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Parenteral Suspensions: Stability Enhancing Liquid Dosage Forms

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ABSTRACT

Oral route is the most common preferred route. In market number of drugs are available with solubility problem. It is difficult to prefer oral conventional dosage form other drugs on this less solubility which result in loss bioavailability. Parenteral suspensions are dosage forms containing drugs having low solubility. Drugs in suspension form increase the solubility, stability of the drugs. Drugs in sulfonation form have large surfaces areas. Parenteral suspensions provides onset of action for prolonged line on compared to solution.

Keywords: Stability, Parenteral suspensions, Syringebility, Dosage forms.

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INTRODUCTION:[1-3]

Parenteral preparations are defined as solutions, suspensions, emulsions for injection or infusion, powders for injection or infusion, gels for injection and implants. These are sterile preparations intended to be administrated directly into the systemic circulation in humans or animals.

Parenteral suspensions are dispersed, heterogeneous systems containing insoluble drug particles which, when are to be resuspended in either aqueous or vegetable oil vehicles before giving it to the patient.They are either given by intramuscularly or subcutaneously.

Ideal characteristics of parenteral suspensions: [2,5,6]

- Sterility during its storage and use.
- Injectability of suspensions are related to viscosity.
- The size of the parenteral suspensions should be small and uniform.
- Re-suspension of particles occurs very easily.
- The particles which are dispersed and are not settled rapidly after shaking.
- During shelf-life the cake formation does not occur.
- The stability and elegance should be maintained during its shelf-life.
- It is isotonic and non-irritating.
- The particle size should be less than 5 mm and the solid should contain 0.5%-5.0%.
- The suspensions that are manufactured should be tested for microbial contamination.

Advantages of parenteral suspensions:[3]

- The parenteral suspensions are insoluble in conventional solvents and are used therapeutically.
- The dosage forms increases the resistance of the suspensions to hydrolysis and oxidation which are present in the form of solids.
- The hepatic first pass effect is eliminated.
- The formulation of controlled release drug is possible in this dosage form.

Disadvantages of parenteral suspensions:[2-3]

- Formulation difficulty: The suspending agents, viscosity inducing agents, wetting agents, stabilizers, and preservatives are difficult to select for this type of parenteral suspensions.
- Manufacturing difficulty: The processes such as crystallization, particle size reduction, wetting, sterilization are facilitated which are required to maintain the aseptic conditions for manufacturing.
- Non-uniformity of the dose at the time of administration.
- The physical stability is very difficult to maintain in this dosage form.

Factors affecting release of drugs from parenteral suspension:[3,9]

- At the injection site the drug is soluble in the form of biological fluids.
- The drugs which are released can be affected by different steps involved in the process of suspensions.
- The challenge to formulate an injectable suspension is accepted by parenteral.
- These suspensions are usually diluted and are limited for viscosity because of injectability constraints and syringeability.
- These suspensions use high solid contents and increase the viscosity of the system.
- pka of the drug and dissolution rate of solid from its dosage forms.

Important properties pf the parenteral suspensions for the formulation development:

Suspension ingredients:

- It contains both active ingredients and excipients.
- The therapeutic effect of the active ingredient must not interfere.
- The sterilization and stability during the shelf-life should be maintained.
- The excipients used in parenteral preparations should be physically and chemically compatible with active ingredients.
- The preparations must be non-pyrogenic, non-toxic, non-haemolytic and non-irritating.
- The parenteral preparations must be effective at low concentration.

Typical excipients used in parenteral suspensions:

- Flocculating or Suspending Agents.
- Wetting agents.
- Solvent Systems.
- Preservatives.
- Anti-oxidants.
- Chelating Agents.
- Buffering Agents

➢ **Flocculating or suspending agents:[3]**

In these processes three techniques are used to formulate a suspension

(a) Controlled flocculation
(b) Structured Vehicle
(c) Combination of (a) and (b)

- **Surfactants:**

These flocculating agents are used to form flocs in a controlled manner that settles rapidly but re-disperses easily upon agitation. The hydrophilic colloids affects the repulsive forces also provide the mechanical barrier of the particles.

Examples: Lecithin, Polysorbate 20, Pluronic F-68,

- **Hydrophilic colloids:**

These are used as structured vehicles, these form pseudoplastic or plastic systems with some degree of thixotropy. It has high viscosity and poor syringeability.

Examples: Sodium Carboxy Methyl Cellulose, Acacia, Gelatine, Methyl Cellulose, Polyvinyl pyrrolidine.

- **Electrolytes:**

These reduce the repulsion between the particles and allow the flocs to form and the surface charge of the particles are influenced.

Examples: Potassium / sodium chloride, Potassium / sodium citrate, Potassium / sodium acetate.

➢ **Wetting agents:[3,10]**

The contact angle between the surface of the particles and the wetting liquid is reduced. Hydrophilic powders are suspended in aqueous system which are useful. The hydrophilic lipophilic balance value is in the range of 7-9 should only be selected for the process of wetting agents. The concentration of the surfactants should vary from 0.05%-0.5% based on the solid contents of the suspensions. The excessive amounts may cause caking or provide an undesirable taste or odour to the product.

