Advances in Research
6(3): 1-12, 2016, Article no.AIR.22442
ISSN: 2348-0394, NLM ID: 101666096

SCIENCEDOMAIN *international*
www.sciencedomain.org

Pharmacopoeial Standards and Specifications for Pharmaceutical Aerosols: In-Process and Finished Products Quality Control Tests

Md. Sahab Uddin[1*], Mahbubul Hossain[1†], Abdullah Al Mamun[1†], Sonia Zaman[1], Md. Asaduzzaman[1] and Mamunur Rashid[1]

[1]Department of Pharmacy, Southeast University, Dhaka-1213, Bangladesh.

Authors' contributions

This work was carried out in collaboration between all authors. Author MSU designed the study, wrote the protocol, managed the analyses of the study and prepared the draft of the manuscript. Authors MH and AAM managed the literature searches and helped with author MSU. Authors SZ and MA revised the final manuscript. Author MR reviewed the scientific contents of the manuscript. All the authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AIR/2016/22442
Editor(s):
(1) Soumendra Karmahapatra, Department of Pharmacology, Ohio State University, Columbus OH, USA.
Reviewers:
(1) Rahul Rama Hegde, IFTM University, India.
(2) Marilene Estanqueiro, University of Porto, Portugal.
(3) Anonymous, Canada.
Complete Peer review History: http://sciencedomain.org/review-history/12834

Review Article

Received 1st October 2015
Accepted 4th December 2015
Published 29th December 2015

ABSTRACT

Pharmaceutical aerosol is a pressurized system that depends on the power of a compressed or liquefied gas to expel the contents from the container. Therapeutic performance of pharmaceutical aerosols is affected by various factors such as actuator tube design, orifice diameter, concentration of surfactant in the system, moisture content and deposition of emitted dose, vapor pressure of propellants, spray pattern, efficiency of valve crimping and measurement of particle size aerosols. Unique feature of this dosage form is the presence of propellants, whose properties like flash point, viscosity and density and presence of active ingredients, containers, valves and actuators also modify the aerosol performance. A pharmaceutical aerosol must satisfy certain standards to claim it to be a quality drug. The main standard for the quality of any drug is the intrinsic and extrinsic elements which contribute directly or indirectly to the safety, potency, efficacy, stability, patient

**Corresponding author: E-mail: msu-neuropharma@hotmail.com;*
[†]Equal contributors

acceptability and regulatory compliance of the products. In process quality control (IPQC) tests are performed in order to remove error from every stage in production. After the manufacturing process is complete finished product quality controls (FPQC) test are performed with respect to the specification of the pharmacopoeias with a view to checks that the quality parameters are within the acceptable limits or not. So, the total quality of pharmaceutical aerosols depends on both IPQC and FPQC tests. The objective of this study is to provide various in-process and finished product quality control tests for pharmaceutical aerosols as per pharmacopoeial standards and specifications.

Keywords: Pharmaceutical aerosols; standard; specification; in-process quality control; finished product quality control.

1. INTRODUCTION

Pharmaceutical aerosols are products that are packaged under pressure and contain therapeutically active ingredients which are released upon activation of an appropriate valve system. The term ‘‘aerosol’’ refers to the fine mist of spray that results from most pressurized systems. They are intended for topical application on the skin as well as local application into the nose (nasal aerosols), mouth (lingual aerosols), or lungs (inhalation aerosols). These products may be fitted with valves enabling either continuous or metered-dose delivery [1]. Inhalation aerosols are fine suspensions or dispersions of solid particles in a gas, intended for local action in the respiratory tract. Various types of inhalers such as nebulizers, metered dose inhalers (MDIs) and dry powder inhalers (DPIs) are available [2]. Various factors such as actuator tube design, orifice diameter, and concentration of surfactant in the system, vapor pressure of propellants, and efficiency of valve crimping and particle size of the plume emerging from the inhaler etc. affect the therapeutic performance of aerosols. Exceptional aspect of pharmaceutical aerosols is the presence of propellants, whose properties like flash point, viscosity and density also modify the aerosol performance [3].

