A Comprehensive Review on Infusion Solution

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INTRODUCTION

Infusions are sterile, aqueous solutions or emulsions with water as the continuous phase. These infusions are comes under the large volume parenteral dosage forms. They are usually made isotonic with respect to blood. It means the osmolality of infusion is similar to blood osmolality (275-295mOsmol/kg). They are principally intended for administration in large volume. Infusions do not contain any added antimicrobial preservative. Solutions for infusion, examined under suitable conditions of visibility are clear and practically free from particles. Emulsions for infusion do not show any evidence of phase separation [1-2].

TYPES OF IV SOLUTIONS

The iv solutions are classified into different types based on osmolarity of the solution.

Isotonic

The osmolarity of these type of solutions is same as serum and other body fluid. It will not cause any osmotic effect on the body. Ex: 5% dextrose, 0.9%NaCl, lactated ringer's solution.

Hypertonic

This has a higher osmolarity than serum. It will pull fluid from the interstitial and intracellular compartments into the blood vessels. Ex: 5% dextrose in half normal saline, 3%NaCl.

Hypotonic

This has a lower osmolarity than serum. Fluid moves from the blood vessel into the cells and interstitial spaces. Ex: Sterile water, Half normal saline, 0.33%NaCl.

FORMULATION OF INFUSION

The infusions contain active drug and different types of excipients in their formulation. In this formulation the isotonicity agent is the main excipient along with the drug [3-4].

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A thorough evaluation of properties of the active drug or drugs is essential in developing a stable and safe parenteral dosage form.

**Solvent**

The most widely used solvent for infusions is water for injection (WFI). As a solvent, WFI is used in preparing the bulk solution and as a final rinse for equipment’s and packaging preparation. WFI is prepared by distillation or reverse osmosis, although only distillation is permitted for sterile water for injection. Sesame oil, cottonseed oil and other vegetable oils are used as vehicles for water insoluble drugs such as corticosteroids and oil soluble vitamins.

**Solubilizer**

Solubilizers are used to enhance and maintain the aqueous solubility of poorly water soluble drugs.

**Buffers**

Buffers are added to a formulation to adjust the pH in order to optimize solubility and stability. For parenteral preparations, the pH of the product should be close to physiologic pH. The selection of buffer concentration (ionic strength) and buffer species is important.

**Tonicity Adjustment Agent**

It is important that injectable solutions that are to be given intravenously are isotonic, or nearly so. Because of osmotic pressure changes and the resultant exchange of ionic species across red blood cell membranes, non-isotonic solutions, particularly if given in quantities larger than 100 ml, can cause haemolysis or crenation of red blood cells. Dextrose, sodium chloride, or potassium chloride is commonly used to achieve isotonicity in a parenteral formula.

**EVALUATION OF INFUSION SOLUTIONS**

These infusion solutions are parenteral dosage forms. The evaluation of these infusions is also similar to the evaluation of injections. The evaluation tests are

- Sterility test
- Pyrogen test
- Particulate matter
- Leakage test
- Osmolarity test

**CONTAINER CLOSURE SYSTEM**

The packaging systems is an integral part of the parenteral infusion product providing long term protection and maintain physical and chemical stability of the product formulation. Packaging system consists of container and closure. An infusion bag is intended to contain a drug substance or drug product with which it is, or may be in direct contact. The infusion port is a part of the container. Containers must be chosen with care and after taking into consideration the nature of the articles and the likely effects of transportation and storage, even for short periods of time [5-6].

**The main requirements of infusions packaging system include the following**

- Maintain sterile barrier around the product.
- Aid in aseptic removal of product.
- Should not add to air borne contamination.
- Evident opening features.

Containers for parenteral infusion preparations are made from materials that are sufficiently transparent to permit visual inspection of the contents, do not adversely affect the quality of the preparation [7].

