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Quality Determination (In-process & Finished product Quality Testing Parameters) of Triamcinolone Acetonide Injectable Suspension

Abstract

Triamcinolone acetonide is an antiinflammatory drug that has been used for more than 50 years for the treatment of various inflammatory disorders including the arthritis & gout etc. Moreover, in recent years its use has been rapidly increased for the treatment of retinal vasculature disease and Uveitis, periocular and intraocular treatment. This review summarizes the whole manufacturing process of this formulation along with the complete in-process QC & Finished dosage form test parameters that ensures the efficacy and safety of this drug. Furthermore, the industrial requirements in the production and QC department to manufacture this product are emphasized to optimize the production as well as the quality of the Product.

Key Words: Quality Control, Parenteral, In-Process, Triamcinolone Acetonide

Introduction

Triamcinolone Acetonide is used therapeutically as an anti-inflammatory drug that reduces the allergic reactions, swelling and various inflammatory disorders for example, arthritis, gout, Skin diseases and numerous other medical problems including retinal vasculature disease and Uveitis (Jermak, Dellacroce, Heffez, & Peyman, 2007; Yilmaz et al., 2009). It is available in parenteral form for those who cannot take it orally. It is basically Corticosteroid that acts on the steroid receptors present on the intracellular receptors.

Immediate supervision of the physician is compulsory during administration or should only be done by the Doctor. This drug is available in market in the two dosage forms:

1-Extended-release powder for suspension

2-Suspension

Description

Brand name: Tramacort A
Generic name: Triamcinolone Acetonide Injectable Suspension USP
Composition: 40mg/ml
Manufactured by Trigon Pharmaceuticals (pvt) Ltd.

Industrial Layout Requirement

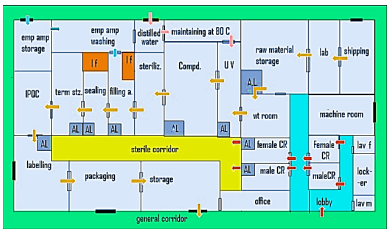

Figure 1: Complete layout of the Industry to manufacture the Triamcinolone Acetonide in parenteral Dosage form

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Personal Flow

A unidirectional flow is maintained within the production area to avoid any crowded and discontinuous pattern.

Sterile Corridors are used, and positive air pressures are maintained. Air locks are used for entry and exit from the production area to avoid the entry of air from outside into the manufacturing area

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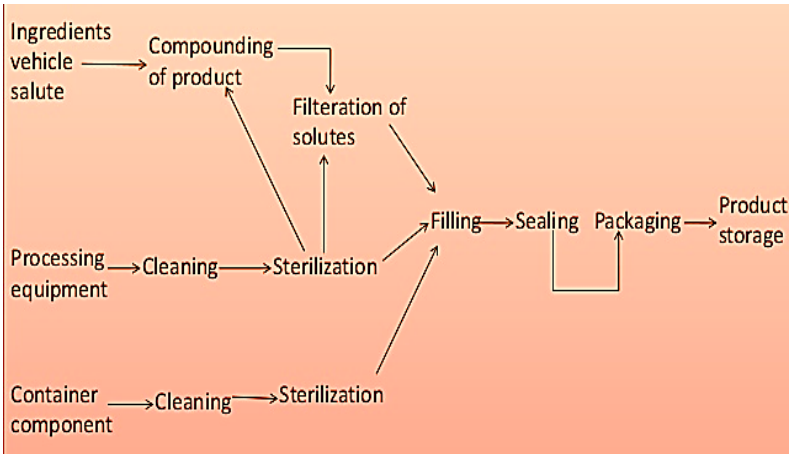

Figure 2: Flow of the raw materials and intermediates during the Manufacturing of Triamcinolone Acetonide Injectables

