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Comprehension Review Article

A Comprehensive Review in Parenteral Formulations

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Parenteral Formulations are sterile, pyrogen-free, administered by injection through one or more layers of the skin.

Advantages

- Provide rapid clinical response in emergency cases such as epilepsy, asthma. Cardiac and hypertensive crisis (especially IV route).
- Offer alternative route to patients who are unable or unwilling to receive oral medications, such as unconscious or nauseous patients.
- Certain parenteral products can provide prolonged drug action, e.g., benzathine penicillin-G can provide a prolonged action of up to a month when given I.M.

Disadvantages

- Difficulty of removal of the drug from the body in case of intoxication.
- Local irritation as a result of needle insertion.
- High cost of production.
- Administration of drug through wrong route may prove fatal [1].

Routes of administration of parenteral products

- Intradermal route (I.D.).
- Subcutaneous route (S.C.).
- Intramuscular route (I.M.).
- Intravenous route (I.V.).

Intradermal route

The drug is injected into the superficial layer of the skin (between the epidermis and dermis) into the anterior surface of the forearm.

Uses

- For diagnostic tests, e.g., test for susceptibility to certain bacterial diseases such as tuberculosis and diphtheria.
- Administration of BCG vaccine (used for immunization against tuberculosis). Volume given: about 0.1 ml [2].

Subcutaneous route

The drug is injected into the subcutaneous tissues beneath the dermis, usually into the upper arm or thigh or the lower part of the abdomen. Volume: not more than 1 ml because of limited S.C. area. However, sometimes larger volumes can be given if hyaluronidase enzyme (available as injection) is co-formulated with the drug. The enzyme will break down hyaluronic acid which holds the S.C. cells together and the S.C surface area will be increased. Thus, more drug will spread allowing accommodation of more volume of injection.

Drug absorption from S.C. area is rapid compared the I.D. area because: (a) larger S.C. surface area (b) richer vascular supply of S.C. area.

Examples of drugs given by S.C. route

- All insulin preparations.
- Some vaccines such as rabies and cholera vaccines.

Intramuscular route

The drug is injected deeply into the skeletal muscle of the upper arm or the gluteal muscle of the buttocks.

Advantages over I.D. and S.C.

- Highly vascular and larger surface area, therefore 2 - 5 ml in upper arm and 5 ml in gluteal muscle.
- Suitable for aqueous, oily solutions and aqueous suspension.

Examples

- Oily solutions of drugs: Depo-testosterone (containing testosterone propionate dissolved in sesame oil).
- Aqueous suspensions drugs such as Depo-medrol (containing methylprednisolone suspended in water).

The two preparations are slowly-dissolving formulations if injected I.M. and thus provide prolonged action.

- Vaccines: cholera, diphtheria, influenza, are given I.M.

Intravenous route

Used for large or small volumes of drug solution. Vein mostly used: the median basilic vein of the inner forearm [3].

Advantages

Rapid rug action, therefore used in emergency cases.

Disadvantages

Drug cannot be recovered in cases of poisoning.

Form of drug given

- Most drugs given I.V. are aqueous solutions.
- Emulsions of very fine droplets, e.g.; phytonadione (vit-K used as anticoagulant to stop hemorrhage).

Volume: up to 1000 ml by slow I.V., in replacement therapy: Ringers solution containing NaCl, KCl and $CaCl_2$), Dextrose-NaCl I.V. solution.

General procedure for the preparation of parenteral products

Parenteral products must be free from particulate matter and microorganisms; therefore, room of preparation must be free from dust and microorganisms. This is achieved as follows:

1. Fitting laminar air flow system to suck dust and microorganisms; uv radiation will kill microorganisms.
2. Room walls and benches cleaned by antimicrobial agents.
3. Workers should wear sterilized clothes and disinfected gloves and masks to protect their mouths and noses and wear plastic glasses to protect their eyes from uv lamps.

Steps involved in the preparation of parenteral products [4].

1. Cleaning and sterilizing all equipment and containers. Cleaning: using automatic washing and rinsing machines. Sterilization: dry or moist heat.
2. Purity of ingredients: drugs, vehicles, additives. For water as solvent use water for injection.
3. Compounding of the preparation: add small quantity first then larger to form solution.
4. **Filtration:** Use millipore membrane composed of cellulose acetate filters, for thermolabile solutions; removes microorganisms.
5. Distribution of preparation into final containers: bottles, ampoules, plastic bags. Glass preferred since its high temperature during sterilization. Amber coloured glass used for photolabile drugs but this interferes with visual inspection for foreign material.
6. Closing and sealing of containers.
7. **Sterilization:** Of filled and closed containers.
8. Visual inspection for clarity.
9. **Labeling:** Name and quantity of ingredients, storage conditions, manufacturing and expiry dates.