**Containers used for infusions**

1. Plastic containers
   a. Bottles
   b. Bags

**Plastic Containers**

Plastic containers for parenteral preparations are manufactured from one or more polymers. The polymers most commonly used are polyethylene, polypropylene and poly vinyl chloride. Only virgin plastic material, which is practically odourless, is used in the manufacture of the containers. Additives such as antioxidants, lubricants, plasticizers, stabilizers, etc. may be used but no pigment may be used for purposes of colouring. Recycling of excess material of well-defined nature and proportions may be permitted after appropriate validation. The containers may be bags or bottles. The containers must withstand the sterilization conditions to which they will be submitted. The design of the container and the method of sterilization chosen are such that all parts of the containers that may be in contact with the infusion are sterilized. The containers are impermeable to microorganisms after closure. The containers are such that after filling, they are resistant to damage from accidental freezing which
may occur during transport of the final preparation. The containers remain sufficiently transparent to allow the appearance of the contents to be examined at any time, unless otherwise justified and authorized.

The empty containers display no defects that may lead to leakage and the filled and closed container shows no leakage. For satisfactory storage of some preparations, the container should be enclosed in a protective envelope. Plastic packaging has always been important for ophthalmic drug dosage forms and is gaining in popularity for injectable dosage forms. Plastic bottles for large volume injectable (LVIS) have been used for many years. Plastic vials for SVIS may be a wave of the future plastic packing offers such advantages of cost savings elimination of the problems caused by breakage of glass and increase convenience of use [8-10].

Flexible Infusion Bags
Flexible containers for parenteral infusion are manufactured from one or more polymers, if necessary with additives. Flexible plastic containers store the widely used electrolyte and sugar supplements. A few pure intravenous drug compounds are now available in “ready-to-use” bottles or bags. Such packaging eliminates the need to add the drug product to the larger infusion (5% dextrose) containers [9-11].

Design of Infusion Bag
Containers for intravenous fluids must be designed to maintain solution sterility, clarity (freedom from particulate matter), and non-pyrogenicity from the time of preparation, through storage, and during clinical administration.

Depending on port system the bag consists of following parts
- 2 connector tubes.
- 1 injection port (site that allows an injection to be made at the time of use).
- A site suitable for the attachment of an infusion set designed to ensure a secure connection through which the injections are administered at a regulated flow rate into suitable veins.
- They usually have a part that allows them to be suspended and which will withstand the tension occurring during use.

Advantages of Infusion bags
For infusion solutions, plastic bags, in contrast with glass containers, are lightweight, less likely to break, and no air must enter the container to replace the fluid being administered and a range of application advantages have made bags popular particularly with standard solutions.

Flexible plastic Infusion bags feature the following advantages
- They are user-friendly, i.e. it is not possible for the infusion system and in particular the drop chamber to run empty because the bag collapses the end of the infusion there is an automatic stop of the fluid column thus making it a closed system which in turn makes an air embolism impossible.
- The infusion sets functions without venting.
- It is easy to mix the contents when admixtures are made.
- They are flexible (important for pressure infusions).
- They are transparent (important for detecting possible precipitations).
- They are easy to use for a pressure infusion.
- Unlike glass containers, flexible plastic containers does not require air introduction for the fluid to leave the container and flow through the administration set. Atmospheric pressure pressing on the containers forces the fluid to flow.

Disadvantages
The main disadvantage comes from a possible drug-plastic interaction.
TYPES OF BAGS

The infusion solutions are filled in to the infusion bags. For this purpose there are different types of bags. The chemical component was different in this bag. Based on chemical component there three types of bags are there.

A. Poly Vinyl Chloride (PVC) bags
B. Polyolefin bags
C. Polypropylene (PP) bags

Some of the drugs will show the interaction with the bags. So the selection of bag is based on the nature of the drug. Among these three types of bags the polypropylene bags are having more advantages. So mostly it can be used for the filling of the infusion solutions.

Poly Vinyl Chloride (PVC)

Poly vinyl chloride use has been predominant in the production of certain types of flexible products because of its ease of processing using a wide variety of techniques. Poly vinyl chloride flexible infusion bags are commonly used for the infusion of drug admixtures due to their advantages, such as lightness, flexibility, and convenient storage, over the conventional glass containers [12-13].