Material Flow

Raw Materials Requirement Per Ampoule

- Triamcinolone Acetonide 40mg
- Sodium Chloride 6.5mg
- Benzyl Alcohol 9.9mg
- Carboxymethylcellulose 7.5mg
- Polysorbate 80 0.4mg
- Sodium hydroxide / HC QS to adjust pH between 5 to 7.5

Area Requirements for parenteral Manufacturing

Table 1. Requirements of the Area for the Parenteral Manufacturing

Functions	Area	
	Square Meter	Percentage
Production	11094	45.1
Warehouse	7606	30.9
Utility	1716	4.1
Quality Control	1716	7.0
Administration	1018	4.1
Maintenance	1014	4.5
Employee Services	1014	4.1
Security	39	0.9
Total	**24607**	**100**

Quality Testing of Raw Materials

Quality Assurance inspector checks the raw material section after specific intervals and raw materials are tested before purchasing form the supplier. These tests are performed for every excipient as mentioned in USP.

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Table 2. Quality Control Tests for the Raw Materials

Identification	Limit Tests	Identification
Purity	Physical properties	Purity
Particle size	Organic volatile Impurities	Particle size

Raw Materials Storage

Each raw material is stored in a separate container having a label attached on it, indicating

- Material name & Internal Code
- Date
- QC and QA clearance
- Batch no. given by supplier
- Expiry date or date beyond retesting is necessary.

Temperature and humidity are controlled within *23-27 degree* and *45-55%* respectively.

Dispensing

Dispensing of raw materials is done in a separate area within the raw material store. Raw material store supredent, Quality Assurance Inspector, Production pharmacist and Technician for weighing purpose must be present at the time of dispensing. Each raw material is weighed according to batch requirement and dispensed in a separate container / package. Dispensing conditions are mostly the same as the raw material store.

Line Clearance 1

Quality Assurance Inspector gives the line clearance and dispensed materials are carried form the raw material store to the Sterile Production Area.

Line Clearance 2

Quality assurance inspector check the conditions of the mixing as required and then gives the clearance for the mixing operation.

Mixing & Blending

Mixing is done at 25degree temperature and 35-40 % humidity is maintained during the mixing process. Specific equipment is used depending upon the batch size.

In-Process Quality Control of Mixed Ingredients

After the mixing, sample is sent to the QC lab to check the homogeneity of the mixing and other different tests needed to be performed to check the quality of the sample according to the USP mentioned procedures.

- Content Uniformity / Blend Uniformity
- Particle size

Preparation of Water for Injection

Water required as a solvent (aqeous phase) is treated by several methods that provide the characteristics mentioned in the table. These characteristics must be fulfilled in order to use this water as an excipient for pharmaceutical purpose.

Table 3. Water for Injection Requirements

S.No	Parameters	Specifications
1	Appearance	Clear, colorless, no visible particles
2	Odor	Odorless
3	pH	5.0-7.0
4	Acidity or alkalinity	NMT0.1 ml of 0.01M NaOH/Hcl
5	Chloride	0 ppm
6	Oxidizable Substances	0 ppm
7	Sulphate	0 ppm

Dechlorination

Removal of chlorine done by high dosage of UV or filtration through activated Carbon Media.

Ion Removal

Removal of ions done by membrane process (reverse osmosis & Nano filtration membranes), exchange

process or distillation process. Ions, particulate matter, organic compounds and even living organisms are removed in this process.

Bacterial Control

Bacterial control is usually applied during the during the processing, storage and even distribution. Equipments used are UV lights, ozone generation systems and heating systems for the non-thermal, Chemical and Thermal removal of bacteria respectively.

Removal of Specific Impurities

Depending upon the source of Water different types of impurities can be present in water that must be removed by proper process e.g., iron, manganese, hydrogen sulphide, hardness ions, particulate matter, and high conductivity.

Storage

Stored in special tanks containing ultraviolet lamps. It can be stored for a period up to a month. Care and hygiene are maintained during the storage and bacterial control is still incorporated in this stage.

