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EXCIPIENT USED IN PARENTRAL FORMULATION

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ABSTRACT

Parenterals are the sterilized preparation which is administered directly into the systemic circulation. This medication is specifically used to inject drug directly into the bloodstream or body tissue. Excipients are used in parenteral formulations to improve the stability (buffers, antioxidants, chelating agents, Cryoprotectant and lyoprotectant), to maintain isotonicity (tonicity agents), assure safety (antimicrobial preservatives), solubility (solubilizer), and control the duration of drug delivery (polymers). This article highlights the detail about the listed excipient and drug products in parenteral preparations. The reader will be able to understand and appreciate the purpose of adding excipients to parenteral drug products. It suppresses the body's natural defense mechanisms. Excipients are the major part of pharmaceutical preparations and are defined as any ingredient used in a dosage form except the active ingredient. Ideal properties of excipients are they must be considered safe, inert and multifunctional. Safety of excipients is the top most priority for pharmaceutical formulations. Therefore, proper studies should be conducted before the selecting an excipient. This review article provides a summarized detail of the excipients used in parenteral products.

KEYWORDS: Parenterals, Excipient, lyophilized, stabilizer, solubilizer, antioxidants, antimicrobial, preservative, buffering agent, mannitol, bulking agent, sterilization.

1. INTRODUCTION

In British pharmacopoeia (BP) *parenteral formulation* is a sterile preparation used for administration of drug product through injection, infusion, or implantations techniques into human or animal body. Some of the ideal properties that a parenteral product must have are they must be sterile, pyrogen-free; no coloring agent may be added solely for the purpose of

coloring the parenteral preparation. Preparation must be isotonic, in case of solution, free from particulate matter.

Pharmaceutical excipient (also known as additives) are defined as the compound added to the finished drug product to serve specific function. It is used for the purpose of bulking up the formulation that contains potent active ingredients. The other purposes of excipients are to maintain the stability of drug, provide efficacy of the product and improve acceptability of dosage form by the patient.

The excipient that are present in pharmaceutical product which are already marketed and accepted by the *Food and Drug Administration (FDA)* are approved as safe but it does not provide complete assurance when compared or formulated with other excipient & drug molecule as it may lead to unwanted or toxic effect. For this reason only the ultra high purity graded excipient are used for parenteral preparation. The ingredients that are used during the manufacturing process but are not present in the finished product are also studied under excipient category such as inert gases, water for lyophilized product.

Traditionally the excipient was considered as inactive or inert ingredient but the excipient may or may not be as inert as the term suggest.

2. EXCIPIENT USED IN PARENTERAL FORMULATION

- Buffering agent
- Preservatives (Antimicrobial agent, Antioxidant, Chelating agent)
- Co-solvent
- Suspending agent
- Emulsifying agent
- Tonicity agents
- Cryoprotectant
- Miscellaneous Excipient:
  - Aqueous vehicles
  - Non aqueous vehicles

I. BUFFERING AGENT

Buffer is an aqueous mixture of weak acid or weak base with its salt that has ability to maintain pH of the solution and bring it back to normal value.

Buffering agent work as the excipient by forming the bulk of lyophilize product. It stabilizes and prevents the degradation of a molecule during freeze-drying and storage. Most commonly used buffering agent is sucrose and trehalose among disaccharides. Among sucrose and trehalose, trehalose is more preferable buffering agent (lyoprotectant) as because it has a less hygroscopicity and very low chemical reactivity.

- ***Mannitol***: It is the most widely used excipient. Mannitol is having a very high melting temperature of about -1.4°C. It is an amorphous bulking agent highly preferred over crystallization because crystallization may show adverse affect in the physical stability of the product.
- ***Lactose:*** It is a one of the excellent bulking agent but it is a reducing sugar. The critical temperature of lactose is approx -32°C.
- ***Sucrose:*** It's temperature is nearly similar to that of lactose i.e. -31°C as of lactose. If we compare sucrose with lactose, sucrose is having higher density then lactose which result in collapse during drying.
- ***Polyethylene glycol (PEG):*** It increases viscosity of water. PEG is having a critical temperature of about -22°C. It is also used as a co-solvent and viscosity modifier in parenteral preparation.