Fig 2. polyvinyl chloride bag

The advantages are, however, countered by various disadvantages

Numerous studies have reported on the drawbacks of the PVC bags. The major problem of the PVC bags for drug infusion purpose is that di-(2-ethylhexyl) phthalate (DEHP), the main plasticizer used in manufacturing PVC bags, can leach into the infusion solutions. DEHP, when injected into the human patients, may have adverse effects on their bodies including chronic toxicities on the liver and the reproductive systems. Besides plasticizers, the other problem of the PVC infusion bags is the adsorption of drugs into the inner surfaces of the bags, thereby decreasing the infusion concentrations. It is recognized that PVC causes the sorption of the lipophilic drugs, such as diazepam and nitroglycerine.

To overcome these problems, several types of non-PVC bags comprised of polyolefin, such as polyethylene and polypropylene (PP), have been developed. As the non-PVC products do not contain DEHP, concerns over leaching can be eliminated and the polyolefin materials are known to inhibit drug adsorption to a certain degree, this is other strong point of polyolefin infusion bags over PVC bags. The use of a non-PVC material such as polyolefin for dilution of the drug incompatible with PVC, is recommended.

Polyolefin

A polyolefin is a polymer produced from a simple olefin (also called an alkene with the general formula \( C_nH_{2n} \)) as a monomer. Polyolefin is the collective description for plastic types that include, polyethylene produced by polymerizing the olefin ethylene [Low density polyethylene, linear low density poly ethylene and high density polyethylene] polypropylene (PP) produced by polymerizing the olefin propylene, poly methyl pentene, polybutene-1 (PB-1).

Prior to 1954 most attempts to produce plastics from polyolefin had little commercial success. Polypropylene invented in 1955 by Italian scientist by addition reaction of propylene gas with a stereospecific catalyst titanium trichloride brought a revolution [14].

Polypropylene (PP)

polymerized propylene, a very light, highly resistant, thermoplastic resin used to make coatings, plastic pipe, packaging material, fibers for clothing fabrics, etc . Polypropylenes are predominant used in the production of certain types of flexible containers because of its ease of processing using a wide variety of techniques Polypropylene (PP) IV bags have become available recently and were used in this study. These bags are environmentally friendly, inert, and have low adsorption of active ingredients; moreover, weight losses due to the evaporation of
water across the container wall are insignificant with this type of plastic [15].

**Fig 3. polypropylene bag**

More over Polyolefin plastics can be made biodegradable by creating weak links in the polymer chain so that bacteria and other microorganisms can break it down. PP stability need no longer be of concern to those considering using radiation sterilization for medical devices.

**Structure of Polypropylene Polymer**

Polypropylene is a widely used polymer of excellent mechanical and thermal properties therefore its application, especially in the medical industry, has expanded continuously for the last decade. Because of superior characteristic and low cost PP is a material for production of syringes, packages, catheters etc. One of the most important aspects concerning fabrication of such products is elimination of bio burdens. The application of ionizing radiation for the sterilization purposes has prompted studies on the response of polypropylene on irradiation.

Polypropylene consists of the homopolymer of propylene or of copolymer of propylene with not more than 25% of ethylene or of a mixture (alloy) of polypropylene with not more than 25% of polyethylene. It may contain additives. A certain number of additives are added to the polymer in order to optimize their chemical, physical and mechanical properties in order to adapt them for the intended use. They may contain at most 3 antioxidants, one or several lubricants or anti blocking agents as well as titanium dioxide as opacifying agent when the material must provide protection from light.

**PRODUCTION OF PP**

A certain number of additives are added to the polymer in order to optimize their chemical, physical and mechanical properties in order to adapt them for the intended use. They may contain:

- Not more than three antioxidants
- One or several lubricants or anti-blocking agents and
- Titanium dioxide as opacifying agent when the material must provide protection from light.

Some examples of Anti-oxidants includes,
1. Butylhydroxytoluene (plastic additive 07): Maximum 0.125 per cent
2. Pentaeorthytritolerakis (plastic additive 09): Maximum 0.3 per cent
3. Dioctadecyl disulphide (plastic additive 15): Maximum 0.3 per cent
4. Didodecyl 3, 3 Ω-thiodipropionate (Plastic additive 16): Maximum 0.3 per cent

The total of antioxidant additives listed above does not exceed 0.3 per cent.

