Advances in novel parentral drug delivery systems

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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. 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.

Key words: *Bioavailability, controlled release, drug targeting, parenteral drug delivery, sustained release, therapeutic index*

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]

These 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.

SOLID LIPID NANOPARTICLES

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.[3] 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.[4,5] A typical structure of SLN is presented in Figure 1. Various drug molecules have been incorporated in injectable SLN for treatment of different diseases are shown in Table 1.

Advantages[4,6,7]
- 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
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
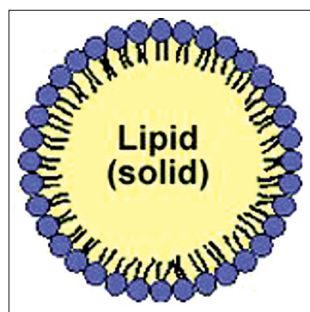
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Figure 1: Solid lipid nanoparticle

Table 1: Overview of various actives incorporated in injectables lipid nanoparticles[5]

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

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.[8,10]

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.[11]

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.[12]

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.[13,14]

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.[15,16]

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.[18]

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.[19] Transferrin-conjugated SLN of quinine dihydrochloride,[15] an antimalarial drug, were prepared to target it to the brain for the management of cerebral malaria.

Treatment of rheumatoid arthritis

Actarit SLN were prepared with the aim of passive targeting. [20] These SLN were shown to enhance the therapeutic efficacy with concomitant reduction in the various adverse effects such as nephrotoxicity and gastrointestinal disorders.[21]

Treatment of other diseases

Cholesteryl butyrate SLN[22] as a prodrug carrier was used for anti-inflammatory therapy of ulcerative colitis.

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.[23]

IN SITU FORMING PARENTERAL DRUG DELIVERY SYSTEMS

Biodegradable injectable *in situ* forming drug delivery systems represent an attractive alternative to microspheres and implants as parenteral depot systems. The controlled release of bioactive macromolecules via (semi-) solid *in situ* forming systems has a number of advantages, such as:
a) ease of administration,
b) less complicated fabrication,
c) less stressful manufacturing conditions for sensitive drug molecules.

From a manufacturing point of view, *in situ* forming depot systems offer the advantage that they are relatively simple to manufacture from polymers adapted for this approach. Compared with microspheres, which have to be washed and isolated after preparation, operating expenses for the production of *in situ* forming applications are marginal, thus lowering investment and manufacturing costs.[24]

Classification of injectable *in situ* forming implants (according to their mechanism of depot formation)

Thermoplastic pastes

Semi-solid polymers can be injected when melted and form a depot upon cooling to body temperature. The requirements for such In Situ Forming 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.[25]

In situ cross-linked polymer systems

The formation of a cross-linked polymer network is advantageous because of the possibility to control the diffusion of hydrophilic macromolecules. Such a system could ideally release peptides and proteins over a prolonged period of time. *In situ* cross-linking implants have been a challenging objective, as polymers containing double-bonds and free radical-initiation are necessary. Various *in situ* forming parenteral drug delivery systems are shown in Table 2.

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 Atrigele technology.[26]

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°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.[27]

ORGANOGELS

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.[28,29] Detailed classification of organogels is shown in Figure 2.[26]

Organogel formulation used in parenteral drug delivery[28,30]

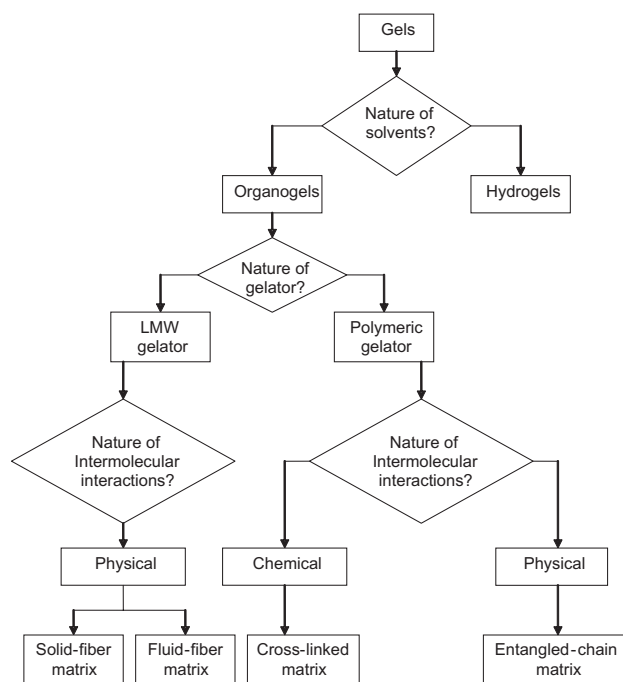Rivastigmine and leuprolide are sed in organogel formulation

Figure 2: Classification of organogels[21]

Table 2: *In situ* forming parenteral drug delivery systems[17]

	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

by subcutaneous route, in which N-stearoyl l-alanine methyl or ethyl ester is used as organogelators.

LIPID NANO DISPERSIONS

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:
a) Only a small number of parenteral lipid excipients are approved.
b) There is increasing number of drugs that are partially or not soluble in conventional oils and other lipid solvents.
c) The ongoing requirement for site-specific targeting and controlled drug release.

These advanced parenteral lipid nano dispersions include nanoemulsions and nanosuspensions.[31,32]

Characteristics of desired parenteral formulation of a marketed drug
a) Exhibits high drug solubilization/loading capacity.
b) Is at least as efficacious as the marketed formulation.
c) It has a shelf-life of at least 2 years.
d) Should be easily processed and manufactured using standard equipment.
e) Is amenable to fast track development status by addressing 'unmet medical needs.'

