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A Comprehensive Review on Injectable Solutions as Dosage Forms

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Abstract:- Injectable solutions are sterile, pyrogen-limited preparations intended to be administered parenterally. Solutions are clear, transparent, and free from particulate matter. Formulations are designed with suitable excipients. They are safe and effective in drug delivery systems. Injectable preparations may be packaged in prefilled syringes, vials, collapsible bag systems, or flexible plastic containers, and packaged with or without the addition of a secondary protective container. They come in packages with a capacity of 4ml, 5ml, 10ml, and so on. They are administrated in an intravenous (IV), intramuscular (IM), and subcutaneous (SC) manner. All injectable solutions need to undergo a pre-formulation stage. In this stage, many physical and chemical parameters of the drug are evaluated for the suitability of the drug to be formulated as an injectable dosage form to comply with the new drug applications. They are commonly used to deliver medications, vaccines, or fluids directly into the bloodstream or body tissues and stored according to cGMP guidelines.

Keywords:- *Injectable Solutions, Parenteral, Pyrogen-Free Particulate, Medicines.*

I. INTRODUCTION

The progression of injectable solutions over time has been grounded on the foundations of innovations and discoveries made by pioneering scientists, clinics, and laboratories, as well as the effort of the pharmaceutical industry to incorporate them into practical and applicable products. Hence, development of drugs that are ideal candidates for injections is desired, particularly by developing new injectable formulations of small molecules, such as hormones, antibiotics, and proteins that are very soluble in organic solvents but poorly soluble in water [1].

Injection or parenteral dosage forms consist of sterile preparations intended to be given by injection. These are chemically stable and free of particulate contamination, and they permit continuous administration of a drug. A stable, biocompatible injectable solution is a popular choice for the safe and effective delivery of drugs.

In addition to injection of sterile drug solutions, commercially available injection products include depot parenteral preparations of drugs dissolved in low viscosity, lipophilic solvents. When administered intramuscularly, these preparations exhibit prolonged drug release over intervals of days, weeks, or months. Together with injectable emulsions and liposomes, the parenteral route of delivery affords unique opportunities for achieving and maintaining high blood levels of biopharmaceuticals, including proteins and peptides, as well as insoluble etoposide and taxol, which are poorly absorbed when taken orally [2]. An injectable emulsion is a liquid preparation containing oily droplets dispersed in aqueous vehicle. It is a heterogeneous system with two immiscible liquids. An injectable emulsion consists of a hydrophobic drug in an oil-in-water emulsion system. Protein and peptide compounds can also be formulated as injectable emulsion systems. The oily phase is prepared by dissolving the drug in edible oils. For preparing injection emulsions, the oily phase should not produce irritation or toxicity to the tissue. Examples of oils used in injectable emulsion formulations are soybean oil, corn oil, castor oil, peanut oil, safflower oil, and cotton seed oil. The emulsifying agent is also an important factor in preparing injectable emulsions. Generally used emulsifying agents are nonionic surfactants like polysorbate 80. To prepare injectable emulsion formulations, these oily phases, aqueous phases, and emulsifying polymers can be selected. Furthermore, injectable emulsion preparation techniques can be selected based on the formulation properties [1].

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Injectable solutions refer to clear, sterile pharmaceutical dosage forms, containing the active ingredient (or ingredients) dissolved in a suitable solvent or mixture of solvents [2]. It may contain substances such as buffers, tonicity agents, stabilizers, preservatives and antioxidants. The solution is prepared in a container that meets the specifications of the respective route of administration to be proposed. Care must be taken to avoid any unforeseen incident during the handling and evaluation of these solutions, as these problems can lead to serious complications (counted in deaths). The injectable solutions should be free from bacterial, pyrogens and particulate matter. It should be suitable in terms of PH(5.5 to 7.5), osmotic balance, solubility, stability and particle size of dissolved drug. Parenteral preparations should have very narrow limits for their certain characteristics and hence need to be designed very carefully.