Sterilization of parenteral products

Sterilization is the process of killing or removing of all living microorganisms from a certain preparation or material. Most essential methods are:

1. Dry heat.
2. Moist heat or steam.
3. Filtration.

Quality control (or evaluation) of parenteral preparations [5].

The following tests are done to ensure that the parenteral products meet the required standards of safety and effectiveness:

1. Sterility test
2. Clarity test
3. Pyrogen test
4. Leaker test

Sterility test

All Parenteral products should be sterile. Sterility test is performed on randomly selected samples.

Principle of the test: A quantity of the material is transferred to a suitable liquid culture medium contained in a tube. A number of culture media are used:

a. Thioglycolate liquid medium: used to support he growth of anaerobic organisms. It is incubated for 7 days at 35 - 37°C.

b. Soybean-casein liquid medium: to support the growth of aerobic organisms. It is incubated for 7 days at 35 - 37°C.

c. Sabaraud liquid medium to support the growth of fungi, incubated at 25 - 27°C.

Positive controls for 10 days

a. A thioglycolate liquid medium is cultured with the bacterium Clostridium sporgenese which is anaerobic, incubated for 7 days at 35 - 37oC.

b. Soybean-casein liquid medium is cultured with aerobic Staph. Aureus to confirm the fertility of the medium; incubated at 35 - 37oC for 7 days.

c. Sabaraud liquid medium is cultured with the fungus Candida albicans to confirm fertility of the medium; incubated at 25 - 27oC for 10 days.

Negative controls

a. The three-culture media containing no microorganisms and no sample are also incubated at the specified temperature and times as negative controls to confirm the sterility of the media. If the sample contains antimicrobial agent then it must be inactivated by dilution or by addition of a specific inactivator, e.g., phenyl mercuric nitrate is inactivated by thioglycollic acid.

Observations of the sterility test

1. The tested material is sterile if no growth or turbidity in a, b, c, g, while d, e, f, show growth. If growth observed in a, b, c, g, or no growth in d, e, f, the test should be repeated with fresh sample. If there is growth repeat test. If still there is growth, then preparation is unsterile and is rejected.

Pyrogen test

Pyrogens are metabolic products which are produced by all microorganisms from their cell wall. They consist of liposaccharide and they are water soluble, filterable and thermostable. They are not removed after sterilization by moist heat or filtration. In the human body they cause febrile reaction (fever, headache, backache). Major source of pyrogens is water which is used as a vehicle. Pyrogens can be removed by adding oxidizing agent (potassium permanganate + small quantity of barium) to oxidize pyrogens to non-volatile organic solids (filterable).

Pyrogen test

It is performed on all aqueous parenteral preparations. Rabbits are used for the test since they show same response to pyrogens as humans.

Principle of the test

Measuring the rise in temperature (fever) caused by pyrogens, using a thermometer placed in the rectum of the rabbit.

The sample (10 ml/kg) is injected into the ear vein of 8 rabbits. The temperature is recorded before injecting and the after injecting at 1, 2, and 3 hours. The rectal temperature should not exceed 0.6oC from normal recorded temperature.

Recently: *in vitro* pyrogen testing.

Principle the test solution is added to a lysate solution. If pyrogens are present a gel will be formed; if pyrogens are no present the solution remains clear. The method is more sensitive and rapid than the *in vivo* testing (in rabbits).

Clarity test [6].

Clarity is defined as the freedom of parenteral preparations from any foreign matter. The clarity of solutions is visually inspected under strong light.

Leaker test

This test is specific for ampoules to test that they are effectively sealed with no leak. Steps:

1. The ampoules are immersed in a tank containing dye solution (1% methylene blue)
2. The tank is closed and the air inside is evacuated to form negative pressure inside the tank.
3. The vacuum will create high pressure on the weak points on the ampoule seal and will also assist the passage of the dye into the leaking ampoule.
4. The ampoules are washed and any leaking one will contain the blue dye and should be rejected.

Added substances (or Additives) [7]

Additives are substances included in the formulation of parenteral products for one or more of the following reasons:

1. To maintain the solubility of the drug.
2. To maintain he stability of the drug.
3. To maintain the sterility of the product.
4. To maintain the isotonicity of the product.
5. To ease the administration of the product.

Additives used to maintain the solubility of the drug

To enhance the solubility of poorly water-soluble drugs, one of the following procedures can be adopted:

The addition of one or more water miscible solvents to the hydrophobic drug

Examples of the water miscible solvents:

a. Polyethylene glycol (PEG).

b. Propylene glycol (PG).

c. Glycerol and ethanol.

Complex formation

The addition of certain complexing agents to drugs to enhance water solubility.

