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Original Article

Quality Control Test's for Parenteral Preparations: A Review.

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Abstract

The present study deals with the elaborated overview of comparative study of in-process and finished product quality control tests for Parenteral products taking compendia specifications of Indian Pharmacopoeia (IP), British Pharmacopoeia (BP), United States Pharmacopoeia (USP), European Pharmacopoeia (EP) and Japanese Pharmacopoeia (JP) into consideration. Injectables occupy a considerable prominence in world market irrespective of diminishing growth in the pharmaceutical market for 2-3 years. The advancements in technology up-gradation and investments have provided immense growth opportunities for Injectable to emerge in the world's pharmaceutical industry in recent years. According to research report, "UK Injectable Market Outlook to 2017", the market is anticipated to grow at a rate of approximately 4.5% during 2012-2017. The increasing need of injectables for diseases like diabetes, infectious diseases and arthritis is primarily driving the market. A lot of investment is being done in research and development of Injectable in order to improve their medical outcomes. Here it is worth mentioning that many countries governments have significantly contributed towards the development of innovative medicines. Certain pharmaceutical firms in world injectable market have established their foothold given the diverse and innovative product offerings. Several small pharma majors too have been aggressively competing with big pharmaceutical players in order to establish themselves in the market. This review highlights the basic types of injectable preparations and their quality control tests with their standards.

Keywords: Indian Pharmacopoeia (I.P), British Pharmacopoeia (B.P), United States Pharmacopoeia (USP), European Pharmacopoeia (EP), Japanese Pharmacopoeia (JP) Injectable Preparations, Powders for Injection, Implants, Sterility Testing.

1. Introduction

Injectable Preparations are also called as Parenteral preparations. Injectable preparations are sterile preparations and are administered by injection, infusion or implantation. An injection is an infusion method of putting fluid into the body, usually with a syringe and a hollow needle which is pierced through the skin to a sufficient depth for the material to be administered into the body.

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An injection follows a Parenteral route of administration; that is, administration via a route other than through the digestive tract. There are several methods of injection or infusion used in humans, including intradermal, subcutaneous, intramuscular, intravenous, intraosseous, intraperitoneal, intrathecal, epidural, intracardiac, intraarticular, intracavernous, and intravitreal. Rodents used for research are often administered intra cerebral and intra cerebro ventricular injections as well. Long-acting forms of subcutaneous / intramuscular injections are available for various drugs, and are called depot injections. Injections are among the most common health care

procedures, with at least 16 billion administered in developing and transitional countries each year. 95% of injections are administered in curative care, 3% are for immunization, and the rest for other purposes, such as blood transfusions. Approximately 40% of injections worldwide are administered with unsterilized, reused syringes and needles, and in some countries this proportion is 70%, exposing millions of people to infections[1,2].

Characterization of Injectables[4]

Injectables are characterized for the following tests:

- Solubility & Excipient Compatibility
- Physiochemical Characterization of API
- Hygroscopicity Evaluation
- Plasma Compatibility Studies
- Aggregation Analysis by SEC (Peptides)
- Thermal Characterization
- Filter Compatibility Assessment
- Adsorption

Types And Standard Tests Of Injectables[1,2,3,4,5,6,7]

1 Injection
2 Powder for injection or Infusion.
3 Intravenous Infusion
4 Extractable volume
5 Concentrated solutions for injections.
6 Implants

1. Injections

Injections are sterile solutions, emulsions or suspensions prepared by dissolving emulsifying or suspending the active ingredients and other additives in water for injection or other suitable non aqueous vehicle or in mixture of two, if they are miscible.

2. Powder for injection or Infusion

Powder for injections are sterile solid substances (including freeze dried material) which are distributed in their final containers which, when shaken with the prescribed volume of the appropriate sterile liquid, rapidly form clear and practically particle-free solutions or uniform suspension. Powders for injection (PIs) are a popular parenteral dosage form for drugs that cannot be marketed as ready-to-use injectables because of their instability in an aqueous environment. PIs are relatively simple with respect to formulation and process development. However, their performance and stability.

