ISSN: 2456-043X
International Journal of Engineering Science and Generic Research (IJESAR)
Available Online at www.ijesar.in
Journal Index In ICI World of Journals - ICV 2016 – 68.35
Volume 10; Issue 2; 2024; Page No. 16-23

Advancements in Parenteral Preparation Techniques: A Review Article

***Rohit, Rajesh Kumar, Prachi Sharma, Ajeet Pal Singh & Amar Pal Singh**

Department of Pharmaceutics, St.Soldier Institute of Pharmacy, Lidhran Campus Behind NIT(R.E.C) Jalandhar-Amritsar by Pass, Nh-1, Jalandhar-1440011, Punjab, India.

Abstract

Parenteral preparations play a critical role in modern medicine, allowing for the administration of drugs directly into the bloodstream, bypassing the gastrointestinal tract. This review article provides an overview of the various aspects of parenteral preparation, including formulation, stability, and sterility considerations. The article discusses the different types of parenteral dosage forms, such as injections, infusions, and implants, highlighting their advantages and limitations. Emphasis is placed on the importance of quality control measures, including particle size analysis, pH adjustment, and container-closure integrity testing, to ensure the safety and efficacy of parenteral products. Additionally, the article addresses recent advancements in parenteral delivery systems, including novel drug delivery technologies and sustained-release formulations. Overall, this review aims to provide a comprehensive understanding of parenteral preparation, highlighting its significance in the field of pharmaceutical science and clinical practice.

Introduction

Solutions, suspensions, emulsions for injection or infusion, powders for injection or infusion, injectable gels, and implants are all considered parenteral preparations. These are sterile formulations meant to be administered straight into an animal or human's systemic circulation. Like other pharmaceutical dosage forms, they must be safe for the intended use and meet pharmacopeia-described pharmaceutical quality criteria.

Parenteral preparations need to be free of pyrogens in addition to being sterile. It is possible to achieve sterility through various sterilisation techniques that are suitable for the formulations. On the other hand, pyrogen-free products necessitate the use of pyrogen-free pharmaceutical ingredients, drug substances, or APIs (Active Pharmaceutical Ingredients) and excipients are typically provided in single-dose glass or plastic containers (polyolefin or PVC is less recommended these days), or increasingly in pre-filled pens or syringes for convenience of use. This article will outline the primary obstacles encountered in the formulation of parenteral preparations, as well as how Roquette's solutions satisfy the demands of the formulator(1).

Injection:-

Instead of being injected into the alimentary canal, these are intended to be injected through the skin or another external border tissue. This makes it possible to directly inject the preparations' active ingredients into a blood artery, organ, tissue, or lesion while using force or gravity to do it. Parenteral articles are carefully made with methods designed to ensure that they meet Pharmacopeial requirements for particle matter, pyrogens, sterility, and other contaminants. When suitable, they might also include substances that stop germs from growing. An injection is a preparation intended to be given intravenously, or to dilute or compose a parenteral object before to administration.

* A container containing many single doses of a sterile substance meant for parenteral administration is called a pharmacy bulk

package. The materials can only be used to fill empty sterile syringes with sterile transfer devices or to make admixtures for infusion. Their intended application is as part of a pharmaceutical admixture plan.

Only one sterile transfer device or dispensing set that allows the contents to be administered gradually may be used to open the closure after constitution. The bulk pharmacy package can only be used in a clean air compounding facility or a laminar flow hood, among other suitable workspaces.

Only preparations from the previously mentioned Nomenclature categories 1, 2, or 3 may be included in this bulk package. Pharmacy bulk packages are exempt from the multiple-dose container volume limit of 30 mL and the need that they contain a material or an appropriate mixture of chemicals to inhibit the growth of germs, even when they contain more than one single dose(2).

Critical considerations in the formulation development of parenteral biologic drugs

- Generally speaking, biologic medications offer superior target

treatments.

- Biologics are difficult to develop and produce, and their delivery always requires a cold chain.

• Taking into account the needs of patients while creating dose forms for parenteral administration.