Quality control (QC) is the part of GMP (Good Manufacturing Practice) that is concerned with sampling, specifications, testing and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, sale or supply, until their quality have been judged to be satisfactory according to specifications [4,5]. The process of QC is carried out to confirm an expected level of quality in a product by eliminating errors at every stage in production [6]. QC is a team work and we have to keep in mind that quality must be incorporated into a drug product during product and process design [7]. So, it is possible patently be apprehended that, quality is not an accident but a result of intelligent efforts [6]. The total quality of the product is assured by the in process quality control (IPQC) and finished product quality control (FPQC) tests. IPQC tests are carried out at regular intervals before the manufacturing process is completed. The function of IPQC involves monitoring and if necessary adaptation of the manufacturing process with a view to comply with pharmacopoeias [8]. FPQC tests are performed when the manufacturing process is completed in order to check qualitative and quantitative characteristics along with test procedures and their acceptance limits, by which the finished product must comply throughout its valid shelf-life [9]. The total dealing process (IPQC and FPQC tests) represents rigorous QC tests to make products completely indefectible before they are launched into the market [7].

In terms of pharmaceutical development and manufacture, the regulatory entities are continually developing their requirements to meet the challenges of these new technologies and to ensure their safety, quality and efficacy in the global marketplace. The ultimate responsibility for the safety, quality and efficacy of medicines and medical devices lies with the various national regulatory bodies designated to safeguard public health [10]. In Europe, in the USA and in the UK this function is performed by the European Medicines Agency (EMA), Food and Drug Administration (FDA) and Medicines and Healthcare products Regulatory Agency (MHRA) respectively [11-13]. In USA, as the FDA has a command that the marketed drug product should be safe and effective; the drug product must conform particular criteria for quality and purity [14]. In 2002, the FDA launched a new initiative “Pharmaceutical cGMPs (current Good Manufacturing Practices) for the 21st century” in which it proposed a new approach to pharmaceutical manufacturing [15].

The main role of the pharmacopoeias is to define the standards with which medicines shall comply and the methods by which compliance will be adjudged [10]. There are diverse types of pharmacopoeias such as British Pharmacopoeia (BP), United States Pharmacopoeia-National Formulary (USP-NF), European Pharmacopoeia (PhEur), International Pharmacopoeia (PhInt), Japanese Pharmacopoeia (JP) and Indian Pharmacopoeia (IP) in different parts of the world and the role of these pharmacopoeias are to embellish quality specifications for active pharmaceutical ingredients (APIs), finished pharmaceutical products (FPPs) and general requisites, e.g. for dosage forms [7]. So, it is momentously incumbent to maintain the quality of aerosols by variegated numbers evaluation, based on the series of tests carried out during the formulation development and finished product testing stages [16]. The purpose of this study is to give an outline about the in-process and finished product quality control tests for pharmaceutical aerosols based on pharmacopoeial standards and specifications.

2. UNIVERSAL TESTS FOR PHARMA-CEUTICAL AEROSOLS

2.1 Description

This test is often called appearance on a specification and is a qualitative description of the pharmaceutical aerosols. For example, the description of aerosols on a specification may read: black cap, blue body, imprinted with ‘‘R_x’’ on cap [7,17,18].

2.2 Identification

The purpose of an identification or identity test is to verify the identity of the active pharmaceutical ingredient (API) in the pharmaceutical aerosol. This test should be able to discriminate between compounds of closely related structures that are likely to be present [7,17,18].

2.3 Assay

This test determines the strength or content of the API in the pharmaceutical aerosol and is sometimes called a content test [7,17,18].

2.4 Impurities

This test determines the presence of any component that is not the API or an excipient of pharmaceutical aerosol. The most common type of impurities that are measured is related substances, which are process impurities from the new drug substance synthesis, degradation products of the API, or both [7,17,18].