Example

Sodium benzoate is used to solubilize caffeine by forming a highly water-soluble complex.

The addition of surface-active agents and suspending agents [8]

Example of surface-active agents

1. Tweens
2. Spans

Uses of surface-active agents

a. To enhance the solubility of certain oil soluble drugs, e.g., vitamins (A, D, E, and K).

b. To enhance the wettability and promote the dispersion of solids in the solvent of parenteral suspensions.

c. To prevent the formation of foams.

Examples of suspending agents

1. Sodium carboxy methyl cellulose.
2. Methyl cellulose.
3. Polyvinyl pyrrolidone.
    - They are used to reduce the sedimentation rate of the suspended particles in parenteral suspensions.
    - They should not be used in high concentration to avoid the increase in the viscosity of the injected suspension.

Additives used to maintain the stability of the drug [9]

It is important to protect such drugs from:

1. Hydrolysis
2. Oxidation

Drug can be protected from hydrolysis by:

a. Preparation of the drugs in the form of dry solid powder to be reconstituted with a suitable vehicle at the time of administration.

b. Preparation of the drug as an insoluble suspension.

c. Partial or total replacement of water with other Nonaqueous solvents (PG, PEG …).

d. Adjusting the pH of the formulation to the pH of maximum stability by using buffers.

Drugs can be protected against oxidation by one or more of the following procedures:

I. The addition of antioxidants:
    a. Water-soluble antioxidants.
    b. Oil-soluble antioxidants.

II. The displacement of oxygen with other inert gases (N, CO_2), used for single dose injections.

III. Addition of chelating agents (EDTA, citric acid …) to complex with divalent or trivalent actions ($Fe2^+$. $Fe3^+$, $Cu2^+$, $Cu3^+$ or $Mg2^+$), which are present as traces in water, to inhibit oxidation.

Additives used to maintain the sterility of the product [10]

Antimicrobial agents or preservatives are added to multiple dose containers to prevent the growth of microorganisms.

Properties of antimicrobial agents used:

a. Compatible with other ingredients used.

b. Non-toxic. Non-irritant and inert.

c. Should not be absorbed by rubber or plastic closure.

d. Should be thermostable.

Examples of preservatives used

a. Quaternary ammonium compounds.

b. Phenyl mercuric nitrate.

c. Phenol, cresol and chlorobutanol.

d. Benzyl alcohol.

e. A combination of methyl parabens and propyl parabens.

Additives used to maintain the isotonicity of Parenteral products [11]

Parenteral solutions should be isotonic with blood plasma.

- Hypotonic solutions cause hemolysis of RBCs.
- Hypertonic solutions cause shrinkage of RBCs.

Additives used o ease the administration of parenteral products

Examples

1. Local anesthetics (procaine, xylocaine …) are used in I.M. injections (tetracycline, keflin injections) to reduce he pain.
2. Hydrocortisone and heparin are added to amphptericin-B I.M. injection in order to reduce inflammation and pain and to enhance blood flow so as o increase drug absorption.

Vehicles used in Parenteral preparations [12]

Aqueous vehicles

Water is the most commonly used vehicle for parenteral preparations and is the most suitable since aqueous preparations are well tolerated by the body and are the safest to be used.

Different types of water used include

- Water for injection.
- Sterile water for injection.
- Bacteriostatic water for injection.

Nonaqueous vehicles

- Water-miscible vehicles.
- Water-immiscible vehicles

Water for injection

It is obtained by de-ionizing and distilling water. It should contain no more than 1 mg/100 ml of total solids. It must be pyrogen-free but it is not required to be sterile.

Sterile water for injection

It is water for injection which has been sterilized and packaged in single dose containers having a volume not exceeding 1 litre. It is pyrogen-free and does not contain an antimicrobial agent. For example: an injectable solution may be prepared from dry powder of sterile Ampicillin sodium by adding sterile water for injection.

Bacteriostatic water for injection

It is sterile water for injection containing one or more suitable bacteriostatic agents. It is packaged in multiple dose containers to allow the repetitive withdrawal of water form container without exposure to bacterial contamination.

Volume not more 5 ml since bacteriostatic agents are toxic if used in large concentration.

Incompatibilities of bacteriostaic water for injection [13]

Examples

- When bacteriostatic water for injection containing benzyl, alcohol is used to suspend sterile chloramphenicol for I.M. injection, the suspension formed is found to be very viscous and very difficult to withdraw from container. However, chloramphenicol sodium succinate does not interact with benzyl alcohol and forms a clear solution.
- Certain acidic dugs, such as barbiturates and sulphonamides, are incompatible with parabens which are used as bacteriostatic agents.

