

**REVIEW****A REVIEW ON FORMULATION AND EVALUATION OF PARENTERALS****S. Gousia Begum,\* D. Maheshwara Reddy, R. Akhila, N. Bilkisfathima, B. Guru Sai Supriya,  
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**Submitted on: 15.06.18;****Revised on: 10.07.18;****Accepted on: 18.07.18****ABSTRACT:**

The parenteral route of administration is the most effective route for the delivery of the active pharmaceutical substances with narrow therapeutic index, poor bioavailability especially for those drugs, prescribed to unconscious patients. To maintain a therapeutic effective concentration of the drug, it requires frequent injections which ultimately lead to patient discomfort. In parenteral drug delivery, major progress has been done in the field of formulation technologies so as to provide a targeted and sustained release of drug in predictable manner. The present article reviews recent patents and major advancements in parenteral drug delivery systems along with general introduction. This article also deals with importance of novel systems in drug delivery to overcome the problems associated with conventional parenteral drug delivery systems.

**KEYWORDS:** in situ Depot forming systems, liposomes, Nano dispersions, noisome, parenteral drug delivery.**Corresponding Author: S. Gousia Begum**  
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**Phone: +91-9703067599****Indian Research Journal of Pharmacy and Science; 17(2018)1513-15121;**  
**Journal Home Page: <https://www.irjps.in>**  
**DOI: 10.21276/irjps.2018.5.2.15**

## INTROUCTION

The term parenteral is derived from two Greek words para means outside, enteron means together, these are intended injection of the drugs through the skin, not rather than alimentary canal, so that active ingredients are administered directly into blood vessel or tissue or organ by using force of gravity<sup>1</sup>.

### Advantages:

- It provides rapid onset of action.
- It provides immediate therapeutic action.
- It can be administered accurate dose.
- It can be given to patient who cannot take oral medication.
- It minimises the first pass effect.
- It provides more bioavailability<sup>2</sup>.

### Disadvantages:

- It should be administered aseptically.
- It provides pain at the site of injection.
- The administration of drug through wrong route may provide fatal effect.
- Self-administration is not possible.
- If pyrogenic preparation leads to very harmful effect<sup>2</sup>.

## Formulation of Parenteral

### 1. Vehicle

### 2. Additives

**1. Vehicle:** These are used for carrying the drug substances or dissolving the drug.

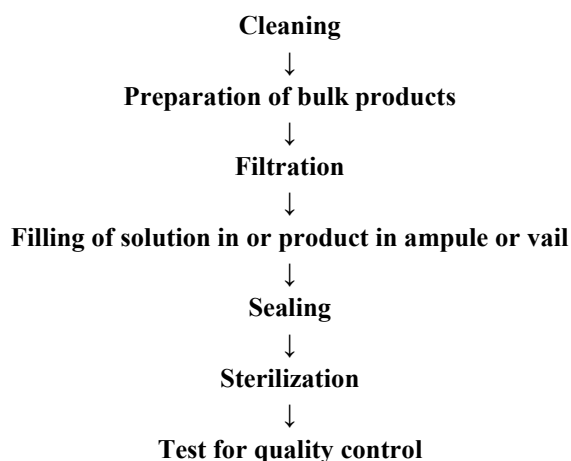
They are two types: a) aqueous vehicles, b) Non-Aqueous vehicles

**a) Aqueous vehicles:** water is used as vehicle for majority of injections because water is tolerated well by the body and is safest to administer<sup>3</sup>. The aqueous vehicle used are

e.g.: Water for injection.

**Water for injection [WFI]:** Water for injection is the most widely used solvent for parenteral preparation<sup>4</sup>.