3. IPQC AND FPQC TESTS FOR PHARMACEUTICAL AEROSOLS

QC tests are necessary to ensure the proper performance of pharmaceutical aerosols. Pharmaceutical aerosols are assessed based on the series of tests carried out during the formulation development, in process testing and finished product testing stages [19]. Guidelines of standard quality control tests for pharmaceutical aerosols are described in various pharmacopoeias and regulatory bodies. In addition to these European Pharmaceutical Aerosol Group (EPAG), International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) are scientifically investigated the standard and regulations for orally inhaled drug products [20,21]. EPAG is a voluntary non-profit making organization dedicated to the pharmaceutical industries that are developing orally inhaled and nasal drug products (OINDPs) within Europe. The objectives of the EPAG are to focus on pharmaceutical issues relevant to pulmonary and nasal delivery products, including clinical aspects as appropriate, to establish scientifically based best practices, to provide consensus comment to industry and government agencies to promote safety and quality standards, and to recommend harmonized standards and methodology. Current areas of activity are particularly focused on the regulatory environment and guidance, industry best practice and aerosol science. EPAG has established several sub terms (Impactor, Nasal product methods, Nebulisers, Quality by Design, Lactose and Reduced Stability Testing) to scientifically investigate issues that present considerable problems in the context of oral and nasal inhaler evaluation, evaluate where further knowledge is needed, and aid decision making with supportive data of high quality. EPAG has a number of direct contacts within several regulatory agencies, such as those in the UK, Sweden, Germany and Canada [22]. IPAC-RS is an international association that seeks to advance the science, and especially the regulatory science, of OINDPs by collecting and analyzing data, and by conducting joint research and development projects. IPAC-RS members include innovator and generic companies that develop, manufacture or market orally inhaled and nasal drug products for local and systemic treatment of a variety of debilitating diseases

such as asthma, chronic obstructive pulmonary disease and diabetes. IPAC-RS aims to build consensus and contribute to effective regulations and standards by sharing the results of its research through conferences, technical journals, and discussions with regulatory bodies. IPAC-RS engages, as appropriate, in scientific and technical discussions and consensus-building with international authorities and standard-setting bodies such as the US FDA, the EMA, Health Canada, the USP, the International Conference on Harmonization (ICH), the International Organization for Standardization (ISO), and regulatory agencies in other world regions. IPAC-RS also collaborates with trade associations and academic researchers around the globe [23].

IPQC and FPQC tests for pharmaceutical aerosols according to pharmacopoeial standards and specifications are listed below:

3.1 Propellant

Gas chromatography or IR spectrophotometry methods are used to determine the identity of propellant, and when a blend of the propellants is used, to determine the composition. The purity and acceptability of the propellant are checked by determination of moisture, halogen, and non-volatile residue [24,25].

3.2 Valves, Actuators and Dip Tubes

These parts are subjected to physical and chemical inspection. For this testing a representative sampling of the valves from each batch is made according to existing methods of sampling (Military Standard Mil-STD-105D). Twenty five valves are selected and placed in suitable containers. The containers are filled with specific test solutions given in Table 1. A button actuator with 0.02 inch orifice is attached to the valves. The filled containers are placed in a suitable atmosphere at a temperature of 25±1ºC. When the products have attained the temperature of 25±1ºC, the filled containers are actuated to fullest extent for at least 2 seconds. This procedure is repeated for a total of 2 delivered from each 25 test units. The individual delivery weights in milligrams are divided by the specific gravity of the test solution to obtain the valve delivery per actuation in microliters [25].

The test procedure applies to two categories of metered aerosol valves having the following limits given in Table 2.

Out of 50 individual deliveries, if 4 or more are outside limits for the specified valve delivery, the valves are rejected. If 3 individual deliveries are outside limits, another 25 valves are sampled, and the test is repeated. The lot is rejected if more than 1 delivery is outside the specification. If 2 deliveries from 1 valve are beyond limits, another 25 valves should be tested. The lot is accepted if not more than 1 delivery is outside the specification [25].

