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International Journal of Pharmaceutical and Biological Science Archive 1 (1) 2013, 82-86

REVIEW ARTICLE

DIFFERENT ASPECTS AND STRATEGIES ON QUALITY CONTROL AND QUALITY ASSURANCE OF AEROSOL DOSAGE FORM IN PHARMACEUTICAL INDUSTRY

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Received 10 May 2013; Revised 15 May 2013; Accepted 30 May 2013

ABSTRACT

Aerosols are the dosage forms who expulse the medicament on the power of compressed gases that are also termed as propellants. Quality control is a segment within the pharmaceutical company which mainly helps to ensure the quality of product.

While quality assurance is a section which will determine all the parameters that will affect quality of Product. The purpose of this work is to represent the different aspects and strategies for quality control and quality assurance of aerosol dosage form within the pharmaceutical companies. In this article regarding quality control section the different testing methods are described which covers both in-process and finished product testing. While in quality assurance section the GMP and brief description of process validation of aerosol dosage forms is described.

INTRODUCTION:

Aerosols are basically the dosage form who depends upon the power of compressed gases for the expulsion of product concentrate. The aerosol formulation basically consists of Propellant and medicaments which are to be propelled. An examination of these aerosol dosage forms revels the advantages over the other dosage forms they are:

1. A dose can be removed without contamination of remaining material.

2. Stability is often improved for the materials that are adversely affected by oxidation and moisture.

3. The medication can be directly delivered to the affected area in a desired form like spray, stream, and foam.

4. Irritation produced by topical application of topical medication can be eliminated.

The components of aerosol package are a. Propellant b. Container c. Valve and Actuator d. Product concentrate. Propellants are responsible for generating pressure within the container. Containers in which the product is filled. While valve helps in expulsion of product concentrate. The actuators allow easy opening and closing of valve and it is integral part of every aerosol package. And the product can be delivered basically in 3 forms solution, suspension, and emulsion beside this other forms like semisolid are also available.

Quality control is a segment within the pharmaceutical industry which deals mainly with testing, sampling, documentation, specification, and release procedures. It mainly ensures that necessary and relevant tests are carried out and material is not released for its sale until its quality is judged to a satisfactory. Basically there is no difference in methods which are used to produce pharmaceutical aerosol and non pharmaceutical aerosols only difference is in the standards and specifications for their production.

Propellants: - before the propellant is used it is subjected to some rigid tests. A sample is removed and it is sent to the lab where it is examined for the vapor pressure. Also its density is checked. Gas chromatography is pronouncly used to identify the propellant. The purity and acceptability is tested by moisture, halogen and non volatile residue determination.

Valves, Actuator, and dip tubes: - These are the parts which are subjected to physical and chemical examination. But such examination is more complex for non pharmaceutical products. The examination point must determine whether the valve is fit to be used. They are sampled according to the standard procedures. The provide the acceptance of metered dose valves for pharmaceutical use a suitable test method was developed by the aerosol specification committee in which 25 valves are selected and placed on to a suitable container into which a specific test solution was placed. These containers are fitted with button type

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actuators and these containers are placed into a suitable atmosphere of 250c and after that the valve is actuated for the period of at least 2 sec this procedure is repeated for ten times. The test unit is weighed before actuation and after actuation the difference between it represents the delivery in milligrams. But this test is not designed to determine the lack of suitability of valve for for specific formulation. The limits for the test are for the valves delivering 54µl or less the limit are ±15% and for the valves delivering 55 to 200µl the limits are ±10%.

Containers: - containers are sampled according to the standard procedures. Both the uncoated and coated containers are examined for defects in lining several quality control aspects include specification for the degree of conductivity of electric current as a measure of exposed metal. Glass containers must be examined for the flaws. The dimension of the neck other parts weight of the bottle must be determined.

Weight checking: - This is usually done by adding the empty containers to the filling line which are filled with a concentrate are removed and weighed. Similar procedures are being adopted for the weight of propellant which is being added. After completion of the filling operation the filled container is again weighed to determine accuracy of filling.

Leak testing: - It is a means of checking the crimping of valve must be available to prevent defective containers due to leakage. For the metal containers it is determined by measuring the crimp dimensions and ensuring that they meet specifications. Final testing of valve closure efficiency it is done by passing the final container into water bath.

Spray testing: - It serves that the dip tube clear of pure propellant, to clear of pure concentrate product, and to check for the defects in valve and spray pattern. Amongst which spray pattern is mainly determined by spraying the product on to a paper which is impigmented with dye talc mixture the particles strike the paper and causes dye to go solution and too adsorbed on to a paper this gives spray pattern which compared amongst the different batches.