Nanoemulsions
Definition
Nanoemulsions or miniemulsions are transparent or translucent oil-in-water (o/w) or water-in-oil droplets with a mean droplet diameter in the range between 100 and 500 nm.[28] They are also known as submicron emulsions and unlike the thermodynamically stable microemulsions, nanoemulsions are kinetically stable with great stability in suspension due to their small droplet size.[33,34,35]

Advantages of nanoemulsions over macroemulsions or coarse emulsions
Higher surface area and free energy without the inherent creaming, flocculation, coalescence, and sedimentation associated with macroemulsions.[36,37]

Nanosuspensions
Definition
Nanosuspensions of drugs are submicron colloidal dispersions of drug particles which are stabilized by surfactants.[34]

Advantages of nanosuspensions
Used to formulate drugs that are insoluble in both water and oil, and are usually employed when the use of other lipid-based systems are limited.

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.[34,38]

Formulation considerations for nanoparticulate systems
Physical stability is an essential requirement for a nanoparticulate system. Poorly formulated particles can aggregate over time leading to higher number of large particles, thereby creating a potential safety concern. Nanoparticles may also sediment over time in storage. If not appropriately stabilized, the sediment may be difficult to resuspend. Finally, if the drug has finite solubility in the suspending buffer, the drug particles can dissolve and recrystallize on large particles, a phenomenon commonly known as Ostwald ripening. Particle size of the final formulation is particularly important for parenteral dosage forms, because that may also impact safety of the product. Processes such as spray drying, freezing, or lyophilization can be implemented to facilitate stabilization of the particles. Excipients and stabilizers have to be carefully chosen to stabilize the particles and prevent particle size change during processing and storage. Most of the excipients such as tonicity adjusters, chelating agents, preservatives are commonly used in parenteral solutions.[39,40] Some of the important parameters to be considered for formulating parenteral nanosuspensions are presented in Table 3.

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.[41] A typical structure of Niosome is presented in Figure 3. Various drugs incorporated into niosomes by different methods are shown in Table 4.
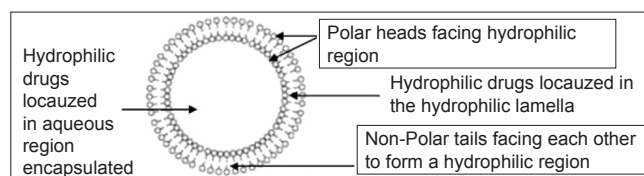

Figure 3: Niosome structure

Table 3: Choice of excipients for parenteral nanosuspensions[2]

Excipients	Functions	IV	SC/IM
Surfactant	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

Table 4: 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

Advantages of niosomes[42,43]

1. They entrap solute in a manner analogous to liposomes.
2. They are osmotically active and stable.
3. Handling and storage of surfactants requires no special conditions.
4. 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.
5. They exhibit flexibility in their structural characteristics (composition, fluidity, and size) and can be designed according to desired application.
6. They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
7. 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.
8. The surfactants are biodegradable, biocompatible, and nonimmunogenic.
9. 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.
10. 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

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.[44,45]

Niosomes at targeted site

Uptake by the liver and spleen make niosomes ideal for targeting diseases manifesting in these organs.[46] 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.[47]

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.[1,48]

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]

Applications

Liposomal anticancer 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.[49,50] It was observed that doxorubicin-loaded stealth liposomes circulate for prolonged periods, accumulate, and extravagate within tumors and also improve tumoricidal activity in mice.[51] In one study, it has been reported that in patients, liposomal doxorubicin accumulates within Kaposi's sarcoma lesions and produces a good therapeutic response.[52] 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.[53,54]

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.[55] Liposomes encapsulating antigens are subsequently encapsulated within alginate lysine microcapsules to control the antigen release and to improve the antibody response.[56] Liposomal vaccines may also be stored dried at refrigeration temperatures for up to 12 months and still retain their adjuvanticity.[52,57]

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.[52] Some of the actives incorporated in injectable liposomes are presented in Table 5.

FUTURE OPPORTUNITIES AND CHALLENGES

Aforementioned drug delivery systems have greater potential

Table 5: Various actives incorporated in injectable liposomes

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

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:

a) Advanced polymeric carriers for the delivery of therapeutic peptide/proteins (biopharmaceutics);
b) Nano-drug delivery systems that deliver large, but highly localized, quantities of drugs to specific areas to be released in controlled ways;
c) Materials for nanoparticles that are biocompatible and biodegradable;
d) Architectures/structures, such as biomimetic polymers, nanotubes;
e) Controllable release profiles, especially for sensitive drugs;
f) Technologies for self-assembly;
g) 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);

CONCLUSIONS

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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The manuscript system (www.journalonweb.com) allows the authors to check and verify the accuracy and style of references. The tool checks the references with PubMed as per a predefined style. Authors are encouraged to use this facility, before submitting articles to the journal.

- The style as well as bibliographic elements should be 100% accurate, to help get the references verified from the system. Even a single spelling error or addition of issue number/month of publication will lead to an error when verifying the reference.
- Example of a correct style
  Sheahan P, O'leary G, Lee G, Fitzgibbon J. Cystic cervical metastases: Incidence and diagnosis using fine needle aspiration biopsy. Otolaryngol Head Neck Surg 2002;127:294-8.
- Only the references from journals indexed in PubMed will be checked.
- Enter each reference in new line, without a serial number.
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- If the reference is correct for its bibliographic elements and punctuations, it will be shown as CORRECT and a link to the correct article in PubMed will be given.
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