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REVIEW ARTICLE

STERILE PARENTERAL PRODUCTS: A NARRATIVE APPROACH

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ABSTRACT

One of the first group's toaddress these patient safety issues was the NationalCoordinating Committee on Large Volume Parenteral (NCCLVP). Parenteral medications are products which are introduced in a manner which circumvents the body's most protective barriers, the skin and mucous membranes, and, therefore, must be "essentially" free of biological contamination. Most are injected or placed into the body tissues and do not pass thru the liver before entering the bloodstream. This can include injections, topical and inhalation routes. Generally in pharmacy, parenteral refers to injection and the topical and inhalation routes are separated into their own routes of administration. NCCLVP was established by the US Pharmacopeia Convention, Inc., and subsequently developedand recommended standards of practice for the preparation, labeling, and quality assurance of hospital pharmacyadmixture services. 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. This review highlightsformulation of parenteral product and advanced techniques involved in parenteral products.

Keywords: NCCLVP, LVP, Aseptic area, GMP etc.

INTRODUCTION

During the 1960s and 1970s, the practice of pharmacywas evolving and emphasis was placed on patient safetyfactors as a result of patient injuries and deaths that hadoccurred because of problems with medication deliveryand sterile compounding. One of the first group's toaddress these patient safety issues was the NationalCoordinating Committee on Large Volume Parenteral (NCCLVP). NCCLVP was established by the US Pharmacopeia Convention, Inc., and subsequently developedand recommended standards of practice for the preparation, labeling, and quality assurance of hospital pharmacyadmixture services.[1–7]

Parenteral medications are products which are introduced in a manner which circumvents the body's most protective barriers, the skin and mucous membranes, and, therefore, must be "essentially" free of biological contamination. Most are injected or placed into the body tissues and do not pass thru the liver before entering the bloodstream. This can include injections, topical and inhalation routes. Generally in pharmacy, parenteral refers to injection and the topical and inhalation routes are separated into their own routes of administration.

- Not all sterile dosage forms are administered by injection
- Topical ophthalmic medication
- Topical wound healing medications
- Irrigation solutions

Parenteral dosage forms differ from all other drug dosage forms, because they are injected directly into body tissue through the primaryprotective systems of the human body, the skin, and mucous membranes. They must be exceptionally pure and free from physical, chemical, and biological contaminants. These requirements place a heavy responsibility on the pharmaceutical industry to practice current good manufacturing practices (cGMPs) in the manufacture of parenteral dosage forms and on pharmacists and other health care professionals to practice good aseptic practices (GAPs) in dispensing parenteral dosage forms for administration to patients. Certain pharmaceutical agents, particularly peptides, proteins, and many chemotherapeutic agents, can only be given parenterally, because they are inactivated in the gastrointestinal tract when given by mouth.

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Parenterallyadministered drugs are relatively unstable and generally highly potent drugs that require strict control of administration to the patient. Due to the advent ofbiotechnology, parenteral products have grown in number and usage around the world. Parenteral preparations may require the use of excipients, for example;

- To make the preparation isotonic with respect to blood
- To adjust the pH, to increase solubility
- To prevent deterioration of the active substances or
- To provide adequate antimicrobial properties, but not to adversely affect the intendedmedicinal action of the preparation or, at the concentrations used, to cause toxicity or undue local irritation.

Parenteral preparations are sterile preparations intended for administration by injection, infusion or implantation into the human or animal body[8]. The term "Parenteral" is applied to preparation administered by injection through one or more layers of skin tissue. The word is derived from the Greek words para and enteron, meaning outside of intestine and is used for dosage forms administered by routes other than the oral route. Parenteral preparations may require the use of excipients, for example to make the preparation isotonic with blood, to adjust the pH, to increase solubility, to prevent deterioration of the active substances or to provide adequate antimicrobial properties but not to adversely affect the intended medicinal action of the preparation or, at the concentrations used, to cause toxicity or undue local irritation. Examples of applications for prolonged release parenteral delivery include: fertility treatment, hormone therapy, protein therapy, infection treatments (antibiotics and antifungals), cancer therapy, orthopedic surgery and postoperative pain treatment, chronic pain treatment, vaccination/ immunization, treatment of CNS disorders, and immunosupression. Modified release (MR) parenteral drug products are available in several dosage forms, including microspheres, liposomes, gels, suspensions, in situ forming implants, lipophilic solutions, solid lipid nanoparticles (SLN) and drug eluting stents.