The different quality control tests which are performed on pharmaceutical aerosols are: -

1. Flame projection.
2. Flash point.
3. Vapor pressure.
4. Density determination.
5. Moisture determination.
6. Identification of Propellant.
7. Aerosol valve discharge rate.
8. Spray pattern determination.
9. Net content determination.
10. Dosage with metered valves.
11. Foam stability determination.
12. Particle size determination
13. Biological testing.
14. Therapeutic activity testing.
15. Toxicity testing.

The **Quality Assurance** is wide ranging concept concerning all matters that are collectively or individually influences the quality of product. It is the totality of arrangements made with object of ensuring that the products are of the quality required for the intended use. The first part which comes into this section is the GMP which is needed to be followed by the Pharmaceutical industry who manufactures the aerosol product.

GMP for the Manufacture of Pharmaceutical aerosol Products as per the schedule M of Drug and cosmetic act 1940 is as follows:-

1. General: - The Manufacture of the aerosol product should be done under the conditions which shall ensure minimum microbial and particulate contamination. If the medicament is in the suspended state then the uniformity of suspension must be established.

2. Building and civil works: - The building shall be located on solid foundation. All the surfaces of building shall be impervious smooth and nonshedding. Ceiling shall be solid continuous and covered to the walls. Light fittings and air-grills shall be flush with the ceiling. The manufacturing area shall be segregated into change rooms, container preparation area, bulk preparation area, filling area, quarantine area and spray testing and packaging area. Separate area should be provided for de-cartoning of components before they are washed. The propellants for filling purpose shall be delivered into manufacturing area by filtering them through 2F filter.

3. Environmental conditions: - Where the cleaned components are exposed the area shall be supplied with filtered air of grade c. The requirement of temperature humidity should be based on the requirements of the product. The difference in room pressure between manufacturing area and support area should not be less than 15 Pascals. There shall be written schedule for the monitoring of environmental conditions.

4. Garments: - Gloves should be made up of material which should not have interaction with propellant which are used by the manufacturer. Disposable gloves should be used. Personnel protective wears like footwares, safety glasses should be used. Personnel in manufacturing and filling area should wear suitable single piece garments made out of nonshedding.

5. Sanitation: - There shall be written procedures should be adopted for the sanitation of manufacturing facility. Special care should be taken to handle residue and rinses of propellants.

6. Equipments: - Manufacturing equipments should be closed system. The vessels and supply lines should be of stainless steel. Suitable check weights, spray testing machines, labeling machines shall be provided in department.

7. Manufacture: - There shall be approved master formula record. The primary packaging material must be cleaned by compressed air. The valves should be carefully handled. In process control include periodical checking of weight of bulk formulation filled in the container.

8. Documentation: - Documents must show following information. Temperature humidity of manufacturing area, Periodic filled weights of the formulation, Records of rejection on line check weighing, Records of rejection during spray testing.

Process Validation:

USFDA defines the process validation as 'Establishment of documented evidence which provides high degree of assurance that specific process will consistently produces a product that will meet its predetermined quality specifications and quality attributes'. A validated manufacturing process is one which has been proved to do what it purports to do. The process validation of aerosol dosage forms basically involves:

Preparation of validation Protocol:

A. Development Report: - A development report should be prepared prior to process validation protocol prepared by research and development group and it will serve as the basis for items to be included in validation protocol. Parameters like process limits, formulation compatibility with process equipments, time limitation on production should be addressed.

B. Preparation and execution: - The process validation protocol of aerosol product should be written by a validation specialist familiar with aerosol product. Others experienced in oral dosage forms like solution or suspension would also be helpful. These technical specialists may be within research, validation or technical support departments, since this work will be done prior to approval of new product. And approval should be given by quality assurance, quality control, production management, and research. This validation protocol should be prepared after master batch record is approved and signed by responsible parties. The validation specialist should execute protocol.

C. Final process and product: - The aerosol product must be prepared with the manufacturing equipment and process intended for routine production. Changes in any manner like addition of raw material, method of weighing, mixing conditions should considered as major changes should be documented and subjected to revalidation.

D. Worst case condition: -evaluation of worst-case conditions will justify many of process limits. A sub protocol for testing worst-case conditions must be specified in validation protocol. An alternative procedure should be there to test these conditions during development.