- As manufacturing technologies advance to include artificial intelligence and continuous manufacturing, the cost of biologic medicines is expected to reduce significantly over the next ten years.(3)

Molecular modality

A variety of molecular methods are included in biological treatments. Following traditional small-molecule treatments, proteins transformed the pharmaceutical industry and today account for the majority of authorised biologic medications (about 74%). Natural biologics—viruses, genes, and cells—that interact in a variety of ways are now being used to target hard-to-treat illnesses like infectious disorders and cancer. Among growth factors, monoclonal antibodies, and protein therapies. (4)

Dosage form configuration

A biological drug product's best dosage form configuration is determined by a number of considerations, such as the product's intended dose, stability of the macromolecule, material compatibility, designated therapeutic area, mode of administration, patient compliance, and cost-of-goods analysis from the standpoint of commercialization. For the development of biologics, liquid and lyophilized formulations are the most prevalent dosage form configurations.

(4)

Route of administration

Biologics are often difficult to deliver via nonparenteral routes (e.g., oral) of administration because of issues such as enzymatic degradation, poor permeation, variable pharmacokinetics/pharmacodynamics (PK/PD) profiles, and low bioavailability [50]. Therefore, substantial attention has been paid to the parenteral routes of administration, which currently comprise ∼85% of all biological deliveries. There are a few recent clinical studies advancing the intratumoral delivery of oncology drugs(4).

Concluding remarks

The cost-of-goods (COGs) of parenteral biologic medicines are directly impacted by the interdependence of formulation, stability, and shelf life. Many initiatives are underway to create parenteral dosage forms that use lyophilization, spray-drying, or immobilisation technologies to reduce or eliminate the need for cold-chain (frozen/refrigerated) products. It will be crucial in the upcoming years to use cutting-edge computational techniques for the creation of

patient-centered dose forms and connected/remote monitoring devices.

(4)

Selection of excipient for Parenteral Formulation Development

EXCIPIENT USED IN LYOPHILIZATION

Bulking Agents and Lyoprotectants

Bulking agents comprise most of the lyophilized product and provide the cake the proper structure. These are usually used for low-dose, high-potency drugs that don't have enough mass to support their own structure. These are considerably more important when the total solid content is less than 2%. In these cases, a bulking agent is added to the formulation matrix. Because proper cake formation leads to suitable pore construction, which permits vapour to exit the product during the drying cycle, the lyophilized cake's structure is essential.

Mannitol:

It is the excipient that is most frequently and extensively utilised in lyophilized products. After crystallisation, mannitol has an extremely high eutectic melting point (-1.4°C) and is well-processed during lyophilization. However, in some situations, the bulking agent's crystallisation could negatively impact the product's physical stability; in these cases, an amorphous bulking agent is recommended.

Lactose:

Despite being an effective bulking agent, it is a reducing sugar that can cause instability in the formulation by reacting with proteins in a Maillard reaction. The critical temperature for 1% lactose is -32°C. Sucrose has a collapse temperature of -31°C (2%) which is similar to lactose's, however it is not a reducing sugar and does not undergo the Maillard reaction. During drying, sucrose may slightly collapse since it has a higher density than lactose. (5)

Polyethylene glycol (PEG):

It gives cakes a nice structure and makes water more viscous. The critical temperature of the PEG 2% solution is -22°C. In addition to lyophilization, it is employed in parenteral, including ophthalmic, applications as a co-solvent and viscosity modifier.

Polyvinyl pyrollidone (PVP):

Povidone K 12 and K 17, which are low-molecular grades, are utilised as dispersants, solubilizers, and inhibitors of crystallisation, especially for injectables. Antibiotics in solution or lyophilized form are specifically employed in this application. Povidones with greater molecular weights may not be suitable for parenteral administration due to their higher K-values.

Preservatives Used For Parenteral Preparations

Antioxidants, Antimicrobial and Chelating agents

While antimicrobial compounds are used to stop the growth of microorganisms in the drug product, antioxidants are used to prevent or minimise the oxidation reaction of the medicine or excipeints over the product's shelf life. The most often utilised antioxidants in sterile formulations include monothioglycercol, ascorbic acid, acetylcysteine, and sulphurous acid salts (bisulfite, metabisulfite). Benzalkonium chloride, phenol, meta-cresol, benzoalcohol, parabens (methyl, propyl, butyl), chlorobutanol, Thimerosal, phenylmercuric salts (acetate, borate, nitrate), etc. are some of the antibacterial agents that are frequently employed. A material that has the ability to make many connections with a single metal ion is known as a chelating agent, in addition to being antioxidant and antibacterial. Contrary to popular belief, preservatives are present in a number of single dose medications because of legacy.(6)

Solubilizing agents

Agents that aid in the dissolution of the medicine or improve its solubility in the formulation are

referred to as solubilizing agents; these agents can be roughly categorised as co-solvents and surfactants. Surfactants work by lowering the drug components' surface tension, increasing dissolution, while co-solvents are defined as solvents that, when combined with another solvent, can dissolve a solute.