Types of Sterile Products

Parenterals	Packaged in a manner for administration via hypodermic injection either in the form prepared or after addition of a suitable solvent or suspending agent
Ophthalmics	Intended for instillation in the eye
Irrigating solutions	Contact with blood vessels of wounds or abraded mucous membranes
Topicals for exposed tissue	Ointments, gels or creams for burns, would healing and other skin damage
IV Systems	Administration devices
Implants	A matrix for insertion into a defect site
Pulmonary dosage forms	Inhalation delivery systems

Parenteral therapy is used to:-

- Produce a localized effect.
- Administer drugs if the oral route cannot be used.
- Deliver drugs to the unconscious patient.
- Rapidly correct fluid and electrolyte imbalance.
- Ensure delivery of the drug to the target tissues.

Parenteral injections are either administered directly into blood for a fast and controlled effect or into tissues outside the blood vessels for a local or systemic effect.

Parenteral products are sterile formulations that are administered into the body by various routes including injection, infusion and implantation. Injections are subdivided into small and large volume parenteral fluids. Small volumes parenteral are sterile, progen-free injectable products. They are packaged in volumes up to 100 ml small volumes parenteral fluids are packed as:

- Single dose ampoules.
- Multiple- dose vials.
- Prefilled syringes.

Large volume parenteral products having a volume of 100 ml or greater intended to be administered by intravenous routes are called as transfusion fluids or intravenous infusions. They are formulated as single dose injections that are administered by intravenous infusions. They are sterile aqueous solutions or emulsions with water for injections as the main component.

Large volume parenteral products include:-

- Infusion fluids.
- Total parenteral nutrition solutions.
- Intravenous antibiotics.
- Patient-controlled analgesia.
- Dialysis fluids.
- Irrigation solutions.

Large volumes parenteral are variously formulated and packaged and have been used to:-

- Restore fluid and electrolyte imbalance in patients suffering from dehydration, shock or injury.
- Provide nutrition in circumstances were patients are malnourished e.g. total parenteral nutrition.
- Act as a vehicle for administration of medicines.
- Perform dialysis.
- Allow irrigation of body parts.

While water for injection is the main component of these products they also incorporate other ingredients including:-

- Carbohydrates, e.g. dextrose, Sucrose and dextran
- Amino acids
- Lipid emulsions which contain vegetable or semi-synthetic oil
- Electrolytes such as sodium chloride
- Polyols including glycerol, Sorbitol and mannitol

Characteristics of sterile dosage forms:-

- Sterility
- Freedom from particulate matter
- Freedom from pyrogens
- Stability
- Isotonicity

Route of Drug Administration:[9]

Parenteral	Injectable Preparations
Epidural	Injected into the dura matter (epidural space) of the spinal cord
Intravenous	Injected into the vein. This allows for immediate adsorption. Intravenous includes IV push, IV piggyback and IV infusion or drip.
Intramuscular	Injected into the muscle.
Subcutaneous	Injected into the fatty layer under the skin.
Intradermal	Injected into the top layer of the skin at a slight angle.
Intracardiac	Injected into the heart.
Intraocular	Injected within the eye.
Intrathecal	Injected into the space surrounding the spinal cord.
Intra-articular	Injected into the joint.

FORMULATION OF PARENTERAL PRODUCTS

Formulation Principal:-

Parenteral drug are formulated as solution, suspension, emulsion, liposomes, microspheres, powder &nano-system to be reconstituted as solution. These are commonly used in parenteral formulation focusing an solution & freeze dried products.

Vehicles:-

Water: The vehicle of greatest importance for parenteral product is water is suitable quality for compounding & rinsing product contact surfaces may be prepared either by distillation or by reverse osmosis, to meet united status pharmacopoeia specification of WFI

Example: Sterile water injection. Water For injection

Water miscible Vehicles: A number of solvent that are miscible with water have been used as a portion of a vehicle in the formulation of parenteral. These solvents are used primarily to solubilize certain drugs in aqueous vehicle & to reduce hydrolysis.

Example: Ethyl Alcohol liquid polyethylene glycol , propylene glycol.

Ethyl alcohol is used particularly in the preparation of solution of certain in Glycosides, Alkaloids, and then this prepare usually giving I.M.

Non- aqueous vehicles:

Fixed oils is a important group of non aqueous vehicle. The USP provides specification for such vehicle that the fixed oil must be vegetable origin so, that they will be the easily metabolized. Fixed oil is used particulars as a vehicle for certain hormones.