Examples: Non-aqueous solvents (Glycerine, alcohol, and Propylene glycol). Non-ionic surfactants (Polysorbate 80,Polysorbate 20, Polysorbate 40).

➢ **Solvent system:[3,11]**

These are classified into aqueous or non-aqueous vehicles. The typical solvent systems depends on solubility, stability, and release the characteristics of the drug. Non-Aqueous vehicles include both water miscible and water immiscible vehicles. The nonaqueous agents are used as co-solvents for the process of water for injection. The water miscible co-solvents can lead to different side effects.

Examples: Intramuscular injection of propylene glycol – water, Ethyl alcohol – water and Polyethylene glycol are found to cause muscle damage and release of creatinine kinase from isolated rat skeletal muscle.

Organic co – solvents are less myotoxic than propylene glycol and ethanol.

Water miscible examples: Ethanol, Glycerine, Propylene glycol, N-(Beta-hydroxyethyl)-lactamide.

Water immiscible included fixed oils like Sesame oil, Peanut oil, Castor oil, Almond oil, Sunflower oil, Iodinated Poppy seed oil.

➢ **Tonicity agents:[3,12]**

Isotonicity of the parenteral preparations for subcutaneous or intramuscular administration is used to prevent pain, irritation, and tissue damage at the area of administration. Dextrose and various electrolytes are parenteral suspensions. The aqueous solutions of Tonicity Agents are used in parenteral suspensions.

Examples: Dextrose, Sodium chloride.

➢ **Preservatives:[3,13]**

Preservatives should be added to the formulations which are packed in single dose and does not have bactericidal or bacteriostatic property and which promotes the growth. The growth promoting is conducted for the determination of microbiological properties which are preservative free formulations.

The parenteral products which are used in multiple doses are used to protect the products from the accidental microbial contamination during clinical usage and which maintain the stability.

Examples: Benzyl alcohol (0.9% - 1.5%), Methyl Paraben (0.18% - 0.2%), Propyl Paraben (0.02%), Benzalkonium Chloride (0.01% - 0.02%), Thimerosal (0.001% - 0.01%)

The chemically reactive nature of preservatives, stability and compatibility of preservatives should be used in the final formulations. Parabens decreases in stability with increase in ph. concentration which are used in parenteral formulations.

- **Antioxidants or chelating agents:[3,14]**

These are added in the formulations to minimize its degradation which result their over oxidation potential or by terminating the propagation in the free radical oxidation mechanism. These are used in combination with a chelating agents or other anti- oxidants and found to act as synergists and increase the effectiveness of anti – oxidants that block oxidative reaction.

Examples: Water soluble - ascorbic acid-0.02 - 0.1%, sodium bisulphite -0.1 – 0.15%, sodium metabisulfite-0.1 – 0.15%, thiourea- 0.005%.

Auto-oxidation is defined as oxidative degradation by molecular oxygen. The manufacturing process should be avoided in the case of exposure of active ingredients to oxygen.

- **Buffering agents:**

The maintained pH. should be altered in the formulation the pH of the product occurs during the storage because of:

- The reactions take in the place in the product are degraded.
- The components of the product are interacted.
- To control the pH of the formulation buffers are commonly used in the parenteral formulations.

The temperature is high and it should facilitate the faster primary drug and it is non-volatile which determines the stability. Acetate buffer is not used due to its volatile nature and it is lost due to lyophilization. The pH decreased is of about 4 units.

Examples: Citric acid, Sodium citrate.

Manufacturing of parenteral preparations:[3]

Two basic methods are used in manufacturing of parenteral preparations:

1.The sterile powders and vehicles are aseptically combined. This method involves dispersing the sterile products aseptically , milled active ingredients and milling the resulting suspensions as required into the suitable containers. Example: Penicillin G.

2.The sterile products are combined by crystal formulation. These are solubilized in suitable solvent systems, which are sterile counter systems which are added to the active ingredients and are removed aseptically and the resulting suspension is milled. Examples: Testosterone, Insulin.

Official examples of parenteral suspensions:

(1) Sterile ampicillin suspension USP'95 dispense as powder which is to be reconstituted at time of administration.

(2) Sterile Aurothiglucose suspension USP'95 – vegetable oil suspension.

(3) Tetanus toxoid adsorbed USP'95, IP'96 – aq. Suspension.

(4) Betamethasone acetate suspension USP'96 aq. Suspension.

(5) Insulin Zinc suspension USP'95, IP'96 aq. Suspension.

(6) Procaine penicillin suspension IP'96.

CONCLUSION:

Suspension is a better choice of drug dosage form due to its fast onset of action and its bioavailability over the other dosage forms. As the other dosage forms facing the problem of first pass metabolism and other drug stabilities, in respect to above qualities suspension is a good choice of drug. Many pharmaceutical industries are volunteer to manufacture parenteral suspension dosage forms due to its worthwhile over other standard dosage form.

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