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Review Article

# FORMULATION AND EVALUATION OF AN INJECTABLE SOLUTION AS A DOSAGE FORM

**Thomas Sneha\***, Mr. S Mahendran, R. Selvakumar

Department of Pharmaceutics, Nehru College of pharmacy, pampady, Thiruvillwamala, Thrissur, Kerala, India

### ABSTRACT

The present study will outline formulation and the evaluation methods of injectable dosage form. The various initial formulations of the developed and those are examined for drug release profile, bioavailability, and clinical effectiveness and for the pilot plant studies and production scale-up. The drug that we need should be most convenient and in proper form then only it reaches to the desired site of action. This is greatly influenced by which the type of dosage form of the drug. Since, injections include much variety of therapeutic agents. Injections are sterile, pyrogen limited, that is, bacterial endotoxin units limit, preparations intended to be administered parenterally. It is well recognized that the advantages of parenteral injections are immediate systemic drug availability and rapid onset of action.

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Sneha Thomas, Department of Pharmaceutics, Nehru College of Pharmacy, Pampady, Thiruvillwamala, Thrissur, Kerala, India

### INTRODUCTION

The prime function of Research and Developments in pharmaceutical companies is to discover and to develop the new medicines. To achieve these objectives are not easy, in this a small percentage of the synthesized chemical compounds become medicines. <sup>1</sup> A generic drug is the same as a brand name drug in its dosage, safety, strength, how it taken, how it performance, quality and intended use. <sup>2</sup>

The U.S FDA doesn't provide regulatory formal definition for excipients, and then also, according to guidance on nonclinical safety studies, new excipients are inactive ingredients that added intentionally to the therapeutic and diagnostic products. <sup>3</sup> The desired product type must be determined as possible to establish the framework for product development, before formulating a drug substance into a dosage form. <sup>4</sup>

Before a medicinal agent is formulated into one or more dosage forms, the factors to considered are such therapeutic matters are the nature of illness, in which the manner it is treated (locally or systemic action), age and patient's anticipated condition. <sup>4</sup> The drug that we need should be most convenient and in proper form then only it reaches to the desired site of action. This is greatly influenced by which the type of dosage form of the drug.

An ideal dosage form should be:-

- It should be safe and easy to administer.
- It should be easy to handle.
- It should be easy to produce and manufacture
- Provide high patient compliance.
- Should be physically and chemically stable.
- It should maintain its therapeutic activity throughout the shelf life. <sup>5</sup>

## INJECTABLE SOLUTION

Injections include much variety of therapeutic agents. In USP more than 400 injections products are listed.<sup>6</sup> The dosage forms that conveying the drug by means of the injection through skin or the mucous membranes.<sup>7</sup> Some medicines cannot be given by oral due chemical action of enzymes.<sup>8</sup>

The most convenient and simplest form of an injectable product is an isotonic aqueous solution, which have the pH close to that of blood and the body tissues (pH 7.4).<sup>9</sup> Injections that prepared in containers, antimicrobial agents also will add. These are intended to suppress the growth of micro-organisms accidentally inoculated into the solution.<sup>10</sup> Aqueous solutions which given through intramuscularly, the release of drug may be controlled by:

- i. Increasing the vehicle viscosity by using MC, CMC, or PVP and thus decreasing the molecular diffusion and localizing the injected drug.
- ii. Formation of complex with macromolecules like MC, CMC, or PVP from which the drug dissociates at controlled rate.<sup>11</sup>



**Figure 1: An injectable solution**

### Guiding principles for simple parenteral solutions

#### Selection of injectable volume

Pharmacopoeias classify the injection into types:-

- Small-volume parenterals: These are usually 100ml or less. Depends on the intended use these are packaged in different ways.<sup>12</sup>
- Large-volume parenterals: a single dose injection which intended for IV use and is packaged in containers, containing more than 100 ml.<sup>13</sup>

SVPs are usually given rapidly in small volume are called as a bolus. In LVPs also they added like 5% dextrose and 0.9 %sodium chloride injection or infusion is administered through IV infusion. Based on the pharmacokinetics of the drug the bolus or infusions are selected. A bolus administration is preferred for intramuscular or subcutaneous injections. Subcutaneous

route is used if the injection volume is less than 1- 1.5 mL and through intramuscular route usually no more than 2 mL. In the formulation of a solution product, the main step is to select the administration volume and concentration.<sup>14</sup>

### pH and Tonicity requirements

#### pH considerations

The generation of pH/stability and pH/ solubility profiles is the main step in the selection of pH in a formulation. For the maximum physiological acceptability, the target pH is approximately pH 7.4. When the dosing through IV route, a wide pH range can be tolerated and a rapid dilution wit blood also can be achieve. pH value ranging from 2 to 12 can be tolerated in these situations when intramuscular administration is uses the dilution rate is slower and it is further decreases when the subcutaneous route is administered. Tolerability of a formulation depends on its buffering capacity.<sup>14</sup>