Various routes of injections are Subcutaneous (SC), Intramuscular (IM), Intra dermal (ID), Intravenous (IV), Intra articular (IA), Intra ocular (IO), Intrathecal (ITS), Cardiovascular pulmonary route and Epidural. There are different types of solutions for injections package systems, such as Injection vials (Glass and vials), Injection bottles (Glass and polyethylene), Ampoules (With neck closure type and without neck closure type) and Rigid type containers, Flexible corrector type container, and Flexible or Infusion bags.

Injectable solutions are an important dosage form among parenteral dosage forms in the pharmaceutical industry. Injectable solutions play a vital role in the medical field, allowing for the administration of medications and fluids directly into the body. They come in various formulations and are administered through different routes depending on the desired effect. Despite their well-known advantages of giving a rapid onset of action and immediate systemic drug availability, parenteral preparations are less commonly used than oral drugs. They require aseptic conditions for both manufacturing and administration, and they generally involve use of needles and syringes, which can cause pain and anxiety for patients, and healthcare workers.

The prime function of Research and Developments in pharmaceutical companies being that of discovery and development of the new medicines [2]. The pharmaceutical companies spend more than 35% of their overall budget for research and development. This is a time-consuming and complex process. However, the continuous development of innovative injection techniques, coupled with enhanced safety precautions, will further enhance the efficiency and efficacy of injectable solutions, benefiting patients worldwide. Injectable solutions serve as an essential tool in modern medicine, contributing to the improvement and advancement of healthcare practices.

II. FORMULATION OF INJECTABLE SOLUTIONS

Injectable solutions are sterile preparations intended to be administered parenterally by means of injections [2]. These dosage forms may be isotonic or hypertonic, containing the medicinal agents dissolved in a suitable solvent, which is usually water for injection or an aqueous isotonic saline solution. An injectable dosage form consists of a single phase liquid system containing solute—if it is a solution dosage form and keeping one additional phase of a therapeutic system—if it is an emulsion or suspension dosage form. The present work deals exclusively with preparation of injectable solution as dosage form.

The main consideration in formulating injectable solution as dosage form is selection of ingredients, which comprise drug substance, diluent, preservatives, other excipients and vehicle. Preparation of injectable solution is usually performed in sterilized conditions so as to maintain the sterility of the product. Therefore, sterilization of final product is one of the most crucial steps and can be achieved by proper selection of sterilization technique including folding filtration, thermal sterilization, chemical sterilization, radiation sterilization and filtration sterilization[1].

- *Ingredients and Excipients Selection*

Considering the nature of injectable dosage forms, injections are most carefully prepared. The ingredients should be selected with utmost care and precision. There are various requirements that injectable dosage forms should satisfy. The injectable solutions should be isotonic. Heterogeneity and turbidity should be minimal. The compounds utilized should be free from any toxic side effects. All needs of the patients, intended effects, and the subject to be therapeutically treated should be taken into account while selecting the ingredients. Now, after considering the nature of the dosage form, the vehicle with which the drug is to be developed should be taken into account. For novel dosages forms development, ideally, the desired vehicle for drug development should be parenteral dosage forms possessing Liquid state, Aqueous solubility, and is Non irritating [2].

Injection or parenteral dosage forms consist of sterile preparations intended to be given by injection. They are free from particulate matter. They consist of preparations for either local or systemic effect. There are two broad classes of injectable dosage forms. They are parenteral formulation and parenteral device. Parenteral formulations: The parenteral formulations are either sterile solutions or suspension of drug substances for injection. They consist of vehicles designed to reformulate drugs into the desired parenteral form. Some active compounds are presented in solid state, while for others injectable forms are poorly soluble forms, i.e. salts, enamines, complexes, etc. Parenteral device: Parenteral devices are instruments for the delivery of drugs, nutritional fluids, blood derivatives and other preparations by the parenteral route [1].