The oils most commonly used are pea nut oil, sesame, cotton seed oil, olive oil, glycerin. Etc.

Solutes:-

- Added Substances :-

The USP includes in this category all substances added a prento improve or safe-guard it's quality. An added substance may;

1) Antimicrobial Agents :-

The USP states that antimicrobial agents in bacteriostatic or fungistatic conn must be added to a prencontained in multiple close container. The USP provides the test for antimicrobial preservative effectiveness to determine that an antimicrobial substance because antimicrobial may have inherent toxicity for patient & USP prescribe the maximum value & connlimits they are used in parenteral products.

Example:-Benzalkoniamchloride :– 0.001%., Cresol :- 0.5%., Chlarobutanol :- 0.5%., Benzyl alcohol :- 1%.

2) Buffers :-

The use of buffering agents to maintain the PH of the parenteral product during it's storage is important for preventing the degradation, by ionization or by interaction of product with the material of the container. Buffer components are known to catalyze degradation of drugs, the acid salts most frequently as buffer.

Example: - Citrates, phosphates, acetates, sodium, potassium, calcium & magnesium.

3) Antioxidants :-

Antioxidants are added, to prevent the oxidative degradation of the parenteral product. Ascorbic acid &it's salts are good antioxidants.

Example:- Sodium bisalphite & other sulfurous acid salts.

- Sodium formaldehyde sulfaxylate,
- Thiourea, Acetone
- Sodium metabisalphite.
- EDTA.

4) Tonicity:-

They are used in parenteral& ophthalmic products to adjust the tonicity of the solution. The product areadministered to eye & spinal fluid must be isotonic; Injection in subcutaneous tissue and muscle should isotonic to minimize pain& tissue irritation.
Example:-Electrolytes, Monosaccharide, Disaccharides, Sodium chloride

5) Cryoprotectants & Lyoprotectants:-

These are additives that serve to protect biopharmaceuticals from adverse effect due to freezing & drying of the product during freeze dry processes.

Example:-

Sugar such as sucrose, Trehalase,

Amino acid such as – glycine, lysine.

Polymers such as – liquid polyethylene glycol, dextran.

Polyols such as mannitol, Sorbitol

FORMULATION

Suspensions[11-19]

Very difficult to formulate and produce Excellent stability: ships without caking/settling, Critical rheological properties: syringe ability: from container to syringe, Injectability: from syringe to vein.

Components

- Active ingredients
- Aqueous vehicle
- Surfactant for wetting
- Preservatives
- Buffers

Two basic methods:

» Sterile vehicle & powder aseptic combination;

» Sterile solutions are combined first and in situ crystallization.

Emulsions

Rarely used as parenteral products

- Excellent stability requirement;
- Particle size<1um, homodispersity;
- Very limited selection of stabilizers & emulsifiers;

1. w/o, allergy test, SB
2. o/w, sustained-release, depot, IM
3. o/w, nutrient emulsion, IV
4. o/w type, use triglycerides as central core, phospholipid as emulsifier, to provide essential fatty acids and calories

Dry Powders

Purpose: To overcome the intrinsic instability of the drug, be reconstituted before use.

Production Method

- Freeze-drying
- Aseptic crystallization and dry powder filling
- Spray-drying

Freeze-drying

Advantages

- Avoid damage to heat-sensitive drugs
- High specific surface are facilitating complete rehydration
- Improvement in filling accuracy

Disadvantages:

- Protective agents needed
- Stability changing, crystalline/amorphous
- High-cost and complicated

1. Freeze-drying: Under low pressure, under the triple point of water, water was removed by sublimation.
2. Sublimation : ice to vapor directly
3. Triple point of water : three phases coexisting in equilibrium

TYPES OF PARENTERAL CONTROLLED DRUG DELIVERY SYSTEMS[20-25]:

Microspheres

Microspheres designed for parenteral delivery, on the other hand, can be injected into the body using conventional needles and syringes. Thus, they have been the most widely accepted biodegradable polymer system for parenteral uses. However, the manufacturing processes for microspheres are often complex and difficult to control. As a result, there are often questions involving costs and batch-to-batch product uniformity [4, 5].