**Table 1: Buffers used in the approved parenteral products**

Buffer	pH Range
Acetate	3.8 -5.8
Ammonium	8.25 – 10.25
Ascorbate	3.0 -5.0
Benzoate	6.0 – 7.0
Bicarbonate	4.0 – 11.0
Citrate	2.1 – 6.2
Diethanolamine	8.0 – 10.0
Tromethamine (TRIS, THAM)	7.1 – 9.1

#### Tonicity consideration

All parenteral products should be isotonic, especially osmolarities should target between 280 and 290 mOsm/L during a formulation. For LVPs isotonicity is very essential. Either the rapid dilution with blood that will occur after injection or prior to administration the product itself diluted with an LVP, a wider range of osmolarities can be tolerated in SVPs. For hypotonic solutions hypertonic solutions are preferred since the risk of haemolysis associated with the hypotonic solution. By the use of excipients the hypotonic solutions are avoided, since the sodium chloride to raise the osmolality. To avoid the tissue damage parenteral formulations should be isotonic with human plasma.<sup>14-15</sup>

#### Choice of excipients

In pharmaceutical products the formulations should developed by using excipients. In parenteral products the quality, particularly in microbial terms of excipients should be considered necessarily. The injectable grades are usually used for parenteral excipients which have strict bio burden and endotoxin limits. The excipients have pharmacopoeial grade also acceptable. But this is usually to apply In-House microbiological specification limits.<sup>14</sup> The integral part of pharmaceutical products development is excipients, to achieve the desired product profile (stability and efficacy).<sup>15</sup> Excipients are

important to assure safety (antimicrobial preservatives), to minimize pain and irritation on injection, and to control or prolonged drug delivery.<sup>16</sup>

### General guidance for developing formulations of parenteral drugs

The following factors should follow, when a drug is given through parenterally rather than orally:

- i. The onset of action of drug is mostly more rapid but the duration is short.
- ii. Since the drug potency tends not to alter immediately by the liver or stomach, so the dosage form is often smaller.
- iii. The cost for the therapy is higher.<sup>17</sup>

### Pharmacokinetics of the drug:

The absorption rate for routes of administration other than intravenous or intra-arterial, distribution, metabolism and excretion of drugs have effect on route of administration that selected, based on the type of formulation. For example: a drug having a rapid pharmacokinetic profile, there is need of development of modified release dosage formulations. Pharmacokinetics also affects the drug dose and the dosage regimen.<sup>18</sup>

### Drug solubility:

The formulation must contain a co-solvent or a solute which sufficiently increases and maintains the drug in solution, if the drug is insufficiently soluble in the water at the dosage required. Solubility is the major factor that gives the concentration in the dosage form. A dispersed system dosage form developed, when simple formulation additives do not result in the solution.<sup>18</sup>

### Drug stability:

If the drug possesses significant degradation problems in the solution, then freeze dried or sterile solid dosage form should be developed. Sometimes drug concentration affects the stability in turn, affect size and the packaging system used also. Stability determines the storage conditions since it indicates the drug expiration date.<sup>18</sup>

### Advantages of parenteral products:

- ✓ These are useful in :-
  - Unconscious patients.
  - Uncooperative and unreliable patients.
- ✓ Onset of action of drugs is faster; hence it is suitable for emergency.
- ✓ Patients with vomiting and diarrhea.
- ✓ These are suitable for irritant drugs and drugs with high first pass metabolism.
- ✓ Drugs are not absorbed orally.
- ✓ Drugs destroyed by digestive juices.

### Disadvantages

- ✓ Parenteral preparations should be sterile and expensive.
- ✓ They require aseptic conditions.
- ✓ Cost
- ✓ They can't easily self-administered.
- ✓ Causes local tissue injury to nerves, vessels, etc.

Parenteral product formulation depends upon the understanding of several factors that dictate the choice of formulation and dosage form.<sup>19</sup>

## METHODOLOGY

### Development of parenteral products

Based on the requirements of sterility of the finished product parenteral products manufacturing process considered.

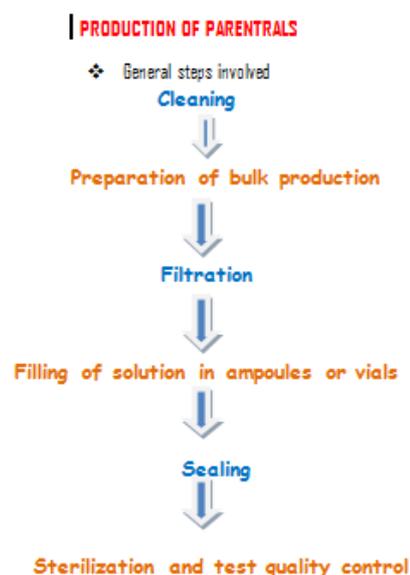


Figure 2: Production of parenterals

### 1. Filtration

If the product is a solution, after its compounding, it should filter. Filtration process is employed for to clarify a solution and removing particulate matter down to 0.2µm in size will eliminate the micro-organisms. It is accomplished by cold sterilization. Filters mainly functions by:

- Sieving or screening:

The particles are retained on the surface of the filter by sieving

- Entrapment or impaction:

If the particles smaller than the dimensions of the pore, they impact on the surface of the pore.