**Advantages of PP infusion bags**

- Low Cost
- Excellent flexural strength
- Good impact strength
- Processable by all thermoplastic equipment
- Low coefficient of friction
- Excellent electrical insulation
- Good fatigue resistance
- Excellent moisture resistance
- PP is known to support temperatures up to 121°C, which is not the case for PVC
• Very good chemical resistance

Applications
• The utilization of plastics in the medical disposable device sector minimized or avoided the risk of cross-contamination and infection and the need for resterilization.
• Glass IV containers have largely been replaced with flexible PVC and PP bags.
• These containers are impermeable to micro-organisms after closure.
• The poly propylene containers are such that after filling, they are resistant to damage from accidental freezing which may occur during transport of the final preparation.
• Free of haze and the sensitivity to high-energy radiation that plagued polypropylene in the past, the new formulations are in high demand for uses previously reserved for glass or other, more costly, plastics.
• Especially important to the new popularity of these plastics are their clarity and their ability to withstand all major methods of sterilization.

INJECTION PORTS
The injection port is one of the components in infusion bag. These injection ports are used to inject the drug from the infusion bag. So these ports are should be sterile in nature and should with stand the sterilization.
The most commonly used injection ports are polycarbonates.

Polycarbonates
Medical devices, which require precise moulding and tolerance to both radiation sterilization conditions and possible in-house steam sterilization, can be made from polycarbonate (PC).

Chemical structure of polycarbonate

PC has a high thermal distortion temperature (Td ~ 130°C), which enables devices made from this plastic to withstand mild steam and also dry heat sterilization. PC is very resistant to chemical attack and can withstand internal pressures such as for use in hyperbaric systems. These grades can be sterilized using steam at 120°C, gamma radiation, or by the ethylene oxide (EtO) method. However, scientific research indicates possible problems with biocompatibility. Being a polycyclic material, PC is inherently radiation resistant. Improvements have been made to provide grades with little to no colour change upon exposure to radiation sterilization conditions.

STERILIZATION OF INFUSION BAGS
Sterilization is a term referring to any process that eliminates (removes) or kills all forms of life, including transmissible agents (such as fungi, bacteria, viruses, spore forms, etc.) present on a surface, contained in a fluid, in medication, or in a compound such as biological culture media. Sterilization is the process designed to produce a sterile state. Sterile state or sterility is defined as the total absence of viable life forms.
Sterilization can be achieved by applying the proper combinations of heat, chemicals, irradiation, high pressure, and filtration [16-17].

Various agents used as sterilants
Elevated temperature, Ionizing radiation, Chemical liquids or gases etc. The success of the process depends upon the choice of the method adopted for sterilization. Considering the thermal methods of sterilization, dry heat sterilization leads to deformation, moist heat sterilization leaves traces of water in the infusion bags which is not acceptable.

Suitable Sterilization Methods for Thermo liable Packaging Materials
The infusion bags are semipermeable and thermolabile in nature. So to sterilize these types of bags suitable sterilization methods can be use.
Most commonly used sterilization methods for infusion bags are,
1. Gas sterilization (ethylene oxide (EtO) sterilization)
2. Radiation sterilization.

Electro beam sterilization
Electron beam (e-Beam) sterilization is a type of radiation sterilization that involves particle radiation. Particle radiation is a result of electrons that are artificially accelerated to high energies to improve the ability of the electron to penetrate a target.
Gamma sterilization
Sterilization by this method is achieved by exposure of the product to ionizing radiation in the form of gamma radiation from a suitable radio isotopic source (such as cobalt-60 or cesium-137). The gamma sterilization process uses Cobalt 60 radiation to kill microorganisms on a variety of different products.

CONCLUSION
Development of infusion premix with 5% dextrose or 0.9% NaCl in single use flexible infusion bags (pvc, pp, polyolefin) avoids further dilutions of the drugs prior to administration. This will be usefull in case of emergencies in like ICU and hospitalization provide better therapy than the available conventional dosage forms. So these infusions helpful in case of continuous medication cases.

REFERENCES