3.3 Containers

Containers are examined for defects in the lining. Several quality control aspects include specifications for the degree of conductivity of electric current as a measure of the exposed metal. Glass containers must be examined for flaws. The dimensions of the neck and other parts must be checked to determine conformity to specifications. The weights of the container should be determined [26].

3.4 Weight Variation

Weight checking is done by periodically adding tared empty aerosol container to filling lines which after filling with concentrate are removed and weighed. The same procedure is used for checking the weight of the propellants. As a further check, the finished container is weighed to check the accuracy of the filling operation [26]. The unit of this test is expressed as pounds and ounces.

Table 1. Ingredients of test solutions [25]

Ingredients (% w/w)	Test solutions A	Test solutions B	Test solutions C
Isopropyl myristate	0.1%	0.1%	0.1%
Dichlorodifluoromethane	49.95%	25.0%	50.25%
Dichlorotetrafluoroethane	49.95%	25.0%	24.75%
Trichloromonofluoromethane	-	-	24.9%
Alcohol USP	-	49.9%	-
Specific Gravity at 25ºC	1.384	1.092	1.388

Table 2. Limits for acceptance of aerosol valves [25]

Deliveries (µl)	Limits (%)
54 or less	±15
55 to 200	±10

3.5 Spray Testing

Many pharmaceutical aerosols are 100% spray tested. This serves to clear dip tube of pure propellant (for products filled by pressure through the stem, body and dip tube), to clear the dip tube of pure concentrate (for products filled by pressure under the cap or around the stem), and to check for defects in valves and spray pattern. For metered valves, it serves to prime valve so that it is ready for use by the patient. Determination of spray patterns involves the impingement of sprays on a piece of paper that has been treated with dye-talc mixture. The particles that strike the paper cause the dye to go into solution and to be absorbed onto the paper. It gives a record of the spray pattern [25,27].

3.6 Flame Projection

The aerosol product is sprayed to an open flame for about 4 seconds and the extension of the flame is measured with the help of a ruler, which is expressed as cm [25].

3.7 Flash Point

For this test Tag Open Cup (TOC) apparatus is the standard test apparatus. The aerosol product is chilled to a temperature of about –25ºF and transferred to the test apparatus. The temperature of the test liquid is increased slowly and the temperature at which the vapors ignite is taken as the flash point, which is usually expressed in ℃ [25].

3.8 Vapor Pressure

The vapor pressure can be determined by pressure gauge. Variation in pressure indicates the presence of air in headspace. A can punctuating device is also available for accurately measuring vapor pressure [25,28]. The unit of this test is expressed as psig.

3.9 Density

It is determined by hydrometer or a pycnometer. For this test a pressure tube is fitted with metal fingers and Hoke valve, which allow for the introduction of liquids under pressure. The hydrometer is placed into the glass pressure tube. Sufficient sample is introduced through the valve to cause the hydrometer to rise half way up the length of the tube. The density can be read directly [25,29]. The density is generally expressed as g/ml.

3.10 Moisture Content

Karl Fischer method or gas chromatography method has also been used for determination of moisture content of aerosol [25,29]. Moisture content is expressed as %.

3.11 Net Contents

The tared cans, placed onto the filling line are reweighed, and the difference in weight is equal to the net contents. The other method is a destructive method and consists of weighing a full container and then dispensing the contents. The contents are then weighed. The difference in weight gives the amount of contents present in the container [29]. The unit of this test is expressed as pounds and ounces.

3.12 Foam Stability

The life of a foam ranges from a few seconds for quick breaking foam to one hour or more depending on the formulation. The methods which are used to determine the foam stability includes visual evaluation, time for a given mass to penetrate the foam, time for a given rod that is inserted into the foam to fall and rotational viscometer [25,29].