- Electrostatic attraction

Opposite charged particle to that of the surface of the filter pore to be adsorbed on the surface.

Membrane filters are used for parenteral preparations because they have high effective in particle- retention, non-shedding property, non- reactivity and have disposable characteristics also. The most common membranes are made up of cellulose esters, nylon, polycarbonate, PVDF, and Teflon. Membrane filters are disposable type and can be discarded after use. It should clean thoroughly while using. Most pharmaceutical industries that preparing parenterals uses 0.2  $\mu\text{m}$  membrane filter.<sup>19</sup>

## 2. Filling

The solutions which sterilized through filtration are to be filled under the aseptic conditions. During the filling of product to the containers, should be for the prevention of contamination, especially the product is sterilized by the filtration and will not be sterilized in to the final container. The second one is called as aseptic fill and by using media fills it is validated. A liquid is more easily exposed uniformly into the container having the narrow mouth than is used for solid. Liquids which are mobile are easier to transfer and subdivide than viscous or sticky fluids, since these require heavy-duty machinery for the rapid production filling.<sup>19-20</sup>

### Liquid

The filling of liquids into containers with high accuracy involves mainly three methods

- Volumetric filling
- Time/pressure filling
- Net weight filling

Volumetric filling machines have pistons or peristaltic pumps. These are most common used method. Time-pressure filling is used for filling of sterile liquids. A filling system is connected by a production tank that equipped with a pressure sensor. The sensor is used for the measurement of pressure and transmits values PLC system that controls the product flow from the tank to the filling manifold. The product is driven by using pressure mainly uses nitrogen with no pump mechanism. Time/pressure filling is preferable usually with the proteins that are sensitive to shear forces.<sup>19</sup>

## 3. Sealing

The filled containers should be filled as soon as possible to prevent the contents being contaminated. It represents the final aseptic procedure.<sup>20</sup>

### Ampoules

Sealing of ampoules are done by melting of the portion of the glass neck. There are two types of sealing:-

- Pull –seals
- Tip-seals (bead –seals)

Tip seals are employed by melting the glass at the tip of the ampoule neck to form a bead like and close the opening. This is performed in a high temperature gas oxygen flame. Pull-seals are performed by heat the

ampoule neck below the tip. The ampoule to be seal is rotated in the flame from a single burner. The tip is grasped and then pulled quickly from the ampoule body, when the glass is softens. Pull sealing process is slower one, but the sealing done by this is more secure than that of tip-sealing.

### Vials and bottles

By closing the opening using the rubber closure (stopper) the glass or the plastic vials are sealed properly. This should be done by after filling with care, to prevent the contamination of the contents inside. Increased chances for contamination are the large opening in the vials than the ampoules. The open containers must be protected from contamination, especially with the blanket of HEPA filtered laminar airflow. By using the aluminium caps the rubber stoppers are held in appropriate place. Rubber closures that uses for the intravenous administration have a permanent hole through the closure.<sup>19</sup>

## 4. Sterilization

Sterilization of parenteral products should be done after sealing it to the final container that is called as terminal sterilization. It should done within as short time as that possible after the filling and sealing are fully completed. This is accomplished usually by the thermal process. Radiation sterilization also will do to the parenteral finished products in sometimes. The care should be taken in the effect of the elevated temperature on the stability of the products. The elevated temperature that required for the sterilization by thermal process is adversely affects in many products like both pharmaceutical and biological. Non thermal methods are used for the heat-labile products. These non thermal methods include filtration through the bacteria retaining filters. Aseptic conditions should be strictly followed for all operations, and then only the contamination is not introduced into the filtrate. Dry-heat sterilization is performed for few dry solids that are not adversely affects by the high temperatures and that require long period of heating. For the sterilization of glassware and metal ware mostly performs the dry-heat sterilization process. After the sterilization process all the equipment will be sterile, dry and pyrogen-free. Autoclaving (saturated steam under pressure) is the most common method used for sterilization process. It is the most effective sterilization method that used for the aqueous liquids or substances, since it can be reached or penetrated by the steam.<sup>19</sup> Radiation sterilization is a terminal sterilization method with an ionizing radiation (gamma rays). There is an advantage for the applying on drugs in their final container, that also without any rise in temperature. One of the disadvantages is the possible formation of radiolytic products which leads to a change in the color and odor of the product.<sup>21-22</sup>