Liposomes

Liposome's on the other hand are versatile carriers for both hydrophilic and lipophilic drug molecules but suffer from several disadvantages like, high production cost, leakage of drug, short half life and low solubility. [6]

Injectable gels

Biodegradable injectable in situ gel forming drug delivery systems represent an attractive alternative to microspheres and implants as parenteral depot systems. It consists of biodegradable polymers dissolved in a biocompatible carrier. When the liquid polymer system is placed in the body using standard needles and syringes, it solidifies upon contact with aqueous body fluids to form solid implant. If a drug is incorporated into the polymer solution, it becomes entrapped within polymer matrix as it solidifies. Drug release occurs over time as polymer biodegrades. Biodegradable polymers used in these systems are Polyhydroxyacids, polyanhydrides, polyorthoesters, polyesteramides and others. Their importance will grow as numerous proteins will lose their patent protection in the near future[29-30].

Surgical implants

Surgical implants can be made from biodegradable polymers using well-controlled manufacturing processes, such as extrusion, injection moulding, and compression moulding. These devices normally have very reproducible release profiles. However, because of their size, they require surgical implantation which often limits the product's market potential due to patient and physician acceptance issues.

SUMMARY OF PARENTERAL

Route of Injection	Volume	Injection Site	Dosage Forms	Examples
Intravenous	1-1000 mL	vein	Solutions, cosolvents, liposomes, emulsions, nanoparticles Admixtures with Lactated Ringers, 5% Dextrose or Normal Saline	
Intramuscular	0.5-2 mL	thigh, arm, buttocks	Solutions, emulsions, oils, suspensions	
Subcutaneous	0.1-2 mL	Under the skin	Solutions (needle-less injectors) or powders (powderject)	Vaccines, scopolamine, epinephrine, insulin
Intraarticular	2-20 mL	Joints	Solutions	Steroids, NSAIDs, antibiotics
Intrathecal	1-4 mL	Spine	Solutions	local anasthetics, analgesics
Intraarterial	1-20 mL	Artery	Solutions and emulsions	Antineoplastics, antibiotics
Intracardial	0.2-1 mL	Heart	Solutions	Ca channel blockers and cardiotonics
Intrapleural	2-30 mL	Lung or pleural cavity	Solutions	Local anasthetic, chemotherapeutic agents
Intravitreal	0.01-0.1 mL	Eye (posterior chamber)	Solutions, suspensions	VEGF inhibitors
Intradermal	0.01-0.05 mL	Under the skin	Solutions	Diagnostics

ADVANCED PARENTERAL DRUG DELIVERY SYSTEM[30-33]

1) 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. The resulting closed sphere may encapsulate aqueous soluble drugs within the central aqueous compartment or lipid soluble drugs within the bilayer membrane. Alternatively, lipid soluble drugs may be complexed with cyclodextrins and subsequently encapsulated within the liposome aqueous compartment. The encapsulation of drugs with liposomes alters drug pharmacokinetics and this may be exploited to achieve targeted therapies. Alteration of the liposome surface is necessary in order to optimize liposomal drug targeting and to achieve prolonged circulation times liposome size between 70-200nm is necessary. Liposomes are the most widely studied modern drug delivery system because of its amazing application for the management of following diseases:

i) 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. It was observed that doxorubicin loaded stealth liposomes circulate for prolonged periods, accumulate and extravagate within tumours & also improve tumoricidal activity. In one study it has been reported that in patients, liposomal doxorubicin accumulates within Kaposi‘s sarcoma lesions and produces a good therapeutic response. 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.

ii) Liposomes as vaccine adjuvants -

Liposomal vaccines can be made by associating microbes, soluble antigens, cytokines or deoxyribonucleic acid (DNA) with liposomes, the latter stimulating an immune response on expression of the antigenic protein. Liposomes encapsulating antigens, which are subsequently, encapsulated within alginate lysine microcapsules to control the antigen release and to improve the antibody response. Liposomal vaccines may also be stored dried at refrigeration temperatures for up to 12 months and still retain their adjuvanticity.

iii) Liposomal anti-infective agents -

Liposomal amphotericin B (Ambisome), 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.