3.13 Particle Size Determination

Cascade impactor and light scattering decay methods are used for particle size determination. Cascade impaction devices classify aerosol particles and droplets on the basis of those particles aerodynamic diameters. The principle of their operation is to separate aerosol particles and droplets from a moving airstream on the basis of particle or droplet inertia impaction. Each stage of the impactor comprises a series of nozzles or jets through which the sample laden air is drawn, directing any airborne towards the surface of the collection plate for that particular stage. Whether a particular particle impacts on that stage is dependent on its aerodynamic diameter. Particles having sufficient inertia will

impact on that particular stage collection plate, whilst smaller particles will remain entrained in the air stream and pass to the next stage where the process is repeated. The stages are normally assembled in a stack or row in order of decreasing particle size. As the jets get smaller, the air velocity increases such that smaller particles are collected [30]. Light scattering decay is based on the principle that as aerosols settle in turbulent condition, here the particle size is determined by changes in light intensity of the Tyndall beam [25]. The unit of particle size is expressed as µ.

3.14 Therapeutic Activity

For inhalation aerosols, the determination of therapeutic activity depends on the particle size. For topical aerosols therapeutic activity is determined by applying the therapeutically active ingredients topically to the test areas and the amount of therapeutically active substances absorbed is determined [31,32].

3.15 Toxicity Study

The topically administered aerosols are checked for chilling effect or irritation in the skin. When the aerosol is topically applied, thermistor probe attached to the recording thermometer is used to determine the change in skin temperature for a given period of time. For inhalation aerosols toxicity study is done by exposing test animals to vapors sprayed from the aerosol container [31,32].

3.16 Description

A description of both the formulation and the full delivery device (e.g., including actuator) should be given where applicable. For nebulization products, the immediate packaging should be described [33].

3.17 Assay

In order to detect the presence of API, aerosols assay has to be done by using the suitable analytical method to produce good finished product. For multi-dose products, the amount of drug substance should be determined per weight unit or per volume unit, as applicable. For single dose products, the assay should be expressed as mass per dosage unit [33].

3.18 Mean Delivered Dose

The amount of drug substance in one actuation should also be determined by calculating the mean of the delivered dose uniformity test results, with corrections as necessary to convert from “per dose” amounts to “per actuation” amounts. Limits of ±15 percent of the label claim are applicable for this test [33].

3.19 Delivery Rate for Topical Aerosols

According to USP-NF, this test is applied to topical aerosols containing drug, in solution or suspension, packaged under pressure, and released upon activation of an appropriate valve system. This test is performed only to topical aerosols where containers fitted with continuous valves. For this test selection should not be less than four aerosol containers, if needed to shake, until the label includes the direction, then the caps and covers are removed, and actuate each valve for 2 to 3 seconds. Each container is weighed accurately, and immersed in a constant-temperature bath until the internal pressure is equilibrated at a temperature of 25ºC as determined by the constancy of internal pressure, as directed under the Pressure test below. Then the containers are removed from the bath, excess moisture is removed by blotting with a paper towel, if needed to shake, until the label includes the direction, then each valve is actuated for 5 seconds (accurately timed by use of a stopwatch), and each container is weighed again. The containers are returned to the constant-temperature bath, and repeat the foregoing procedure three times for each container. Finally, the average delivery rate is calculated in g per second, for each container [34,35].

3.20 Delivered Amount for Topical Aerosols

According to USP-NF, this is suitable for topical aerosols with continuous valves presented as solution or suspension. For this test the containers are returned to the constant-temperature bath, continuing to deliver 5 second actuations to waste, until each container is exhausted. Sufficient time is allowed to ensure between each actuation to avoid significant canister cooling. Finally the total weight loss is calculated from each container which is the delivered amount [34,35].

3.21 Pressure Test for Topical Aerosols

For this test, according to USP-NF, selection should not be less than 4 topical aerosols of solution or suspension where containers fitted with continuous valves, then the caps and covers are removed, and immersed in a constant-temperature bath until the internal pressure is constant at a temperature of 25ºC. The containers are removed from the bath, followed by shaking, the actuator and water are removed, if any, from the valve stem. Each container is placed in an upright position, and the pressure is determined in each container by placing a calibrated pressure gauge on the valve stem, holding firmly, and actuating the valve so that it is fully open. The gauge is of a calibration approximating the expected pressure and is fitted with an adapter appropriate for the particular valve stem dimensions. The pressure is monitored directly from the gauge and commonly expressed in psig [34,35].