Example of some buffering agent

Glycine HCL (pH=3.0-5.1), Citrate (pH=3.0-5.0), Succinate (pH=3.1-5.0), Acetate (pH=3.1-5.0), Tartrate (pH=3.0-5.0), Lactate (pH=3.1-4.4), Maleate (pH=3.1-5.0)

II. PRESERVATIVES

a. ***Antioxidants***: The *Antioxidants* are the substance that prevent or delay the oxidation of active substance and excipient. Acetylcysteine, Ascorbic acid, Sulfurous acid salts (metabisulfite, bisulfate), Monothioglyercol etc. are most widely used antioxidants.

b. ***Antimicrobial:*** The substance used to protect the growth of micro-organisms in the drug product is known as *Antimicrobial agents.* Meta-cresol, Phenol, Parabens (propyl, methyl, and butyl), Benzyl alcohol, Benzalkonium chloride, Thimerosal, Phenyl mercuric salts (nitrate, acetate, borate), Chlorobutanol etc. are used most commonly as antimicrobial agents.

c. ***Chelating agent:*** The substance whose molecules can form bond with a single metal ion is defined as a *Chelating agent*. Calcium disodium EDTA (EDTA = Ethylene di amine

tetra acetic acid), DTPA (DTPA = Diethylene triamine penta acetic acid) are the most commonly used Chelating agents.

Table 1: Some Common Preservatives Used In Pharmaceutical Preparations With Their Concentrations.

PRESERVATIVES	PARENTERALS (Concentration in %)
Methyl Paraben	0.01-0.5
Propyl Paraben	0.005-0.02
Benzyl Alcohol	0.5-10
Phenol	0.065-0.02
Meta cresol	0.1-0.25
Benzylkonium Chloride	0.01

[Brian K. Meyer et al. (2007) they worked on Antimicrobial Preservative Use in Parenteral Products: Past and Present]

III. CO-SOLVENT

These are the substances added to an immiscible mixture to make it miscible. It increases the solubility of poorly soluble compound. There are approximately 20 different approved co-solvent for parenteral product. Glycerin, Propylene, Sorbitol, Glycol, Polyethylene glycol, dimethyl acetamine, Ethanol, cremophor are the most commonly used co-solvent for parenteral preparation. The effectiveness of a co solvent is determined by the power of its solubilization.

Examples of some Solvents and Co-solvents used in parenteral formulation are: Benzyl benzoate, Castor oil, Cottonseed oil, Glycerin (glycerol), Peanut oil, Safflower oil, Seasme oil, Soybean oil.

[J.R. Howard et al. (1985) they worked on The use of co-solvents in parenteral formulation of low-solubility drugs]

IV. SUSPENDING AGENTS

Suspending agents are also known as the wetting agent. These are used in a Parenteral suspension to decrease the interfacial stress between the solid and the liquid to avoid lump formation.

Table 2: Some commonly used Suspending Agent.

S.NO.	SUSPENDING AGENTS	CONCENTRATION RANGE (%)
1.	Gelatin	2.0
2.	Pectin	0.2
3.	Polyethylene glycol 4000	1.7-3.0
4.	Sorbitol solution	50.0
5.	Methylcellulose	0.03-1.05
6.	Sodium carboxymethyl cellulose	0.05-0.75

V. EMULSIFYING AGENTS

Emulsifying agents are used in sterile emulsions. For this purpose lecithin is generally used. A mixture of lecithin is used as the primary emulsifier, and Span 20 is used as the secondary emulsifier. Parenteral emulsions are the Oil in Water emulsions used to feed those patients who are unable to eat normally.

Table 3: Some commonly used emulsifying agents, their HLB values, characteristics and functions.