E. Timing: - The protocol must be approved and signed before the first production batches are started. Since complex manufacturing and lengthy finished product test are involved.

F. Testing and specifications: - Due to extensive testing of aerosol products, the sampling and testing scheme must be carefully reviewed. Most of the products to be tested for content uniformity require to demonstrate reproducibility and also have to show that loss of propellant is under control. Limits for the critical tests are suggested to avoid uncertainty over pass/fail situation and should act as guide.

G. Stability: - stability testing of validation batches should be conducted at quality control laboratory under labeled storage conditions accelerated conditions is not required since these are supplemental tests not primary.

Material monitoring:

Valves are critical to functionality of these dosage forms. So in order to be get assured about these valves some test are conducted on them. Even storage and handling of propellants transfer, piping, storage tanks should be get standardized. Packaging components will require special environmental storage conditions. Room temperature and humidity should be get documented during facility qualification. Containers for storing or packaging should be specified weighing of ingredients should include their gross, tare, net weights.

Process Monitoring:

Preparation of formulation (suspension or solution or emulsion): - validation involves confirmation of rate of addition, method of addition and mixing conditions during compounding of aerosol preparations. The specific type of equipments for each operation should be specified. The batch temperature and the room conditions (humidity, temperature) should be specified and fully documented. It includes.

1. Air cleanliness.
2. Purging of propellants.
3. Recirculation.
4. Residual losses and yields.

Checking aerosol line functions: - Here all the parameters concerning the filling operations of aerosols are going to be examined it includes.

1. Crimping of valve.
2. Propellant filling.
3. Check weighing.
4. Leak testing.

Other functions: - It includes examining storage of aerosol products. The shipper's description and spray testing of product. It also includes verify proper number of valve depressions for spray testing, establishing the rejection rate for given valve in the validated process. Other functions like can coding must be considered a process step. The actuators which are used must be specified in batch record. A history of particular valves defect must be known before the validation of production batches has begun.

Table 1: Critical process parameters in process validation of aerosol dosage forms

Sr. No.	Process stage	Specifications
1	Environmental conditions: a. Relative humidity. b. Temperature. c. Compressor air dew point.	15-40%. 20-25^{o}c 2-8^{o}c.
2	Mixing: a. Stirrer time (min). b. Speed(RPM)	30 Min. 200-300.
3	Recirculation: a. Speed (RPM). b. Time	100-150 10 min.
4	Filling stage: a. Weight of formulation per can. b. Gross weight of filled can. c. Crimp parameters. d. Leak test.	11.40-12.00g 18.50-19.10g. Diameter: 17.80±0.1mm. Height: 5.70±0.1mm. No bubbles should observe.

Validation report: It should include validation protocol, tabulated results, process monitoring forms, all analytical results of validation batches. A copy of batch record and raw material releases should be in appendix. The data presentation should be spread out over pages and be easily understood. Stability data can be included in later batches. It should have an conclusion. Appendices should be there to explain detailed equation or specific methods. Recommendations should be there in report. And such report should be approved prior to product distribution and kept permanently in Q.A. Department. And the data in report should be serve as foundation for future troubleshooting.

Types of document required for validation: -

1. Validation master plan.
2. Validation Protocol.
3. Validation reports.
4. Standard operating procedures.

Responsible authorities for validation: -

1. Head of Quality Assurance.
2. Head of engineering.
3. Validation Manager.
4. Production Manager.
5. Specialist of validation discipline in all areas.

Elements of validation:

1. Design qualification: - It is documented review of design at an appropriate stage of project for confirming to operational and regulatory expectations.
2. Installation qualification: - It is documented verification that all the aspect of facility or equipment that can affect product quality adheres to approved specifications.
3. Operational qualification: - It is documented verification that aspects of facility or equipment that can affect product quality operate to specified rages.
4. Performance qualification: - It is documented verification that aspects of facility or equipment that can affect product quality meet predetermined acceptance criteria.

CONCLUSION:

Quality control of aerosols specifies the different tests to be conducted on aerosol components like propellants, containers, valve and actuators, it also specifies leak testing, spray testing also it specifies some tests which are performed on finished products. While the quality assurance firstly specifies the GMP which are to be followed while manufacturing of the dosage forms. It also specifies how the process validation has to be conducted such types of GMP and Process validation helps to support the company commitment towards quality assurance. While the quality control tests which are specified which ensures the quality of Product, it will also ensures that material is not release for its sale until its quality has been judge to satisfactory. So both of these streams will ultimately leads improvement in total quality which covers both product as well as company.

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