3.22 Minimum Fill for Topical Aerosols

This test is appropriate for topical aerosols in solution or suspension. For this test selection of a sample must be filled 10 containers, and removed any labeling that might be altered in weight during the removal of the container contents. Thoroughly cleanse and dry the outsides of the containers by suitable means, and weighed individually. The contents are removed from each container by employing any safe technique (e.g., chill to reduce the internal pressure, remove the valve, and pour). Any residual contents are removed with suitable solvents and then rinse with a few portions of methanol. As a unit the container, the valve and all associated parts are retained and finally heated at 100ºC for 5 minutes. Each of the containers together with its corresponding parts is cooled, and again weighed. The difference between the original weight and the weight of the empty aerosol container is the net fill weight. Determination of the net fill weight of each container is tested. According to USP-NP the requirements are met if the net weight of the contents of each of the 10 containers is not less than the labeled amount [34,35].

3.23 Leakage Test for Topical Aerosols

Topical aerosols of solution or suspension fitted with continuous valves are subjected to this test. 12 aerosol containers are selected, and recorded the date and time to the nearest half hour. Each container is weighed to the nearest mg, and also recorded, in mg, of each as W_1. Containers are allowed to stand in an upright position at a temperature of 25±2ºC for not less than 3 days, and again weighed each container, recording the weight, in mg, of each as W_2, and recording the date and time to the nearest half hour. The time, T, is determined in hours, during which the containers were under test. Finally the leakage rate is calculated in mg per year, of each container taken by the formula:

$$365 \times 24/T \times W_1 - W_2$$

Where plastic-coated glass aerosol containers are tested, dry the containers in a desiccator for 12 to 18 hours, and allow them to stand in a constant-humidity environment for 24 hours prior to determining the initial weight as indicated above. The test is conducted under the same constant-humidity conditions. Empty the contents of each container tested by employing any safe technique (e.g., chill to reduce the internal pressure, remove the valve, and pour). Any residual contents also removed by rinsing with suitable solvents, then rinse with a few portions of methanol. As a unit the container, the valve, and all associated parts are retained, and heated at 100ºC for 5 minutes. Cool, weigh, record the weight as W_3, and determine the net fill weight ($W_1 - W_3$) for each container tested. If the average net fill weight has been determined previously, that value may be used in place of the value ($W_1 - W_3$) above [34,35].

According to USP-NF, the requirements are met if the average leakage rate per year for the 12 containers is not more than 3.5 percent of the net fill weight, and none of the containers leaks more than 5 percent of the net fill weight per year. If 1 container leaks more than 5 percent per year, and if none of the containers leaks more than 7 percent per year, the leakage rate of additional 24 containers is determined as directed herein. Not more than 2 of the 36 containers leak more than 5 percent of the net fill weight per year, and none of the 36 containers leaks more than 7 percent of the net fill weight per year. Where the net fill weight is less than 15 g and the label bears an expiration date, the requirements are met if the average leakage rate of the 12 containers is not more than 525 mg per year and none of the containers leaks more than 750 mg per year. If the leakage rate of the 1 container is more than 750 mg per year, but not more than 1.1 g per year, then the leakage rate of an additional 24 containers is determined as directed above. Not more than 2 of the 36

containers leak more than 750 mg per year, and none of the 36 containers leaks more than 1.1 g per year. This test is in addition to the customary in-line leak testing of each container [34,35].

3.24 Number of Discharges per Container for Topical Aerosols

According to USP-NF, this test is performed only on topical aerosols of solution or suspension fitted with dose-metering valves. The number of discharges or deliveries is determined by counting the number of priming discharges plus those used in defining the spray contents, and continue to fire until the label claim number of discharges. The requirements are met if all the containers or inhalers tested contain not less than the number of discharges stated on the label [34,35].