2) Niosomes:

Niosomes are unilamellar or multilamellar vesicles, where in an aqueous solution is enclosed in highly ordered bilayer made up of nonionic surfactants with or without cholesterol (chol) and dicetyl phosphate and exhibit a behavior similar to liposomes in-vivo .They can be used in the treatment of cancer and also used as vaccine adjuvant. Some of its applications are:

i) Anticancer niosomes -

Anticancer niosomes, if suitably designed will be expected to accumulate within tumours. For example niosomal encapsulation of methotrexate and doxorubicin increases drug delivery to the tumour and tumoricidal activity. doxorubicinNiosomes having size 200nm with a polyoxyethylene (molecular weight 1,000) surface are rapidly taken up by the liver and accumulate to a lesser extent in tumour, this technology may prove advantageous for the treatment of hepatic neoplasms. It was also observed that the activity of other anticancer drugs, such as vincristine, bleomycin, plumbagin and a plant derived anticancer agent are improved on niosomal encapsulation.

ii) Niosomes at targeted site-

Uptake by the liver and spleen make niosomes ideal for targeting diseases manifesting in these organs. One such condition is leishmaniasis and a number of other studies has 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.

iii) Niosomes as vaccine adjuvant–

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 enhanced the immunological response.

3) Nanoparticles and Microparticles:

Nanoparticles and microparticles are usually prepared by the controlled precipitation of polymers solubilised in one of the phases of an emulsion. Precipitation of the polymer out of the solvent takes place on solvent evaporation, leaving particles of the polymer suspended in the residual solvent. For particulate dispersions, the required particle size of nanoparticles lies between the range of 30-500nm while for microparticles in excess of 0.5micron. Their applications in management of diseases are:

i) Tumor targeting Nanoparticles and microparticles-

The accumulation of non-stealth doxorubicin nanoparticles within the Kupffer cells of the liver may be used to target hepatic neoplasms indirectly; this is achieved by providing a depot of drug for killing nearby neoplastic tissue. Microparticlesmay also be injected directly into tumours. It was observed that the direct injection of microparticles into solid tumours increases

the tumoricidal activity of the drugs 5- fluorouracil and doxorubicin.

ii) Vaccine adjuvant-

Nanoparticles have also been used as vaccine adjuvants. It was reported that antigens, which adsorbed onto the surface or entrapped in the matrix of polymethylmethacrylatenanoparticles induces an enhanced immunological response. For example polymethylmethacrylate Nanoparticles containing the influenza antigen may protect people against disease to a greater extent than the antigen alone.

iii) Other applications-

Restenosis, defined as the re-obstruction of an artery following procedures such as angioplasty or artherectomy may be treated by the local application of dexamethasone-loaded polylactic acid co-glycolic acid nanoparticles. Cyclosporin A, an immunosuppressant drug used to prevent graft rejection after transplantation by the inhibition of T-lymphocytes, may be targeted to regional lymph nodes by the intramuscular administration of cyclosporin A polylactic acid nanoparticles. In short it can be said that, by virtue of their small size solid nanoparticles provide opportunities for targeted parenteral therapies and may also be used as immunoadjuvants.

4) Prodrugs -

A prodrug is a pharmacological substance, which is administered in an inactive form. Once administered, it is metabolized in the body in vivo into the active compound. The use of prodrugs in cancer chemotherapy as a means of targeting relatively toxic compounds to specific areas of pathology is enjoying renewed activity. Two of the technologies being evaluated at present are antibody directed enzyme prodrug therapy (ADEPT) and the use of polymeric prodrug.

i) ADEPT

an antibody-enzyme conjugate is administered intravenously, localizes in tumour tissue and subsequently activates an administered prodrug predominantly within such tumours. Prodrug activating enzyme is carboxypeptidase G2.

ii) Polymeric prodrugs -

This involves the use of an active substance and possibly a targeting moiety, both linked viam spacers to a water-soluble polymeric backbone. From this basic blueprint a number of polymer drug conjugates used for cancer chemotherapy and have been synthesized with cleavable drug polymer linkers. These include soluble polymeric prodrugs of daunorubicin, doxorubicin, cisplatin and 5-fluorouracil. Passive tumour targeting with polymer drug conjugates improves the tumoricidal activity of anticancer agents. Distribution to potential sites of toxicity, such as the distribution of doxorubicin to heart tissue, is also decreased with polymer drug conjugates. In short, polymer drug conjugates have progressed from an elegant scientific concept to the clinic and may result in a new form of therapeutics for routine use.

FUTURE SCOPE

Many pharmaceutical manufacturers coming forward to formulate parenteral dosage form due to its beneficial characteristics over other conventional dosage forms.The dry-filling process also is much more cost effective because it requires less infra-structure as well as a reduced amount of energy and a shorter amount of time to produce a batch.

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