Multiple dose units or injections

- They usually contain a number of doses (up to 10 doses) in the same container.
- The container is made of borosilicate glass and is known as vial. The vials are fitted or closed with rubber closure to allow the penetration of the needle without the destruction of he rubber closure.
- The closure should reseal after the withdrawal of the needle in order to protect the vial contents from contamination.
- The total volume of such multiple dose injection does not exceed 30 ml.

Examples

1. Vitamin B-complex injection.
2. Insulin injection.

Nonaqueous vehicles [14]

Aqueous vehicles are preferred for parenteral preparations, but it is sometimes necessary to eliminate water from certain preparations for one of the following reasons:

1. To enhance the solubility of certain poorly water-soluble drugs by replacing water with other nonaqueous vehicles.
2. To protect certain drugs from hydrolytic reactions.

Properties of Nonaqueous vehicles used in parenteral preparations

1. Nontoxic, non-irritant and inert.
2. Stable a compatible with other ingredients used.
3. Should have suitable viscosity to be easily withdrawn from the container and easily injected.

Nonaqueous vehicles used in parenteral preparations include [15];

I. Water miscible vehicles.

II. Water immiscible vehicles.

Water miscible vehicles [16]

These are used to:

a. Enhance drug stability.

b. Enhance drug solubility.

The most commonly used water miscible vehicles include

a. Polyethylene glycol (PEG).

b. Propylene glycol (PG)

c. Ethanol

Examples of some injections containing water miscible vehicles

1. Digoxin (cardiotonic), I.M. and I.V.
2. Diazepam (sedative, hypnotic), I.M., I.V.
3. Phenytoin sodium (antiepileptic), I.M., I.V.

Water immiscible vehicles

These include fixed vegetable oil such as sesame oil, peanut, and cotton seed oil.

- Because of it is the most stable, sesame oil is the vehicle most commonly used.
- Mineral oils such as paraffin oil are not used as vehicles since they are not absorbed by the body tissues.

The main uses of oils as vehicles are to

1. Solubilize hydrophobic or oily drugs.
2. Protect water sensitive drugs.
3. Obtain a prolonged or sustained release action.

These drugs

- Should be highly soluble in oil.
- Are slowly released from oily vehicles.
- Should never be administered I.V.
- Should be administered only I.M.

Some examples of drugs formulated in fixed oil [17,18]

1. Dimercaprol injection: dissolved in peanut oil (used as antidote for heavy metal poisoning: arsenic, mercury and gold.
2. Testosterone propionate: dissolved in sesame oil or cotton seed oil (used to treat testosterone deficiency).
3. Fluphenazine decanoate: dissolved in sesame oil, (used to control schizophrenia, tranquilizer).
    - All the above injections are given I.M.

Parenteral Suspensions [19-21]

These are Parenteral products composed o a drug suspended in a suitable vehicle.

Parenteral suspensions are applied in two forms

1. Suspension ready for injection.
2. Dry insoluble solid products, which can be reconstituted with a suitable vehicle at the time of administration.

Some examples of the first forms of suspension include

I. Insulin-semilente: a suspension of zinc-amorphous insulin complex used in the treatment of insulin-dependent diabetes mellitus; duration of action: 12 - 16 hr.

II. Insulin-ultralene: a suspension of zinc-crystalline insulin complex; duration of action 36 hr.

III. Insulin-lente: a suspension containing zinc-amorphous
    - Insulin and zinc-crystalline insulin complex; duration of action 24 hr.

Some examples of the second form of suspension include

a. Sterile methyl prednisolone acetate suspension (Depo-Medrol).

b. Sterile hydrocortisone acetate suspension.

c. Serile chloramphenicol for suspension (Chloromycetin).

d. Sterile benzathine-penicillin G for suspension (Penadur LA).
    - All the above are suspended in sterile water for injection to produce an aqueous suspension.
    - Parenteral suspensions should not be administered by I.V. since the insoluble particles may block the capillaries.

Parenteral suspensions give slow or sustained release of drugs since the dissolve slowly.

Formulation of parenteral products

Several components are used in the preparation of Parenteral

The active ingredients include

1. The vehicle.
2. The active ingredient

In order to formulate a stable, effective and safe parenteral preparation, all ingredients used, including rug, should be evaluated for their purities, solubility, and compatibilities with each other.

In preparing Parenterals, a suitable vehicle for dissolving the drug has to be used.

Parenteral Emulsions [22,23]

- Few drugs are formulated as Parenteral emulsions, mainly as O/W emulsions.
- It is necessary to achieve stable very fine emulsion droplets to prevent aggregation in the blood vessels which may promote the aggregation of platelets resulting in thrombophlebitis.

Examples [24]

1. Intralipid I.V emulsions.
2. Oil soluble vitamins (A, E and D) I.M. injection.
3. Phytomenadione (vit. K) I.V. injection.

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