**Preparation:** The source water usually must be pre-treated by one or combination of the following treatments: Chemicals softening, Filtering, deionization, carbon absorption, or reverse osmosis purification. Preparation for water for injection is shown below:



WFI can be prepared by distillation or by membrane technologies (reverse osmosis or ultra-filtration)

USP: “distillation or a purification process that is equivalent of superior to distillation”<sup>5</sup>

Permissible limits for WFI as per USP are:

- Conductivity ≤ 1.3 μS/cm @25<sup>0</sup> C
- Total organic carbon (TOC) ≤ 500 ppb
- Microbial ≤ 10 cfu /100 ml
- Endotoxin requirement < 0.25 EU/ml

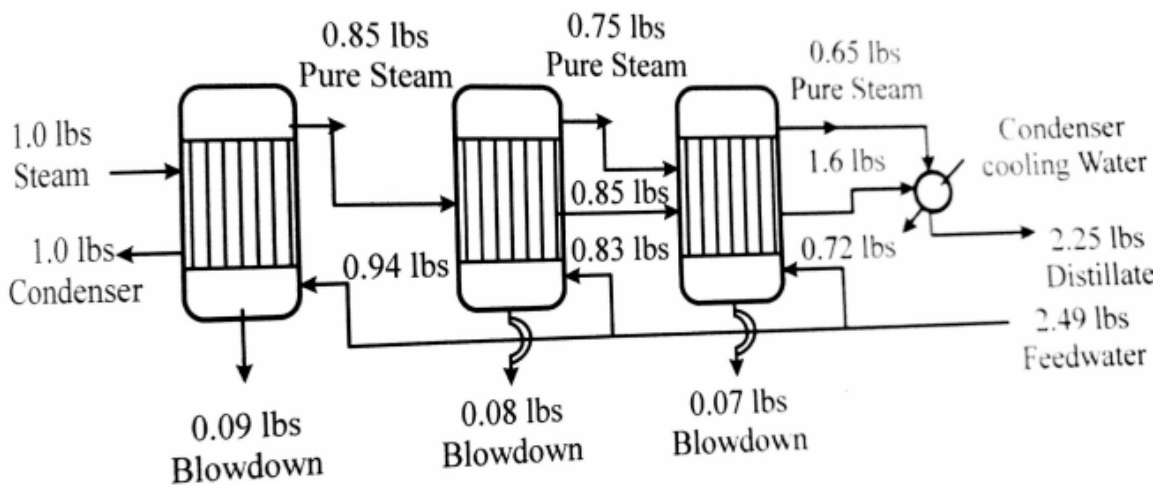
**Preparation techniques for water for injection**

**1. Multi effect still (MES)<sup>6</sup>**

- ✓ Uses plant steam to convert feed water to pure steam

- ✓ Separators allow impurities to drop out of the pure steam
- ✓ Pure steam from first effect used to convert feed water to pure water in subsequent effects
  - 2.Vapor compression {VC}
- ✓ Uses plant steam to convert initial feed water to vapour {pure stream}
- ✓ Pure stream is compressed, elevating temperature
- ✓ Compressed vapour is used to evaporate new feed water, giving up latent heat and condensing as WFI
- ✓ Higher electrical demand, but lower steam demand

**MULTI- EFFECT STILL:**



**Fig 1: Multi-effect Still**

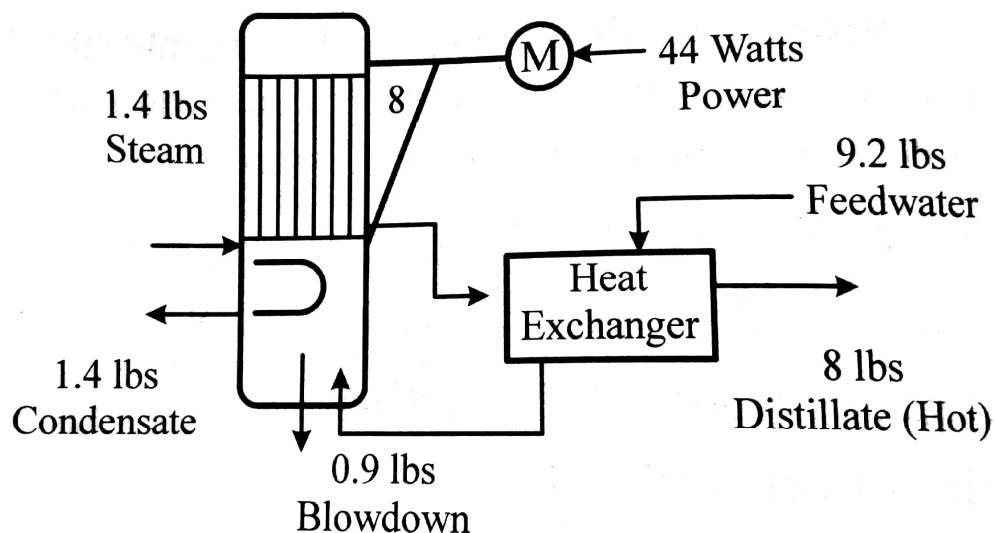
**Vapour compression<sup>7</sup>**

E.g. Water for injection free from CO<sub>2</sub>. Water for injection free from dissolved air.

