Review on Parenteral Drug Delivery System

Shubham Udaysinh Mohite[1], Bhosale Nilesh R.[2], Surnar Prashant B.[3], Basare Ankush N.[4]
[1, 2, 3, 4] PDEA'S Seth Govind Raghunath sable, college of Pharmacy, saswad, pune. Savitribai phule pune university

Abstract- *For instant relief parenteral route is best. Parenteral preparations are sterile preparations because drug dose directly contact with systemic circulation. It is prepared in aseptic condition. Parenteral drug delivery system consist of four types of sub routes like Intramuscular, Subcutaneous, Intravenous, Intradermal. In this article, we study Conventional parenteral formulations & Novel parenteral formulations.*

I. INTRODUCTION

The parenteral word come from the "para" & "enteron" means to avoid the intestine.[1]Parenteral are pharmaceutical preparations intended taken through skin. [2]Parenteral drug delivery include subcutaneous, intramuscular, intravenous, intra-arterial& intradermal. [3] Good advantage for patients who do not like drug administration by mouth and want rapid onset of action. [4] Hospitalized patients are completely depend on parenteral products like fluids, nutrients and electrolytes. Now a days novel parenteral drug delivery system like nanoparticles, intramuscular depot preparations. Novel formulations give targeted, sustained and controlled effect with less dosing frequency of drugs. [2,4,5]Parenteral drug delivery system is more expensive the other dosage forms. It requires aseptic condition during formulation preparation. [6]

II. CONVENTIONAL PARENTERAL FORMULATIONS : [7,8]

Solutions :

It includes SVP (100 ml or less), LVP (greater than 100 ml)& irrigation solutions. [6,8] Infusion preparation include nutrition , basic electrolytes, fluid replacement. [2,6] Most Pharmaceutical drugs have narrow therapeutic index and have more stable aqueous pharmaceutical preparation are prepared as parenteral solutions. [9]

Parenteral solutions	Marketed formulations
Large volume parenteral	0.9% W/V sodium chloride injection, USP 5% sodium chloride injection 5% dextrose injection 10% dextrose injection
Irrigation solutions	0.9% sodium chloride irrigation.

Suspensions :

Suspension used for administering hydrophobic drugs. [5] Major problem occur in suspension formulation is stability and chances of drug non uniformity during administration. [10,11] Suspension provide sustained effect of the drug.[12]

Drug	Brand name
Penicillin G procaine	Bicillin
Medroxyprogesterone acetate	DepoMedrol

Emulsions :

Emulsion is a two phase system in which both phases are immiscible liquids. One phase dispersed in other phase. [13] Emulsion are mostly used in administration TPN. [14] Emulsion is of two types water in oil and oil in water. [15] Emulsion formulation is thermodynamically unstable. [16] Parenteral emulsions are administered by intramuscular & subcutaneous routes. [17] Emulsion provide sustained drug release. [18]

III. NOVEL PARENTRAL FORMULATIONS

Parenteral drug delivery system used in emergency conditions. Suddenly hindrances occur with conventional parenteral formulations are solubility, stability & delivery of drug. [19] Now a day's lot of technological discoveries happen parenteral for giving drug targeting with sustained or controlled release of drug. [20] Novel parenteral drug delivery system consist of nanoparticles, nano-emulsion, nano-suspension, liposomes, niosomes,[21,22]

Micro and Nanoparticles

Surface area inversely proportional to the particle size. As surface area increases more area available for absorption and it have faster dissolution rate. [23]

Lipid Micro and Nanoparticles

pension are come in conventional lipid system for parenteral drug delivery for subcutaneous and intramuscular injection. [24] The administration of lipophilic drug is easy and drug release controlled by partition between oily phase

and aq. Environment at injection site. [25] Newly invented lipid micro & nanoparticle system is developed for parenteral sustained release of hydrophobic & hydrophilic drugs. [26] Solid lipid nanoparticles,Nonstructured lipid carrier, Lipid drug conjugate & polymeric nanoparticles are types of nanoparticles.[27] SLN have excellent physical stability, controlled drug release rate. It have demerits like they have not sufficient capacity of loading& drug expulsion during storage. [28,29] NLC is Nano particulate carrier of lipid which has capacity of increase loading efficiency as well as prevent expulsion of drug. It reduces chances of polymorphic transformation by conjunction of liquid lipid and solid lipid. [30,31] NLC is only used for topical delivery. [32] LDC is also known as insoluble drug-lipid conjugate, hydrophilic drugs but only those which are not so potent are used. Lipid drug conjugate is prepared by salt formation. [33] Methods used for formulation of solid lipid nanoparticles aremicro emulsion technique [34], solvent injection method [35,36], high pressure homogenization [37],solvent emulsification technique [38].