3. Intravenous Infusion

These are sterile aqueous solutions or emulsions with water as continuous phase. When a drug is infused intravenously at a constant rate, a plateau concentration will be reached progressively in the most frequently most of the cases follows first order kinetics. On starting the infusion, there is no drug in the body and therefore, no elimination. The amount of drug in the body then rises, but as the drug concentration increases, so does the rate of elimination. Thus, the rate of elimination will keep rising until it matches the rate of infusion. The amount of drug in the body is then constant and is said to have reached a steady state or plateau.

4. Extractable volume

Suspensions should be shaken before the contents are withdrawn. Oily injections may be warmed but should be cooled to 250 C before carrying out the test.

a) Single dose containers
b) Multi dose containers

Table 1. No of containers to be used for the test as per to BP, USP, EP and JP.

Volume of the solution	No of containers to be used for the test
≥ 10 ml	1
3-10 ml	3
< 3 ml	5

5. Concentrated solutions for injections

Concentrated solutions for injections are sterile solutions that are intended for administration by injection or by IV infusion only after dilution with suitable dilution with a suitable liquid. After dilutions these preparations should comply with the requirements of tests for injection or intravenous infusions as appropriate.

6. Implants

Implants are sterile solid preparations of size and shape for implantation into body tissues

so as to release active ingredient over an extended period of time. An implant is a medical device manufactured to replace a missing biological structure, support a damaged biological structure, or enhance an existing biological structure. Medical implants are man-made devices, in contrast to a transplant, which is a transplanted biomedical tissue. The surface of implants that contact the body might be made of a biomedical material such as titanium, silicone or apatite depending on what is the most functional. In some cases implants contain electronics e.g. artificial pacemaker and cochlear implants. Some implants are bioactive, such as subcutaneous drug delivery devices in the form of implantable pills or drug-eluting stents.

Quality Control Testing of Injectable Preparations[1,2,3,4,5,6,7]

The quality of Injectable is the sum of all parameters that contribute to safety and therapeutic efficacy of the drug. The USP compendial requirements has recommended the following tests for Injectable products.

1 Content uniformity
2 Extractable volume
3 Particulate matter in injections
4 Bacterial endotoxin test
5 Pyrogen test
6 Sterility test

1. Content uniformity & weight

Determine the content of the active ingredient of each of 10 containers taken at random. The preparation under examination complies with the test if the individual values thus obtained are all between 85 and 115 percent of the average value. The preparation under the examination fails to comply with the test if more than one individual value is outside the limits 85 to 115 percent of the average value or if any one individual value is outside the limits 75 to 125 percent of the average value. If one individual value is outside the limits 85 to 115 percent but within the limits 75 to 125 percent of the average value, repeat the determination using another 20 containers taken at random. The preparation under examination complies with the test if in the total sample of 30 containers not more than one individual value is outside the limits 85 to 115 percent and none is outside the limits 75 to 125 percent of the average value.

Table 2. Limits for uniformity of weight.

Pharmaceutical formulation	Average mass	Percentage deviation (%)
Powders for parenteral use	More than 40 mg	10
Powders for eye drops	Less than 300 mg	10
Powders for eye lotions	300 mg or more	7.5

2. Extractable volume

a) Single dose containers

Method I: Where the nominal volume does not exceed 5ml.

Use 6 containers, 5 for the tests and 1 for rinsing the syringe used. Using a syringe with appropriate capacity, rinse the syringe and withdraw as much as possible the contents of one of the containers reserved for the test and transfer, without emptying the needle, to a dry graduated cylinder of such capacity that the total combined volume to be measured occupies not less than 40% of the nominal volume of the cylinder. Repeat the procedure until the contents of the 5 containers have been transferred and measure the volume. The average content of the 5 containers is not less than the nominal volume and not more than 115% of the nominal volume. Alternatively the volume of contents in milliliter can be calculated as mass in grams divided by the density.

Method II: Where the nominal volume is more than 5ml

Transfer the contents of not less than 3 containers separately to dry graduated cylinders such that the volume to be measured occupies not less than 40% of the nominal volume of the cylinder and measure the volume transferred. The contents of each container are not less than the nominal volume and not more than 110% of the nominal volume.