## 5. Packaging of parenterals

Types of containers:

- A. Glass containers
- B. Plastic containers

### Glass containers

In most of the SVIs glass is used as the material choice for the containers. Principally glass containers are composed of silicon dioxide with varying amounts of

various oxides such as potassium, sodium, calcium, magnesium, aluminum, boron, and iron. Silicon oxide tetrahedron forms the basic structural network of glass. Boric oxide will enter into the basic structural network and the other oxides do not enter into this structure.<sup>19</sup>

**Table 2: USP glass types**

Types	General Description	General Use
	Highly resistant borosilicate glass	Buffered and unbuffered aqueous solutions All other uses.
	Treated soda- lime glass	Buffered aqueous solutions with pH below 7.0 Dry powders Oleaginous solutions.
	Soda- lime glass	Dry powders Oleaginous solutions
NP	General purpose soda-lime glass	Not for parenterals. For tablets, oral solutions, ointments, external liquids

### Plastic containers

Sterile preparation like large-volume parenterals, ophthalmic solutions and mainly in small volume parenterals uses thermoplastic polymers as packaging materials. The principal advantage of plastic while comparing with glass, it is not breakable easily and reduction in weight also. In large-volume intravenous fluids currently uses the flexible bags of PVC (polyvinyl chloride) or select polyolefin. This having major advantage that there is no requirement of air interchange.<sup>19</sup>

### Rubber Closures

Rubber closures are made up of using milling machines by multiple ingredients plasticized and mixed together at an elevated temperature<sup>19</sup>. The allergenic proteins from the natural rubber vial closures or stoppers that release into aqueous pharmaceuticals induce some allergic reactions in individuals with latex allergy receiving medications from such vials.<sup>23</sup>

## EVALUATION

### pH

pH is the measure of concentration of protons ( $H^+$ ) in a solution that is the potential of hydrogen. It is the identification of a substance how it is acidic or alkaline by using a scale of acidity from 0 to 14. More the acidic solutions having lower pH, and more alkaline solutions having higher pH values. pH value less than 7 are acids and pH of greater than 7 are alkaline. The neutral solutions that are the substances which are not acidic or alkaline have a pH value of 7<sup>24</sup>

### Particulate matter

In injections and parenteral infusions particulate matter are considered as, the mobile undissolved particles, other than the gas bubbles, unintentionally that present in the solutions. There are two procedures involved in the determination of particulate matter.

Sub-visible particles

❖ Method 1 (light obscuration particle count test)

❖ Method 2 (microscopic particle count test)

Injections and parenteral infusions are examined for sub-visible particles usually method 1 is preferred mostly. Then also some preparations by light obscuration particle count test that followed by microscopic particle count test is necessary to test. No all parenterals are examined by method 1 such as preparations that reduced clarity or increased viscosity, since these tests are carried out according to method 2. For example: colloids, emulsions. Particulate matter contamination is still having a potential cause to the harm patients.<sup>19-25</sup>

### Sterility

Sterility testing is to identify the presence or absence of viable micro-organisms in the sample.<sup>26</sup>

#### A. Immersion (Direct inoculation)

It requires the test article to be inoculated directly into test media.<sup>27</sup>

#### B. Membrane Filtration

It requires the test article to pass through a size exclusion membrane which capable of retaining micro-organisms. Filter should be rinsed. Then the membrane is transferred to the test medium.<sup>27</sup>

**Media types:** mostly used Soya-bean casein digest (SCD) and Fluid thioglycollate media (FTM).<sup>28-29</sup>

**Incubation period:** all test containers should incubated at temperatures as specified in the pharmacopoeial method, that is for each test media at least 14 days, depends on whether filtration or direct inoculation test is used.<sup>28-29</sup>

### Stability

Stability is defined as the capacity of a drug substance or drug product to remain within the established specifications to maintain its identity, strength, quality and purity throughout the retest or expiration dating period. The objective of stability study is to determine

the shelf life, namely the time period of storage at a specified condition within which the drug product still meets its established specifications. Stability testing also gives information about drug vulnerability to degrade by oxidation, hydrolysis, isomerisation, polymerization, decarboxylation, moisture, heat and light. Stability study is performed for specific time at specific environmental condition according to ICH guideline.<sup>30</sup>

## DISCUSSION

This report presents a summary of pharmaceutical development of an injectable solution. It emphasizes a science and risk based approach to product and process development and presents findings as a knowledge-based report, where relevant, supporting data have been summarized in appropriate dosage form or illustrations. Formulation development involved the use of prior knowledge and structured experimentation to investigate the relationship between formulation component levels, API attributes and the drug product quality attributes. Using prior knowledge the material attributes and process parameters, which could have an impact upon final product quality, were identified.

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