Complexing and Dispersing Agents:

Sometimes, complexation is used to increase a drug's solubility in a solvent, particularly water. Cyclodextrins have shown to be incredibly successful additives for solubilizing medications that are hydrophobic. Modified cyclodextrins, like hydroxypropyl-β-cyclodextrin and sulfobutylether-β -cyclodextrin, have been found to solubilize and stabilise a variety of injectable medications, such as interleukin-2, dexamethasone, and estradiol, in the parenteral dosage form without seeming to cause any compatibility issues.

Buffering agents:

Buffers are added to a formulation to adjust and stabilize pH and optimize drug solubility and stability, for parenteral preparations, it is desirable that the product pH be close to physiologic pH. Selection of a buffer concentration (which contributes to the ionic strength of the formulation) and a buffer species is important. For example, citrate buffers in the range of 5–15 mM are typically used in formulations but increasing the buffer concentration to 50 mM will result in excessive pain on sub-cutaneous injection and toxic effects due to chelation of calcium in the blood. Table 7 lists buffers and chemicals used for pH adjustment and maintenance of the drug product pH range, phosphate, citrate, and acetate are the most common buffers used in parenteral products.(6)

Parenteral Production Sterility:

While certain parenteral products can be sterilised at the conclusion of the production process, some cannot be sterilised at the terminal stage using steam treatment due to heat sensitivity of the drug components and/or other ingredients in the formulation. Sterile filtration is frequently the only option in these situations, and it must be used in conjunction with stringent control procedures to guarantee product quality and stop contamination from entering the process at any stage of production.

It is crucial to remember, nevertheless, that creating a process that complies with good manufacturing practice (GMP) guidelines requires careful consideration of a number of factors. One important idea is that sterility and quality cannot be guaranteed by a single control measure, such as testing or terminal sterilisation. For example, a terminal sterilisation method might have a capacity threshold, meaning that more germs can be eliminated from the system if the bioburden is high. Therefore, in order to make sure that the bioburden level is appropriate for the procedure being employed, it is crucial to determine it before performing terminal sterilisation.

Testing after sterilization can also be an issue, as sterility assays have limitations in terms of specificity and sensitivity.

A high bioburden also creates a risk for endotoxin contamination because endotoxins originate in bacterial cells. Even if the bacteria are killed in the process of manufacturing the raw material or final drug, subcellular components may still be present in the formulation, leading to unacceptable levels of endotoxins and pyrogenic compounds in the final drug product. For these reasons, terminal sterilization is not an effective solution on its own and a comprehensive approach to ensuring sterility is necessary. Aseptic filtration followed by terminal sterilization is an ideal way to ensure sterility and compliant endotoxin levels.(7)

Some Quality Control Analysis Parameters for Parenteral Formulations

In order to reach systemic circulation and provide an onset effect, parenteral medications (large/small volume parenteral) are defined as

formulations intended for injection into the skin, veins, artery muscles, or other outer border tissue as opposed to the alimentary canal. Intravenous (IV), subcutaneous (SC), and intramuscular (IM) injections are the most often utilised parenteral routes; intradermal and intra-arterial injections are less frequently employed. Based on the size of the package, they are often divided into two categories: big volume parenteral and small volume parenteral. A package is deemed big volume parenteral if it holds more than 100 millilitres; otherwise, it is classified as small volume parenteral, with the exception of biological.(7)

General and Universal Tests for Parenteral Formulations:

Description: For physical examination, the parenteral formulations' specifications and qualitative descriptions are important. Parenteral formulations, for instance, may be described as follows on a specification: clear formulation, category and labelling comprising ingredients and excipients, imprinted with "Rx" in certain countries in accordance with their laws and regulations.

Identification: Identification or identity test is to characterize the identity of the active pharmaceutical ingredient (API) in the formulations. This test is capable to differentiate between ingredients of closely related structures that are likely to be present.

Assay: This test determines the strength (purity of active ingredients/content of the API) in the parenteral formulations.

Impurities: This test is aimed quantify the presence of any kind of impurities that is not the API or an excipient of parenteral formulations. The most common type of impurities that are measured is related substances, which are processed impurities from the new drug substance synthesis, degradation products of the API, or both.