3. Particulate matter in injections

The preparations intended for parenteral use should be free from particulate matter and should be clear when inspected visually. Two methods are described by USP according to the filled volume of the product to be tested. For large volume parenterals (LVP's), a filtration followed by microscopical examination procedure is used. For small volume parenterals (SVP's) a light obscuration based sensor containing electronic liquid-borne particle counter system is used. The USP standards are met if the LVP's under test contain NMT 50 particles per ml of 10μ m, and NMT 5 particles per ml of 25μm in an effective linear dimensional fashion. The USP standards are met if the SVP's under test contain NMT 10,000 particles per container of 10 μm, and NMT 1000 particles per container of 25μm in an effective spherical diameter.

Table No: 3: Limits for particle number as per IP, BP, EP, JP.

Volume of solution	Particle size ≥ 10 μm	Particle size ≥25 μm
Small volume injections (< 100 ml)	3000 per container	300 per container
Large volume injections (> 100 ml)	12 per ml	2 per ml

4) Bacterial endotoxin test

LAL (Limulus Amebocyte Lysate) test is used to characterize the bacterial endotoxin that may be present. The USP reference standard contains 10,000 USP endotoxins per vial. The LAL reagent is used for gel-clot formation. The test is performed using stated amounts of volumes of products, standard, positive control, negative control of endotoxin. The tubes are incubated at 37±1ºC FOR 60 ±2 minutes. When the tubes are inverted at 180ºC angle, formation of firm gel confirms positive reaction. While formation of a viscous gel that doesn't maintain its integrity or absence of a firm gel confirms negative reaction. The test is invalid if the standard endotoxin or positive product control doesn't show end point within ± 1. Two fold dilution from label claim sensitivity of LAL reagent or if the negative control shows gel-clot end point

The following methods can be used to monitor the endotoxin concentration:

Method A - Gel- clot limit test method
Method B -Semi quantitative gel clot method
Method C - Kinetic turbidimetric method
Method D - Kinetic chromogenic method
Method E - End point chromogenic method

5) Pyrogen test

It is performed by using rabbits as test animals. Initially 10 ml/kg body weight of an animal is injected through rat vein at 37±2ºC within ten minutes from start of administration. The temperatures are recorded at 1, 2 and 3 hours after injection.

6) Sterility test

Growth promotion medium and incubation conditions are selected based on the test microorganism. The sterility test is done using direct transfer and membrane filtration techniques. Membrane filtration technique is suitable for liquids, soluble powders with bacteriostatic or fungi static properties, oils, creams and ointments. Sterility test by direct transfer is performed by aseptic transfer of specified volume from test container to culture medium and incubated for 14 days and visual observation of medium is done on 3rd, 4th, 5th, 7th, 8th and 14th day. A membrane filter with porosity of 0.45μm with diameter of 47mm with flow rate of 55-75 ml of water per minute at a pressure of 70 cm of mercury should be used. The test meets the requirements when no growth is observed and if growth is observed then the test is repeated in the second stage and generally second stage is repeated with double the number of specimens tested in first stage when the test was found to be conducted under faulty or inadequate aseptic techniques.

7) Clarity of Solution

Clarity is performed to ensure that parenteral product is free from foreign particles

Constitute the injection as directed on the label.

a) The solid dissolves completely, leaving no visible residue as undissolved matter.

b) The constituted injection is not significantly less clear than an equal volume of diluents for water for injections contained in a similar container and examined in the same manner.

8) Leak Test

Performed only for ampoules which have been sealed by fusion to ensure that their should not be any leakage in them.

a) Vacuum Chamber Test

b) Dye Bath Test

Conclusion

The objective of the present work was to compare Parenteral Preparation QC tests as per IP, BP, USP, JP and EP for sterile products. The formulations for which the comparison was made included are injections, infusions, powders for injections, concentrates for injections .The available QC tests from various pharmacopoeias supplement each other and one pharmacopoeia gives more details on a special issue than the other. Each pharmacopoeia has its own specifications for each test. Sterile products include Parenteral and eye preparations.