Nanoemulsions

Nanoemulsion are transparent water in oil or oil in water. Globule size is in between 100 to 500nm. Nanoemulsions are also known as sub micron emulsions. [39] Nanoemulsions are thermodynamically stabilized by adding emulsifying agents in two immiscible phases to form a single phase. If the size of droplet in dispersed phase decreases to nano form, the system becomes clear, which is considered as single phase system. [40] Methods of preparing nanoemulsion are based on energy involved in preparation. Methods of preparation of nanoemulsion by high energy are microfludization, high pressure homogenization, ultrasonification similarly methods of preparation of nanoemulsion by low energy are solvent diffusion method, phase inversion temperature. [41] The components of nanoemulsion are oils, emulsifiers, antioxidant, preservatives, tonicity modifiers, Ph adjustment agents. [42]

DRUG	BRAND	INDICATION
Dexamethasone	Limethason	steroid
Vitamin A,D,E & K	Vitalipid	Parenteral nutrition

Nanosuspensions

Nanosuspension is defined as colloidal dispersion of Solid drug in aq. Phase which is stabilized by surfactants. [43] Nanoemulsions can be taken by topical, oral, pulmonary & parenteral administration. Particle size required for preparation of nanosuspension is below 1 micron with average size is 200 to 600 nm [44] Nanosuspension increases dissolution velocity as well as solubility of drug hence nano suspensions has high bioavailability for hydrophobic drugs. [45]

Liposomes

Liposomes are vesicles which contains concentric phospholipid bilayers. Hydrophilic drugs present in inner core while lipid soluble drugs &amphiphilic drugs insert in phospholipid bilayer. [46] Liposomes deliver into veins. They are taken in liver and spleen. Liposomes can be administered by other parenteral routes like topical application & inhalation. [47,48]. Liposomes are classified into multilamellar large vesicles, large unilamellar vesicles, small unilamellar vesicles and giant liposomes.[49] Liposomes are amphotericin nature means entrap hydrophilic as well as hydrophobic drugs.[50] Liposomes are used in dermatology , vaccine adjuvant, immunity related disorders, ophthalmic disorders, in tumor therapy. [51] The adverse effects occur if intravenous administration used because when drug enters into blood stream he is available to every organ which require drug or not. [52]

Liposome type	Method of preparation	reference
multilamellar large vesicles	Hydration method Solvent spherule method	[53] [54]
small unilamellar vesicles	Sonication method French pressure method	[53] [53]
large unilamellar vesicles	Reverse phase evaporation method Modified reverse phase evaporation method Freeze thaw method Microfludization method Extrusion through polycarbonate filters through nitrogen	[55] [56] [57] [58] [59]
Giant liposomes	Detergent analysis method	[53]

In situ depot systems

These is an excellent substitute to implants. This system is also known as biodegradable injectable. [60,61] Biodegradable carrier is dispersed in a solvent and drug is dispersed in a liquid phase is known as in situ depot system. [62,63] These are taken by intramuscular or subcutaneous route. Solid depot formed at the site of injection. [64] Benefits ofsystem include reduced dosing frequency, enhancement of patient compliance. [65] In situ depot system are classified into thermoplastic pastes, in situ polymer precipitation,

thermally induced gelation, in situ cross linked polymer systems, in situ solidifying organogels on the basis of mechanism of depot formation [66,67]

	Thermoplastic paste	Thermogelling system	Polymer precipitation
Injection	Semisolid paste	Aqueous solution	Organic solution
Depot formation	Solidification	Sol to gel transition	Phase separation
Polymer	POE	ABA & BAB	PLGA
Drug burst	Low	Medium	High
Drug loading	Dry powder	Aqueous solution	Organic solution
Injection pain	Low	Low	High
Release	Surface erosion	Pore diffusion	Pore diffusion [68]

Niosomes

Niosomes come in vesicular system. Niosomes are made up of non ionic surfactant with or without addition of cholesterol or other lipids.[69] Examples of non ionic surfactants used in preparation of niosomes are polysorbates(tween) & sorbitan esters(spans). [70.71,72] Niosomes are active and stable. [73] Niosomes are administered by parenteral and topical routes. The surfactants used are non immunogenic, biodegradable & biocompatible. Niosomes are prepared by film hydration method, reverse phase evaporation, ether injection method, sonication & bubble method. [74]

Polymeric particulates

This are prepared from biodegradable polymers. In market most of the parenteral sustained release products are polymeric microsphere preparations which are taken through intramuscular or subcutaneous route. [75] Biodegradable polymers used in polymeric particulates. The preparation of Polymeric particulates is difficult. [76]

Non-ionic surfactants used in preparation of niosomes

Class	Composition	Examples	Ref.
Sorbitan esters	Ester of sorbitol and its mono & di-anhydrides	Sorbitan monostearate	[77]
Polysorbates	Polyoxyethylene derivatives of sorbitan esters	Tween20, Tween 40	[78]

Some niosomes with their application & method of preparation

Drug	Application	Method of preparation	Reference
DNA vaccines	Hepatitis B	Reverse phase evaporation	[79]
Minoxidil	Alopecia	Dehydration – rehydration	[80]
5-Fluorouracil	Skin cancer	Film hydration	[82]
Piroxicam	Anti-inflammatory	Film hydration	[83]
Camptothecin	Antitumor	Sonication	[84]
Tretinoin	Acne, Psoriasis	Film hydration	[81]
Finasteride	Androgenetic alopecia	Film hydration	[85]

Examples of parenteral sustained release products [86]

Delivery system	Product	Application	Trade name	Company
Polymeric micro-particulate system	Risperidone	Schizophrenia	Risperdal consta	Johnson & Johnson
Lipid system	Morphine sulfate	Post operation pain management	DepoDur	SkyePharma
In situ depot forming system	Leuprolide acetate	Advanced prostrate cancer	Eligard	QLT
Implantable system	Leuprolide acetate	Advanced prostrate cancer	Viadur	Alza Corp.

List of various patents on parenteral delivery

Patent No.	Contents	Reference
US20100098735 (2010)	Injectable depot composition and its process of preparation	[87]
US20100272639 (2010)	Polysaccharide nanoparticles	[88]
US20090156670 (2009)	Non aq. Liquid parenteral acenofenac formulation.	[89]
US20030904665 (2009)	Super fast acting insulin compositions	[90]

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