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The delivery is usually achieved by using hypodermic needles in conjunction with syringes or automatic injection systems. Injections include a variety of therapeutic agents. The ingredients utilized are Free from particles, Free from toxic effect, Non irritating, Sterile and Pyrogen free, Isotonic, Stable i.e. No degradation over the period of time, Soluble.

➢ *Sterilization Techniques*

Various sterilization techniques can be adopted to ensure that the injectable solution is devoid of any microbial contamination. Heat sterilization is the most common and inexpensive method for sterilization. Among the most frequently used methods for the sterilization of Injectable pharmaceutical products, steam sterilization is the simplest, most reliable, and reproducible method available. The two commonly used methods of steam sterilization are the gravity displacement process and the pre-vacuum process [1].

The gravity process requires the steam to enter at the top of the sterilizer chamber, forcing the air, which is denser than steam, out of the bottom through the drain valve. The steam must displace all the air in the chamber to ensure thorough steam penetration into the load. To monitor the efficacy of the sterilization process, indicators (chemical or biological) should be used [2].

III. TYPES OF INJECTABLE SOLUTIONS

Injectable solutions are classified into two types: 1) Aqueous solutions and 2) Oil based solutions. Each of these types has its own consideration and standards. Understanding their uses is very essential to evaluate the clinical efficacy of injectable solutions as dosage form, also to consider its drugs and solvents.

➢ *Aqueous Solutions*

Solutions in which the aqueous medium is the vehicle are called aqueous solutions. Such injections are usually isotonic with the body fluids and are adjusted to the desired pH to avoid tissue irritation [2]. In case of stability problems, aqueous solutions are also prepared and stored under frozen state (–20 to –80°C). Aqueous solutions can be prepared by 1) Simple mixing of ingredients 2) Heat method and 3) Sterile filtration method. The aqueous solutions are further classified into 1) Drug solution, 2) Co-solvent system, 3) Hydro-alcoholic solution, 4) Macromolecular solutions, and 5) Oral solutions [1].

➢ *Aqueous Solutions*

The simplest injectable dosage forms are aqueous solutions. They have a unique combination of properties such as high bioavailability, stable pharmacokinetic and clinical drug-response profiles, and ease of preparation and storage 3. These dosage forms can also deliver high doses of medication rapidly by parenteral administration. However, they cannot incorporate drugs with a high molecular weight, possess poor solubility, or undergo hydrolysis, oxidation, or precipitation 1.

It can be stated that aqueous solutions represent an intermediate stage in a complex dosage form continuum, which enhances their clinical efficacy as a dosage form in pharmaceutical and clinical settings.

➢ *Oil-Based Solutions*

Oil-based solutions possess a specific gravity of less than one relative to water and have the advantage of long-term depot injection, which might reduce the formation of advanced therapy medicinal product sites. Oil-based solutions are commercially available for depot formulations of lipophilic drugs, for example, classical paliperidone palmitate, medroxy-progesterone, haloperidol decanoate, and testosterone [3]. In addition, oil-in-water emulsions with a low oil wetting angle have been developed. However, oil-based solutions typically released drug for more than weeks or even several months in vivo, independently of the route of administration, as systemic depot injection, a depot applied into body cavities or intranasal and conjunctival application.

Pharmaceutical oil-based injectable solutions can thus be classified into classical solutions with dissolved drug, stand-alone oily suspension and emulsified oil-based formulations that typically contain an oil-based carrier and a second carrier such as surfactant, polymer, or solid carrier. Classical solutions with dissolved drug are the simplest approach. They have the advantage of fast and easy preparation, long-term stability, and low viscosity. However, they are limited and commercial depots of this approach exist only for lipophilic drugs. Lipophilic drugs less than 2% are prohibited to be used in this oil-based solution. In addition, oil-based solutions may spread at the injection site resulting in a suboptimal release and tissue irritation.

