Club.
4. Wissing SA, Kayser O, Muller RH, Solid lipid nanoparticle for parenteral drug delivery, Advanced Drug Delivery Review, 56, 2004, 1257-1272.
5. Bari Hitesh, A Prolonged Release parentral drug delivery system-An overview, ISSN 0976-044X, 3(1), July-August 2010, Article 001.
6. N.K. Jadhav , K.A. Patil, J.K. Patil, P.A. Patil, S.P. Pawar, A REVIEW ON ORGANOGELS: LIPID BASED CARRIER SYSTEMS, PHARMA SCIENCE MONITOR :AN INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES, ISSN: 0976-7908, Vol-3, Issue-4, Suppl-3, Dec 2012 .
7. Anda V, Leroux JC.Organogels and their use in drug delivery - A review. J Contro Release 2007; 125:179-92.
8. Agrawal Milan, Limbachiya Mahesh, Sapariya Amit, Patel Girish, A Review on parental controlled drug delivery system, IJPSR, 3(10), 2012, 3657-3699.
9. Liu J, Gong T, Fu H, Wang C, Wang X, Chen Q, *et al*. Solid lipid nanoparticles for pulmonary delivery of insulin. Int. J Pharm 2008; 356:333-44.
10. Karim Masud Kazi, Asim Sattwa Mandal, Nikhil Biswas, Arijit Guha, Sugata Chatterjee, Mamata Behera, and Ketousetuo Kuotsu, Niosome: A future of targeted drug delivery systems. J Adv Pharm Technol Res. 2010 Oct-Dec; 1(4): 374–380.
11. Patel RP. Niosomes: A Unique Drug Delivery System. Pharmainfo.net. 2007.
12. Tamizharasi S, Dubey A, Rathi V, Rathi JS: Development and characterization of Niosomal drug delivery of Gliclazide. J Young Pharm 2009; 1:205-09.
13. Abolfazl Akbarzadeh, Rogaie Rezaei-Sadabady, Soodabeh Davaran , Sang Woo Joo, Nosratollah Zarghami, Younes Hanifehpour, Mohammad Samiei , Mohammad Kouhi and Kazem Nejati-Koshki, Liposome: classification, preparation, and applications. Nanoscale Research Letters 2013, 8:102.
14. Date AA, Joshi MD, Patravale VB. Parasitic diseases: liposomes and polymeric nanoparticles versus lipid nanoparticles. Adv Drug Deliv Rev 2007; 59:505-21.
15. Kapoor Shweta: An overview on advanced parenteral drug delivery system in clinical disease management. Pharmainfo Net. 2007.

16. Karan Malik, Inderbir Singh, Manju Nagpal and Sandeep Arora, Atrigel: A potential parenteral controlled drug delivery system,Pelagia Research Library Der Pharmacia Sinica, 2010, 1 (1): 74-81

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