Quality control parameters of parenteral pharmaceuticals:

Test for Uniformity of Content: According to BP, single-dose suspensions for injection that have an API content of less than 2 mg or less than 2% of the total mass, or that have a unit mass equal to or less than 40 mg, comply with the uniformity of content of single-dose formulations unless otherwise prescribed, justified, and authorised. Only the active ingredients that match the monographs are subject to the requirement, even if the formulation comprises multiple active ingredients.

Test for Uniformity of Mass: In accordance with BP, take off any paper labels from a container for this test, then wash and dry the outside. Weigh the container and its contents as soon as you open it. Gently tap the container to release as much air as possible. Clean it if needed with purified water and then 96% ethanol. Dry it at 100–105 °C for an hour, or lower if the container's construction forbids heating to this temperature. Before weighing, let it cool completely in a desiccator. The mass of the contents determines the difference in the weighing.

Carry on with the procedure for the remaining 19 containers. Calculate the average weight. If no more than two of the individual weights deviates from the average weight by more than 10%, and none deviates by more than 20%, the results are consistent with IP.

Test for Extractable Volume of Parenteral Formulations: For Extractable Volume analysis, suspensions and emulsions are shaken before application of formulation and before the determination of the density. Oily and viscous formulations may subject to temperature dependent change according to the instructions on the label, if necessary, and thoroughly shaken immediately before removing the contents. The contents are then brought to (20-25) °C before measuring the volume.

Sterility Test:

In order to ensure safety, sterility—which tries to eradicate all microbe from the formulation—is

one of the most important quality control measures. The BP and USP state that membrane filtration or direct inoculation of the culture media with the product to be evaluated are the two methods available for performing the sterility analysis.Appropriate negative controls are selected for the comparative investigation. Although it can also be used to identify aerobic microorganisms, fluid thioglycollate is mostly utilised for the cultivation of anaerobic bacteria. Soya-bean casein digest medium is suggested for the cultivation of aerobic and fungal microorganisms. Sterileness is the most important and vital characteristic of parenteral products.The absence of all living microorganisms is referred to as sterility. It is an absolute term. Sterility tests are performed using the following methods: A. Direct transfer method /technique.(8)

B. membrane filtration method /technique.

A) Direct Transfer method: -It's a traditional sterility test that involves directly inoculating the required volume of a sample into two test tubes using FTM, SCDM culture medium. When the requirement for repetition in opening container, sampling, transferring, and mixing rises, this approach is easy in principle but challenging in practice, resulting in operator fatigue and detoriation in technique.

B) Membrane Filtration method: -It was made official in 1970 by the U.S.P. It is a more extensively utilized and popular approach than direct transfer method. Successful employment needs a higher level of skill and knowledge than the approach of direct transfer method. This method involves filtration of the sample via hydrophobic membrane filters with a porosity of 0.22 micron and a diameter of 47mm. After filtration, the membrane is divided into two halves and one half is inserted in two test tubes contain FTM, SCDM media. If there is no apparent indication of microbial growth in the culture medium in the test tube, the sample representing the lot is free of intrinsic contamination. If visible microbial growth is detected or the test is deemed invalid due to inadequate environmental conditions, the sterility test must be repeated. This interpretation must be made by personnel who are familiar with aseptic processing, industrial sterilisation methods, and environmental control procedures used in the test facility.

Pyrogen Test

Pyrogens are metabolic products produced by microorganisms, with Gm-ve bacteria producing the most powerful pyrogens. These lipo polysaccharides are chemically and thermally stable, and they can pass through bacteria retentive filters. When these pyrogens are injected into the body, they cause a rapid onset of fever, body aches, and vasoconstriction within 1 hour. The following tests are used to determine the presence of pyrogens in sterile parenteral products.

These are: - C. The Rabbit Test D. The LAL Test

(C) Rabbit test: - This test includes injecting a sample solution into rabbits used as test animals through the ear vein. The test fluid must be warmed to 37 degrees before injection using a temperature sensor probe (Clinical Thermometer, Thermosistor, or equivalent probe) inserted into a rectum cavity of a rabbit at a depth of 7.5 cm. Then temperature of the rectal cavity is measured at 1,2,3 hours after the injection. This test is conducted in a separate location that has been specifically constructed for this purpose, in an atmosphere that is comparable to that of an animal house, and is devoid of stimuli that are likely to stimulate them. This test is done on 3 rabbits at first, but if the desired results are not obtained, the test is repeated on 5 more rabbits using the same sample solution as the first 3 rabbits. The control temperatures of rabbits are established 1 hour before injecting sample solutions. Only use rabbits with a control temperature that does not differ by more than 1 degree Celsius.