A number of solvents that are miscible with water have been used as a portion of the vehicle in the formulation of parenteral. These solvents are used primarily to solubilize certain drugs in an aqueous

vehicle and to reduce hydrolysis. The most important solvent in this group are:

E.g. Ethyl alcohol, Liquid polyethylene glycol, Propylene glycol.



**Fig 2: Vapour Compressor**

**B) Non-Aqueous vehicles:** oils and alcohols are most commonly used. Fixed oils like a rachis oil, cotton seed oil, almond oil, sesame oil that are used for depot formulation of medicament for slow release of drug<sup>8</sup>.

These oils are used for delivering insoluble or slightly soluble drugs

E.g.: Dimer caproyl injection by using a rachis oil as vehicle

- Ethyl alcohol is used in the preparation of hydrocortisone injection.

Propylene glycol is used as a vehicle in the preparation of digoxin injection.

**2. Additives:** The USP includes in this category all the substances added to a preparation to improve or safeguard its quality. The adjuvants should be used only when it is absolutely necessary to use them<sup>9</sup>.

Commonly used additives:

- Solubilising agents,
- Stabilizers
- Anti-microbial,
- Buffers
- Chelating agents,
- Suspending agents
- Emulsifying agents,
- Wetting agents
- Cryoprotectants & Lyoprotectants
- Tonicity factors

**a) Solubilizing agents:** These are used to increase solubility of drugs which are slightly soluble in water. The solubility of drugs is increased by using surface-active agents like tweens and polysorbates or by using co-solvents<sup>10</sup>.

e.g.: Dimethylacetamide, Dioctyl sodium sulfosuccinate

**b) Stabilizers:** The drugs in the form of solutions are more liable to deteriorate due to oxidation and hydrolysis. The stabilizers are added in the formulation to prevent this. The oxidation can be prevented by adding a suitable anti-oxidant, such as, thiourea, ascorbic acid sodium meta bisulphate or the product is sealed in an atmosphere of nitrogen or carbon dioxide. Hydrolysis can be prevented by using a non-aqueous vehicle or by adjusting the pH of the preparations<sup>11</sup>

e.g. Creatinine, glycine, Niacinamide, Sodium caprylate

**c) Antimicrobials:** These substances are added in adequate quantity to prevent the growth of microorganisms during storage. So, these substances act as preservatives. Antibacterial agents are added in single dose container where parenteral products are sterilised by filtration method and in multi task containers to prevent microbial contamination<sup>12</sup>.

e.g.: Benzyl alcohol, Benzalkonium chloride, Butyl-P-Hydro benzoate, Thymol cresol

Chloral butanol, phenol

**d) Buffering agents:** The degradation of the preparation which is due to the change in PH, can be prevented by adding a suitable buffer to maintain the desired PH. Buffer systems must be selected with

consideration of their effective range, concentration and chemical effect on the total product<sup>13</sup>.

e.g.: citric acid, sodium citrate, Acetic acid, Sodium acetate

**e) Chelating agents:** Chelating agents are added in the formulation, to chelate the metallic ions present in the formulation. They form a complex which gets dissolved in solvents<sup>14</sup>.

e.g.: EDTA, Citric acid, Edentate disodium, Edentate calcium di sodium

**f) Suspending agents:** The suspending agents are used to improve viscosity and to suspend the particles for a long time.

e.g. Methyl cellulose, Gelatine & Acacia, Carboxy methyl cellulose

**g) Emulsifying agents:** Emulsifying agents are used in sterile emulsions. For these purposes lecithin is generally used.

e.g.: Lecithin's, Beeswax

**h) Wetting agents:** The wetting agents are used to reduce the interfacial tension between the solid particles and the liquid. So as to prevent the formation of lumps. They also act as anti-foaming agents to subside the foam produced during shaking of the preparation<sup>15</sup>.

e.g.: PEG, Theophylline, Povidone, polysorbate 20

#### **i) Cryoprotectants &**

**Lyoprotectants:** These are additives that serve to protect biopharmaceuticals from adverse effects due to freezing or drying of the product during freeze dry processing.

e.g.:sugar such as sucrose, PEG, Dextrin, Glycine & lysine.