Quality Control Tests for Water for Injection

- Sterility Test
- Bacterial Endotoxin Test
- Pyrogen Test

Addition of Solvent in the Rest of Mixed Raw Materials

This is done under Aseptic Conditions at the temperature of 25 degrees and humidity maintained at 35 percent.

Specific equipment for liquid solid mixing is used depending upon the batch size

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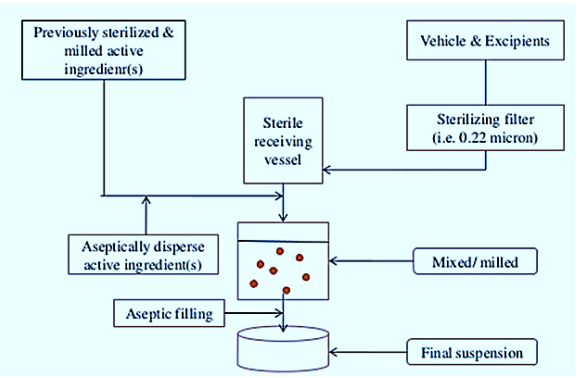

Figure 3: Flow of Sterilized Raw Materials till the Final Suspension

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In-process Quality Control Test for Parenteral Suspensions before Filling

Appearance

A graduated transparent glass cylinder is used to check the appearance. The sediment's Colour and uniformity is checked during this investigation. Presence of air pockets or air breaks is noted. Any material coagulated and sticking to the container wall is checked too.

Density

One of main parameters in the in-process quality control of this formulation is Density and Specific Gravity. Entrapped air in the suspension formulation shows itself in the form of decrease in the density. For the measurements of densities, the suspension formulation must be uniform throughout the container. Hydrometers are used to measure the density.

Viscosity

Viscosity is measured using an Ostwald viscometer. TACA injectable suspension has a viscosity range of 2-12cps.

Particle Size

Particle size is checked by optical microscopic method. TACA of 4% (w/v) has a mean volume diameter of 3-10μm.

pH Value

pH measured using a pH meter. Triamcinolone acetonide injectable suspension should have a pH value between 5 and 7.5.

Pourability

Suspension is checked for the pourability in phases to ensure the proper pourability of the formulation to avoid any problems or defects during the filling procedure or during the handling by the patient.

Zeta Potential

Zeta Potential is measured using a zeta sizer and acceptable range of zeta potential is -20 to +20 mv.

Treatment of Ampoules

Ampoules made of type 1 glass provided by the supplier are used for the filling purposes and they require specific treatment before filling preparation.

- Colour: Colourless transparent ampoules
- Dimensions: 10.75 x 70 x 0.50mm

Line Clearance 3

Quality Assurance inspector also inspects the process of Ampoules treatment and specific conditions e.g. the speed of the washing machine and even the number of persons required in a particular area are checked by QAI and ultimately if all the requirements are fulfilled then Process is continued.

Washing

Automatic ampoule washer is used for cleaning the containers. Ampoules are washed at a speed of 250 ampoules per minute by an automatic machine. There are some specific gripping techniques used in this machine that hold the ampoules and then invert them in order for the cleaning process. Pressurized as well as positive pressure nozzles are used to do the washing of the ampoules. Cleaned ampoules are then collected in a tray after they are washed through a feeding path in a straight position.

There are 6 washing stations in the machine and 3 needles for the air removal and 3 needles for the water removal are present in each station. Cleaning agents are hold and pumped by three pumps with three 25 litre tanks are also present in the machine. Gripper cassettes are also present in each station that holds the ampoules and turn them in the neck down position. Feeding and exiting the machine is done totally automatically

Stainless steel 316 is used to manufacture all the internal surfaces that helps in preventing the corrosion. FDA approved materials are required to make the other parts that are not made with the Stainless steel 316. CGMP standards are used to make the fabrication and materials and their quality is guaranteed by them.(Lee, Shin, Kim, Eun, & Surgery, 2013)

Sterilization of Ampoules

Sterilization of ampoules is done for 13 minutes at 115 degrees.
After that they are cooled at -30 to -40 degrees for some time and then exposed to the conditions for primary freeze drying for about 6 hours.