IV. EVALUATION OF INJECTABLE SOLUTIONS

Injection solutions, whether in vials or ampoules, must comply with numerous physical, chemical, and biological tests. However, tests for pyrogens and sterility must be executed by following suitable pharmacopoeias or methods [2]. Furthermore, injectable solutions must be evaluated for compatibilities, such as toxicity, irritability, etc.

➢ *Sterility*

One important feature of injectable solutions is sterility. Sterility can either be done by using a biological indicator or filter paper. Filter paper is prepared as such that it is saturated directly with an organism. Then it is placed in the flask along with the solution. So if a microorganism survives, the filter paper should turn red. So its presence can be detected by redness [1].

➢ *Ph*

pH determines the ionization of the drug and affects its stability. pH changes before and after incubation were measured by pH meter. 1% w/v of drug is pipetted out into 100 ml of water for injection. pH is determined by pH meter. The system should be calibrated with buffer solutions before doing the test.

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➢ *Drug Content*

It determines the actual dosage of the drug in the formulation. Hence it helps in checking the accuracy of the weight and the uniformity of the drug in different batches of the preparation. 10 ml of solution is taken out, and then the solution is diluted to 100 ml with 0.1M NaOH. The estimation is made by using a UV spectrometer.

➢ *Filtration*

Filter the formulated injection through 0.2 µm filter paper and ambulate it. The solution is filtered using 0.2 µm membrane filter paper and white cotton. The formation of blockages takes place due to drugs.

➢ *Viscosity*

Viscosity determines the flow characteristics of the formulation. It is determined by the viscometer.

➢ *Physical and Chemical Tests*

Injectable solutions are clear, sterile preparations containing medicinal substances dissolved in a suitable vehicle and are free from particulate matter. Biocompatible compounds are utilized in the preparation of injectable solutions that display a gradual release of the medicament, thus prolonging the effect of the drug. Pharmaceutical product quality is consistently tested using physical and chemical tests before marketing. The physical and chemical tests employed in the evaluation of injectable solutions will be discussed. These solutions are subjected to various tests to analyze their physical properties like solubility and stability, particle size, refractive index, and chemical properties like pH, percentage of drug content, and sterility [2]. The results of all these evaluations are as expected when compared to the values from the literature.

Pharmaceutical products need to be tested based on predefined criteria at the time of their development and also should be investigated at the desired intervals during their shelf life for good product quality. Quality control tests are important to screen the product for failures and assure the potential of the product to deliver the desired therapeutic effect on administration. The study done aimed to formulate and evaluate injectable dosage forms from a medicinal compound and ensure that the set objectives were achieved. The injectable form of Dasatinib was developed and has met the designed quality evaluation parameters. The formulation passed all the evaluated physical and chemical tests, thereby meeting the standard requirements of injectable dosage forms. Thus, the formulated dosage form was found to be stable, effective, safe, useful, and favorable for the targeted drug [1].

➢ *Biological Evaluation and Compatibility*

In pharmaceuticals, injectable solutions typically refer to clear or slightly opalescent solutions, free from inclusion or suspended particles. Parenteral preparations in the liquid state contain solutes that are to be administered parenterally after sterilization or sterilization of the product after the preparation is sealed in containers. An injectable solution is a sterile preparation that is free from foreign particles, has no or few dissolved gases, and forms a homogeneous mixture that can be readily injected in a living organism through sterile needles [2]. The emergence of biological products (Biopharmaceuticals) has led to considerable growth in the injectable drug market. Biopharmaceuticals such as monoclonal antibodies and proteins are mainly available in liquid formulations which are injected as a solution (pH 6-8) to avoid protein instability. It has been reported that injectable formulation development is more complex than oral formulations and requires specialized infrastructure and knowledge to handle [1].

The injectable solutions are examined for particulate contamination and there is a need for considering the biological aspects of parenteral products. It has been established that for the marketed injectable solutions, a total of 18 different biological and compatibility tests are recommended by the F.D.A. and have been classified into 4 stages based on the degree of testing; the compatibility tests are additionally required tests on IV fluids connecting devices after the evaluation of injectable solutions. Materials for construction of containers, closures and equipment that may have direct contact with drug products are examined for extractables and leachables.