(D) LAL test: - The gelling property of lysates of limulus polyphemus amebocytes, which are

found exclusively in a few locations along the east coast of North America and southeast Asia, is utilised in this recently developed in vitro pyrogen test method. The fundamental procedure, which is based on horse shoe crab, is combining 0.1 ml of test sample with LAL Reagent and then letting it sit at 37 degrees Celsius for an hour. Only then is a gel clot looked for. A positive LAL Test indicates the presence of endotoxin. Its main applications are in biologicals, devices, pharmaceutics, food, illness states, and heat cycle validation.

This method has several advantages of Rabbit test they are Greater sensitivity and reliability specificity, less variation, wider application, less expensive and simplicity.(8)

References

1. Koch A, Henke S (2021) Mikronadelsysteme und microarray patches. Pharm Ind 83(6):844–850 (1)
2. O.C. Redfern Exploring the structure and function paradigm Curr. Opin. Struct. Biol. (2008)
3. B.K. Muralidhara critical consideration https://www.sciencedirect.com/ (3) (2016)
4. S.J. Shire Formulation and manufacturability of biologics Curr. Opin. Biotechnol. (4) (2009)
5. T. Arakawa Factors affecting short-term and long-term stabilities of proteins Adv. Drug Deliv. Rev. (2001)
6. .D. ParkinsThe formulation of biopharmaceutical productsPharm. Sci A. Technol. Today- Critical considerations in the formulation development of parenteral biologic drugs
7. Robertson MI. Regulatory issues with excipients. Int. J. Pharm. 1999; 187: 273–276. (5) https://www.researchgate.net/
8. Nema S, Brendel RJ. Excipients and their role in approved injectable products: current usage and future directions. PDA J Pharm Sci Technol. 2011; 65:287-332 (5).
9. BP. Parenteral Preparations. In British Pharmacopoeia, Stationary Office London. 1999; Vol. II: 1575.
10. Townsend MW, Deluca MEPP. Use of Lyoprotectants in the Freeze-Drying of a Model Protein, Ribonuclease A. PDA Journal of Pharmaceutical Science and Technology. 1988; 42 .
11. Guidelines Medicinal products for human use Safety, environment and information Excipients in the label and package leaflet of medicinal products for human use July 2003. Volume 3B. European Commission Enterprise Directorate-General Brussels.
12. Meister E, Ellnain M, Gieseler H. Collapse temperature measurement by freeze-dry microscopy and transferability to freeze drying processes: influence of solute concentration on collapse behavior and effect on cycle design. AAPS annual meeting and exposition. Oct 29 – Nov 2, 2006, San Antonio, Texas, USA.
13. . Costantino HR, Griebenow K, Langer R. On the pH memory of lyophilized compounds containing protein functional groups. Biotechnol Bioeng. 1997.
14. Evaluate Pharma Market Report 2022.(8) https://www.sigmaaldrich.com/
15. Remington, the Science and Practice of Pharmacy, Parenteral Preparation, 20th edition. Philadelphia: ISE publication 1 (2000). [2] Ford JL. “Parenteral products”. In: Aulton ME, (ed.) Pharmaceutics: The Science of Dosage Form Design. New York; Longman (1988)((7)
16. Ford JL. “Parenteral products”. In: Aulton ME, (ed.) Pharmaceutics: The Science of Dosage Form Design. New York; Longman (1988)(7) https://d1wqtxts1xzle7.cloudfront.ne.
17. Beecher P. “Encyclopedia of emulsion technology, basic theory”. Marcel Dekker: New York 1 (1983)
18. Singh M and Ravin L. “Parenteral emulsions as drug carrier systems”. Journal of

Parenteral Science and Technology 40 (1986): 34-44
19. Brazeau GA., et al. "Dosage Forms: Parenterals". In: Swarbrick James (Ed.). Encyclopedia of Pharmaceutical Technology. 3rd edition. Informa Healthcare USA, Inc: New York 1 (2007): 1001-1011.
20. Groves MJ. "Parenteral drug delivery system". In: Mathiowitz Edith (Ed.). Encyclopedia of Controlled Release. John Wiley and Sons, Inc: New York 1-2 (1952): 743-777.