Storage

Ampoules then are stored under aseptic conditions in airtight area and controlled temperature and humidity.
Filling & Sealing of Ampoules

Line Clearance 4

Here the aseptic conditions are checked and then allowed to start the filling process and a small sample is tested after filling for the required volume , weight variation, particle contamination and leaker test and oxygen content test are also performed to judge the accuracy of the filling and sealing procedure, If everything is under-controlled then the line clearance is given for the batch filling and sealing operation.

Performance Qualification of Filling Machine

Weight Variation test: 10 containers must be within 85-115% of target content or NMT 1 out of 30 containers outside of the 85-115% and no unit must be outside the 75-125%.
Filling Volume Accuracy: It should be within plus minus 1 % of adjusted volume.

Particle Contamination

This test is performed according to the USP test for particulate matter.

Leaker Test

Leak is detected by submerging the ampoule in deeply coloured dye solution (0.5-1% methylene blue). Capillaries of less than 15 um cannot be detected by this method.

Oxygen Content

If the filler produces a nitrogen purge, the head space gas should be analyzed for oxygen content.

Operation

Ampoules are filled using an automatically filling and sealing machine. Ampoules that are already sterilized are loaded on a tray and then tray is loaded into the slant hopper unit directly. Ampules are delivered to the eccentric ampoule rack that continuously moves in single or two or four or six, one by one.(Kupiec, 2004)

Quality Control Tests of the Filled Ampoules

Following Tests are performed on the filled ampoules according to USP Specifications (Akers, Larrimore, & Guazzo, 2002; Deshmukh, Salunkhe, Deshmukh, & Shete, 2015)

- Deliverable Volume
- Leaker test
- Clarity Test
- Pyrogen Test
- Sterility Test
- Content Uniformity Test

Labelling of Ampoules

Ampoule labelling machine is that prints the label horizontally on the ampoules. This specific label contains all the required information according to the guidelines for labeling of parenterals (Deshmukh et al., 2015).

Packaging of the Ampoules

Within the raw material store packaging store section is separate area where the primary, secondary, and tertiary materials for packing are stored. They are dispensed when given the line clearance by the Quality Assurance inspector and carried to the packaging section where each ampoule is packaged in single unit container and entire batch is packages in tertiary containers (Akers et al., 2002).

Finished Product Tests

Appearance of Phases, Colour & Crystal Determination

A graduated transparent glass cylinder is used to check the appearance. The sediment's Colour and uniformity is checked during this investigation. Presence of air pockets or any breaks is noted. Any material coagulated and sticking to the container wall is checked too.

Sedimentation Volume

TACA Injectable suspension must have a degree of flocculation greater than 5.

Measurement of Zeta Potential

Zeta Potential Measurement is done in the same way as described above in the *IPQC*.

Re-Dispersibility

Upon settling the particles of the formulation, they should be easily redispersible.

Rheological Measurement

Preparation must have good flow properties for the good syringablity and pourability properties.

pH Value

Triamcinolone acetonide injectable suspension should have a pH value between 5 and 7.5.

Universal Tests for Triamcinolone Acetonide Injectable Suspension (USP)

Description

Triamcinolone Acetonide occurs as White to cream colored particles suspended in the aqueous phase.

Identification of Triamcinolone Acetonide Suspension

As per USP identification test is performed to confirm the presence of active ingredient.

Assay

Assay is performed as per USP Monograph specifications.

Triamcinolone acetonide injectable suspension contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{24}H_{31}FO_6$.

Sterility Test

Sterility test is performed according to USP by the membrane filtration method and no growth of microorganisms should be observed in the product (Akers et al., 2002).