In determining the clinical efficacy of injectable solutions, physical compatibility is primarily related to compatibility in respect to similarity in solubility, similar effects on viscosity and therefore ensuring no precipitation, no organic surrounding or, precipitating a drug compound. Actions and influence of such physical properties on its clinical efficacy after parenteral delivery have also to be monitored. Further this compatibility is an essential prerequisite for successful utilization of any and injectable solutions in a medical settings. It must be noted that the basic compatibility ensures storage and development aspects; also formulation substitutes, product compounds etc. But utmost compatibility is required when involving large volume injectables, or bio-pharmaceutical injectables dose formulations [2].

A multitude of properties will affect and as such needs to be checked, a few of the most significant ones would include drug solubility, pH and buffer composition, viscosity and molecular weight, metabolism and nourishment, degrading and surfactants, and polymer charge density amongst others. Prior to initial preparation as a dosage form, injection compatibility can be checked by pH matching or solubility ratio. pH matching and solubility ratio greatly influences viscosity; pH variability can offer 20 to 200 fold change in viscosity on a marginal 1 to 2 unit change in pH [4].

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V. CONCLUSION

Injectable solutions are sterile preparations that contain a drug or therapeutic agent dissolved in suitable solvents to aid the parenteral administration of drugs. These can be introduced into the body through various routes such as intravenous, intramuscular, and subcutaneous. Unlike other dosage forms, these are intended for direct introduction into the systemic circulation, thereby providing rapid drug effects. Injectable solutions offer a greater bioavailability of drugs and are used to prevent the degradation of certain drugs and fluids in the gastrointestinal tract. Pharmaceutical parenteral preparations for injection play an important role in the health care system, and it is vital to ensure the quality, safety, and efficacy of such preparations. The injectable products are classified in different types based on their complexities like simple injectables, biologics injections, liposomal injectables, and complex injectable drug delivery devices. Knowing the regulations to be considered while developing injectable would help in maintaining health care standards and quality housing [2]. Understanding Good Manufacturing Practices (GMP) guidelines, product specific regulatory pathways, quality attributes, testing methods, and facilities required for production and testing would help in navigating through the hurdles of injectable product development.

In the development of novel approach for injectable solutions, the increasing complexity of drugs, excipients, and drug development processes, requires a need for critically assessing current analytical procedures and identifying new technologies. To remain competitive globally, it becomes essential to implement a well-established and documented quality by design approach and critical quality attributes for injectable medicines which may reduce time-consuming process and product waste management. These formulation approaches can also create complex products that deliver drugs to specific tissues to combat the effects of systemic drug administration, such as drug detoxifications. The injectables market is growing rapidly, driven by scientific and technological advancements in the pharmaceutical field [2]. The fastest-growing segment in the parenteral market is injectables, especially biotech products. Due to their therapeutic efficacy and safety, complex injectables are presently the drug formulation of choice. As the first generation of complex injectables such as BCG (Bacillus Calmette–Guérin) injection, and insulin injection has been commercialized successfully, activities regarding the next generation complex parenteral products have been intensified [1].

Therefore, a large variety of injectable treatments are used nowadays in general medicine, orthopaedics, dermatology, urology, and gynecology. A total of 23 conditions treated by injectable treatments were found, with 5 being most common: knee osteoarthritis (21 injections), chronic biceps tendinopathy (5 injections), trigger finger (4 injections), shoulder rotator cuff (4 injections), and hand osteoarthritis (3 injections). Although evaluating effectiveness of injectable solution is challenging due to variations in study design, patient population, methods, and injectate quantity. Nevertheless, an expert opinion is presented for each injectable solution based on observed results [1]. In addition, the new technologies that revolutionize the development of novel approach for administration of medicines gives a promising avenue not only on the enhancement of the efficacy of injectable solutions but also on a better compliance to the patients.

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