CHEMICAL NAME	HLB	MISCIBLE WITH H2O	FUNCTION
Oleic acid	1.6	Immiscible	Antifoam
Glyceryl monostearate	3.8	Disperses with difficulty	W/O emulsifier
Sorbitan monostearate	4.7	Disperses with difficulty	W/O emulsifier
PEG-4 dilaurate	6	Forms milky dispersion	W/O emulsifier
PEG-4 monooleate	8	Forms milky dispersion	W/O emulsifier
Polysorbate	85 11	Form clear dispersion	O/W emulsifier

[Barkat Ali Khan et al. (2011) they worked on Basics of pharmaceutical emulsions]

VI. TONICITY AGENTS

Tonicity of the solution depends upon the amount and nature of the solutes present. It is determined either by molecular concentration of estimation of the freezing point of the point of the solution. Tonicity agents are used to adjust the isotonicity of the solution. Parentral preparations should be isotonic with blood stream or other body fluids to minimize inflammation and injection pain in areas with nerve endings, adding sodium chloride, borax etc. can be used to maintain isotonicity of a solution.

Isotonicity is the important for parenteral preparation because the possibility that the product may penetrate red blood cell and causes hemolysis is greatly reduced if the solution is isotonicity with blood i.e. the cells maintain their tone.

[M. Hareesh Reddy et al. (2016) they worked on Methods of adjusting tonicity and pH values of some drugs and substances]

VII. CRYPROTECTANTS AND LYOPROTECTANT

These are additives that protect biopharmaceuticals during freezing dry processes from adverse effects due to freezing and drying of the product. ***Examples of some Cryoprotectant and lyoprotectant used in parenteral formulation are*** Sugar such as sucrose, amino acid such as Glycine, lysine, etc.

VIII. MISCELLANEOUS AGENTS

a. ***VEHICLES*** are of two types i.e. aqueous vehicles and Non-aqueous vehicles

Aqueous vehicles: Widely used vehicle for parenteral preparations is water and is the most suitable since aqueous preparations are well metabolized by the liver and they are not dangerous to be used.

Different types of water used include.

1. Injectable water.
2. Sterile injectable water.
3. Bacteriostatic injectable water.

Non-aqueous vehicles: Non-Aqueous vehicles are not preferred for parenteral preparations, but it is sometimes necessary to eliminate water from certain preparations for one of the following reasons.

Non aqueous vehicles that are used in parenteral preparations are.

1. Water miscible vehicles.
2. Water immiscible vehicles.

b. ***INERT GASES***

Product stability and integrity of oxygen sensitive drugs can be maintained by the use inert gases such as argon and nitrogen. During the manufacturing and filling of parenteral, nitrogen rich atmosphere should be maintained. In filled vials, air in the head-space is displaced by either nitrogen or argon before sealing.

Example: Oxygen sensitive drugs which are filled in this manner are ergotmanine, tubocurarine etc.

c. *SURFACTANTS*

These are the substances which are added to the formulation to disperse a water insoluble drug to form a colloidal dispersion. In other words, they enhance the solubility of the drug. Surfactants are mainly used in parenteral suspensions and emulsions as wetting and solubilizing agents. Surfactants are used for wetting powdered material. It prevents crystal formation.

Example: • Propylene glycol • Providone • Polysorbate 80 • Lecithin

CONCLUSION

Since age's excipients plays a vital role in the development of parenteral products and many other pharmaceuticals. There are several types of excipients used on the behalf of their specific functionalities like, decreasing the interfacial stress and improving stability, suspending agents such as methyl and ethyl cellulose are used. For maintaining pH buffering agents such as lactose and mannitol are used. For improving the shelf life preservatives such as antioxidants or antimicrobial are used. For enhancing the solubility co-solvents such as glycerol, benzyl benzoate is used. For decreasing the surface and interfacial tension and preventing the coalescence between the molecules emulsifying agents or surfactants are used. There are some vehicles used in parenteral preparation according to the nature of the product which is being prepared, such as aqueous vehicles are used for water soluble substances. Non aqueous vehicles are used for water insoluble substances.

This was the complete conclusion of the excipients used in parenteral preparation.

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