Bacterial Endotoxin Test

TACA Injectable suspension contains not more than 4.4 USP Endotoxin Units per mg of triamcinolone

acetonide by testing according to the requirements for the bacterial endotoxin test (Williams, 2007).

Foreign & Particulate matter Test

The limits for the foreign and particulate matter test for this formulation are the following: all the tested units must not contain more than 6000 average number of particles equal to or greater than 10 micrometer and should not be more than 600 particles per container equal to greater than 25 micrometer (Akers et al., 2002).

Container Contents

Upon individual examination of the containers the volume of each container should not be less than nominal value or in case of the containers having a nominal volume of 2 ml or less, should not be less than the sum of the nominal volumes of the containers taken together (Deshmukh et al., 2015).

Labeling

FDA is responsible for ensuring the compliance with the current regulation to label a product. The date beyond use or expiry date must be present on both the container and package label. Package label must also contain the storage conditions that are recommended if the container is packaged. All other requirements as well as storage conditions must be indicated on the container label if the container is not packaged individually. National and international requirements must be fulfilled during the labelling of the Formulation (Deshmukh et al., 2015).

Specific Test for Parenteral Suspensions (USP)

Uniformity of Dosage Unit

Content Uniformity test is applied on the 10 containers first. If the criteria is not met then 20 more containers are selected and overall content uniformity is checked in 30 containers.

Acceptance value is calculated by the: $Av = |M - x| + Ks$ where x-bar is mean of assay values and K is constant and s is standard deviation while M is the reference value.

Criteria

The acceptance value should be less than or equal to 15. All the assay values must be in the range in between the upper and lower limits.

Antimicrobial Preservatives

Antimicrobial preservative should not be more than 20 % of the labelled amount.

Storage in Warehouse

Finished products then are placed in the warehouse from where they will be shipped to the distributors. Conditions for the storage in the warehouse are the

- Temperature: 23-27 degrees
- Humidity: 35-45 %

Conclusion

Various in- process quality Control parameters are there to be controlled during the manufacturing of the Triamcinolone Acetonide that effect the quality of the final suspension formed. Quality assurance is the main factor involved that must be able to optimize the production by controlling the process and ensures the best quality of each process and the intermediate after each step. Industrial requirements including the area, personal flow as well as material flow must be fulfilled in order to maximize the output by using the quality raw materials that must be tested for their properties after receiving from the supplier

References

Akers, M. K., Larrimore, M. K., & Guazzo, D. (2002). Parenteral quality control: sterility, pyrogen, particulate, and package integrity testing: CRC Press.

Deshmukh, M., Salunkhe, R., Deshmukh, V., & Shete, R. J. J. O. C. P. R. (2015). Quality control test's for parenteral preparations: a review. *5*(2), 1425.

Jermak, C. M., Dellacroce, J. T., Heffez, J., & Peyman, G. A. (2007). Triamcinolone Acetonide in Ocular Therapeutics. *Survey of Ophthalmology, 52*(5), 503-522. doi:https://doi.org/10.1016/j.survophthal.2007.06.004

Kupiec, T. J. I. j. o. p. c. (2004). Quality-control analytical methods: High-performance liquid chromatography. *8*, 223-227.

Lee, Y. C., Shin, S. Y., Kim, S. W., Eun, Y. G. J. O. H., & Surgery, N. (2013). Intralesional injection versus mouth rinse of triamcinolone acetonide in oral lichen planus: a randomized controlled study. *148*(3), 443-449.

Williams, K. L. (2007). Endotoxins: pyrogens, LAL testing and depyrogenation: CRC Press.

Yilmaz, T., Weaver, C. D., Gallagher, M. J., Cordero-Coma, M., Cervantes-Castaneda, R. A., Klisovic, D., & Larson, R. J. J. O. (2009). Intravitreal triamcinolone acetonide injection for treatment of refractory diabetic macular edema: a systematic review. *116*(5), 902-913.