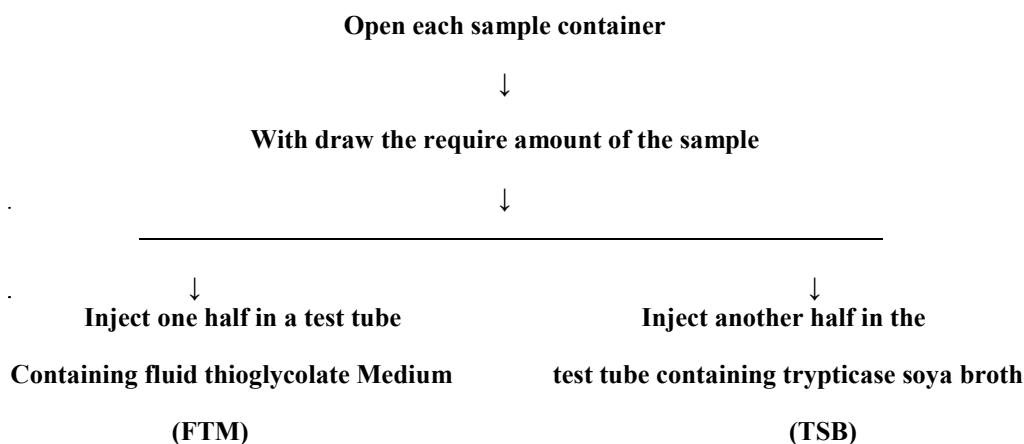
**j) Tonicity factors:** Parenteral preparation should be isotonic with blood plasma or other body fluids. The iso tonicity of the

solution may be adjusted by adding sodium chloride, dextrose and boric acid etc. ..., in suitable quantities. These substances should be compatible within so their ingredients of the formulation<sup>16</sup>.

### EVALUATION OF PARENTERALS:

The following are the evaluation test for the parenteral. They are as follows.

#### 1. Sterility test



Volume of the medium must be sufficient to promote and expedite microbial growth.

Adequate mixing between the sample inoculum and the culture medium must take place to maximise interaction and facilitate microbial growth.

#### **b. Membrane filtration method (MF):**

The steps involved in MF sterility test method are

2. Clarity test
3. Leakers test
4. Pyrogen test

**1. Sterility test:** It is a method carried out to detect confirm absence of any viable form of microbes in product. The method used for sterility test are <sup>17</sup>

a. Direct transfer method

b. Membrane filtration method

a. Direct transfer method: It is a traditional method

1. The filter unit must be properly assembled and sterilised prior to use.
2. The contents are transferred to the filter assembly under strict aseptic conditions.
3. The membrane is removed aseptically.
4. Membrane is cut in half.
5. One half is place in suitable volume of FTM and another in an equal volume of TSB.

**Interpretation of results:**

1. If there is no visible evidence of microbial growth, it may be interpreted that the sample is without intrinsic contamination.
2. If microbial growth is found the sterility test may be repeated.

**2. Clarity test (particulate matter evaluation)<sup>18</sup>:**

1. Particulate matter in parenteral solutions has been recognized as unacceptable. Since the user could be expected to conclude that the presence of visible dirt would suggest that the product is of inferior quality.
2. The entire product should be inspected by human inspectors under good light baffled against reflection into the eye and against black and white background.
3. Any container with visible particle if seen is discarded.
4. Size of the particle that can be seen only be observed by using clarity test apparatus.

**3. Leakers test: [containers or closures integrity test]<sup>19</sup>**

- ✓ Ampules sealed by fusion are subjected for leakers test.
- ✓ It is used to determine if any passage way remains to the outside, that may

cause leakage of the contents or contamination.