References

1. Indian Pharmacopoeia. The Controller of publication, New Delhi; Ministry of Health and Family welfare. Volume I. India 5thed.Particulate contamination. (2007) 28, 54,182,187,188-90.
2. British Pharmacopoeia. Published on behalf of Medicines and Health care products Regulatory Agency; The Department of Health, social services and public safety. Great Britain. Volume II, 6th ed. (2010) 6502-10.
3. United States Pharmacopoeia. 29 National formulary 24(USP 29- NF 24) Supplement1 is current from April 1, 2006 through July 31, (2006) 37.
4. European Pharmacopoeia. Prepared under Council of Europe and European Pharmacopoeial Commission, (2005) 5thed: 337-44.
5. Japanese Pharmacopoeia. The Ministry of health, Labour and Welfare Ministerial Notification No. 2852001 14thed: 112-19.
6. N. Srujana, Venkata Nitin Chilukuri, Valluru Ravi, Balamuralidhara.V, Pramodkumar. T.M: Comparative Study of In-Process and Finished Product Quality Control Test's Of IP, BP, USP, EP, JP for Parenterals: Am. J. Pharm Tech Res., 2, 3 (2012) 306-325.
7. M. Jayasree, C. Sowmya, L. Divya, M.Niranjan Babu, V. Rajasekhar Reddy, V. Lavakumar: Injectable Preparations-An Emerging Dosage Forms: International Journal of Advanced Pharmaceutics: 4, 1 (2014) 36-41.

Table 4. Rabbits Temperature Results according to IP, BP, USP, EP, JP.

Pharmacopeia	No. of rabbits in a group	Passes if temp. is not more than (^{0}C)	Fails if temp is more than (^{0}C)
IP	3	1.4	
	8	3.7	Each rabbit temp raise should not be more than 0.6 0C
USP	3	--	
	8	3.3	
BP & EP	3	1.15	2.65
	6	2.80	4.30
	9	4.45	5.95
	12	6.6	6.6
JP	3	1.3	2.5
	6	3.0	4.2
	9	5.0	5.0

Table 5. Specifications for injections and Powders for Injection's as per IP, BP, USP EP & JP.

SR. No.	Test	IP	BP	USP	EP	JP
1	Uniformity of Content	85-115%	85-115%	85-115%	85-115%	85-115%
2	Extractable Volume	100-110%	--	100-110%	100-110%	100-110%
3	Particulate matter in injections	≥ 25 µm-2% can be present	≥ 25 µm-2% can be present	≥ 25 µm-2% can be present	≥ 25 µm-2% can be present	≥ 25 µm-2% can be present
4	Bacterial endotoxin Test	Should not give positive result				
5	Pyrogen test	Temperature should not increase more than $0.^{60C}$ for each rabbit	Summed temperature of 3 rabbits should not be more than 1.15^0C	Temperature should not increase more than 0.6^0C for each rabbit	Summed temperature of 3 rabbits should not be more than 1.15^0C	Summed temperature of 3 rabbits should not be more than 1.3^0C
6	Sterility Test	No growth in 14 days				

Table 6. Specifications for concentrates as per USP.

SR. No.	Test	USP
1	Bacterial endotoxin Test	Should not give positive result
2	Pyrogen test	Temperature should not increase more than 0.6^0C for each rabbit
3	Sterility Test	No growth in 14 days

Table 7. Specifications for Infusion as per IP, BP, USP EP & JP.

SR. No.	Test	IP	BP	USP	EP	JP
1	Extractable Volume	100-110%	--	100-110%	--	100-110%
2	Particulate matter in injections	≥ 25 µm-2% can be present	≥ 25 µm-2% can be present	≥ 25 µm-2% can be present	--	≥ 25 µm-2% can be present
3	Bacterial endotoxin Test	Should not give positive result				
4	Pyrogen test	Temperature should not increase more than 0.6^{0C} for each rabbit	Summed temperature of 3 rabbits should not be more than 1.15^0C	Temperature should not increase more than 0.6^0C for each rabbit	Summed temperature of 3 rabbits should not be more than 1.15^0C	Summed temperature of 3 rabbits should not be more than 1.3^0C
5	Sterility Test	No growth in 14 days				

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