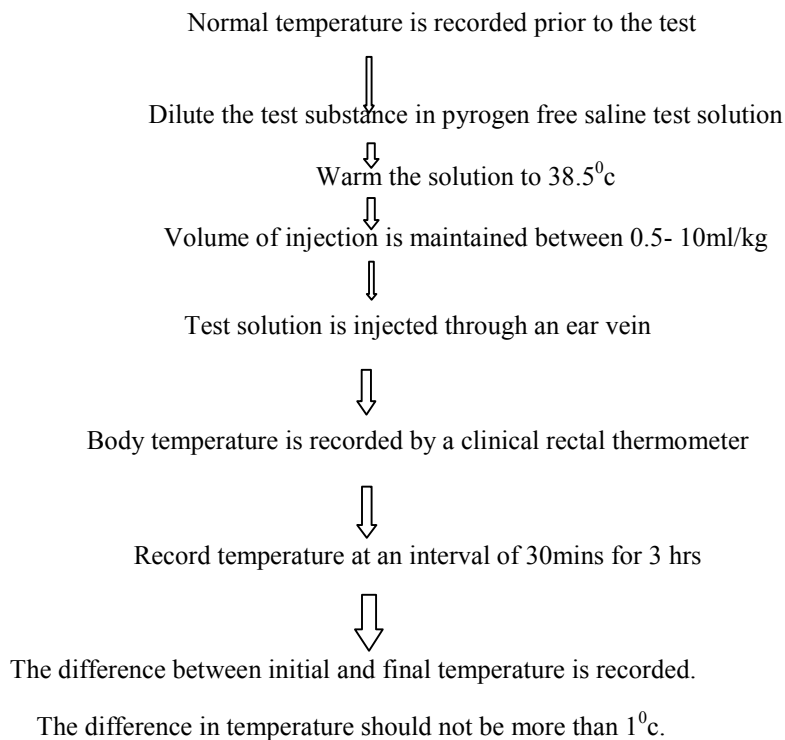
- ✓ This test is usually performed by producing a negative pressure within an incompletely sealed ampule.
- ✓ The ampule is entirely submerged in a deeply coloured dye solution [1% methylene solution]
- ✓ After carefully rinsing the dye solution from the outside colour from the dye will be visible with in a leaker.
- ✓ All the leakers are discarded.
- ✓ Vials and bottles are not subjected to leakers test because the sealing material is not rigid.

**4. Pyrogen test<sup>20</sup>:**

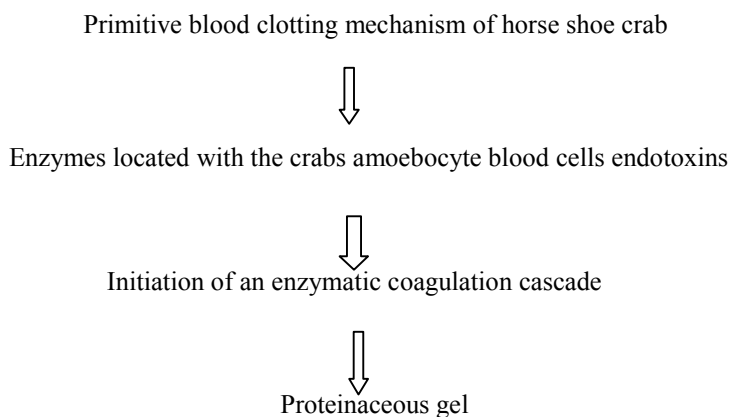
1. Presence of pyrogen may cause fever and alteration in blood coagulation.
2. The tests used for pyrogen detection are:
  - a) Rabbit test
  - b) LAL test

**a. Rabbit test: [Sham test]**

- 1. Rabbits are used as the test animal because they show a physiological response to pyrogens, similar to that of human beings.
- 2. Three healthy adult rabbits of either male or female, each weighing not less than 1.5kg are selected

**Method:****b. LAL test:**

- It is also known as limulus amoebocytelysate [LAL test] or bacterial endotoxins test.
- The test is used to detect or quantify endotoxins of gram negative bacterial origin.
- LAL test is based on the primitive blood clotting mechanism of the horse shoe crab.
- The presence of pyrogen is indicated by the formation of a proteinaceous gel upon incubation of the mixture of LAL reagent and test solution.

**Mechanism of LAL test:**



❖ **Pass-Fail test**

1. If a firm gel is formed -pyrogen present.

2. If an intact gel is not formed -pyrogen absent.

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CONFLICT OF INTEREST REPORTED: NIL ;

SOURCE OF FUNDING: NIL