3.25 Delivered-dose Uniformity for Topical Aerosols

The test for delivered-dose uniformity is required for solution or suspension type topical aerosols fitted with dose-metering valves. For collection of the minimum dose from each of 10 separate containers, the sampling Apparatus A or B stated in USP-NF is used [34,35].

For this test according to USP-NF unless otherwise specified in the individual monograph, the requirements for delivered-dose uniformity is met if not less than 9 of the 10 doses are between 75 percent and 125 percent of the specified target-delivered dose and none is outside the range of 65 percent to 135 percent of the specified target-delivered dose. If the contents of not more than 3 doses are outside the range of 75 percent to 125 percent of the specified target-delivered dose, but within the range of 65 percent to 135 percent of the specified target-delivered dose, select 20 additional containers, and follow the prescribed procedure for analyzing 1 minimum dose from each. The requirements are met if not more than 3 results, out of the 30 values, lie outside the range of 75 percent to 125 percent of the specified target-delivered dose, and none are outside the range of 65 percent to 135 percent of the specified target-delivered dose [34,35].

3.26 Uniformity of Delivered Dose for Pressurized Metered-dose Inhalers

This test is applicable for pressurized metered-dose preparations for inhalation. Pressurized metered dose inhalers usually operate in a valve-down position. For inhalers that operate in a valve-up position, an equivalent test is applied using methods that ensure the complete collection of the delivered dose. The dose collection apparatus must be capable of quantitatively capturing the delivered dose. The apparatus consists of a filter-support base with an open-mesh filter-support, such as a stainless steel screen, a collection tube that is clamped or screwed to the filter-support base, and a mouthpiece adapter to ensure an airtight seal between the collection tube and the mouthpiece. Use a mouthpiece adapter that ensures that the front face of the inhaler mouthpiece is flush with the front face or the 2.5 mm indented shoulder of the sample collection tube, as appropriate. The vacuum connector is connected to a system comprising a vacuum source and a flow regulator. The source is adjusted to draw air through the complete assembly, including the filter and the inhaler to be tested, at 28.3 L/min (±5 percent). Air should be drawn continuously through the apparatus to avoid loss of the active substance into the atmosphere. The filter-support base is designed to accommodate 25 mm diameter filter disks. The filter disk and other materials used in the construction of the apparatus must be compatible with the active substance and solvents that are used to extract the active substance from the filter. One end of the collection tube is designed to hold the filter disk tightly against the filter-support base. When assembled, the joints between the components of the apparatus are airtight so that when a vacuum is applied to the base of the filter, all of the air drawn through the collection tube passes through the inhaler [36].

If there are no instructions to the patients, the inhaler is shacked for 5 s and 1 delivery is discharged to waste. By depressing the valve for a sufficient time, the inverted inhaler is discharged into the apparatus in order to ensure complete discharge. The procedure is repeated until the numbers of deliveries that constitute the minimum recommended dose have been sampled. After that the amount of active substance is determined. The procedure is repeated for a further 2 doses [36].

The inhaler is discharged to waste, waiting not less than 5 s between actuations, until (n/2) + 1 delivery remain, where n is the number of deliveries stated on the label. 4 doses are collected using the procedure described above. Again the inhaler is discharged to waste, waiting

not less than 5 s between actuations, until 3 doses remain and these 3 doses are collected using the procedure described above. For preparations containing more than 1 active substance, the test for uniformity of delivered dose for each active substance should be carried out [36].

According to BP and IP unless otherwise justified and authorized, the preparation complies with the test if 9 out of 10 results lie between 75 percent and 125 percent of the average value and all lie between 65 percent and 135 percent. If 2 or 3 values lie outside the limits of 75 percent to 125 percent, the test for 2 more inhalers should be repeated. Not more than 3 of the 30 values lie outside the limits of 75 percent to 125 percent and no value lies outside the limits of 65 percent to 135 percent [36,37].

3.27 Number of Deliveries per Inhaler for Pressurized Metered-dose Inhalers

For this test according to BP 1 inhaler is taken and discharged the contents to waste, actuating the valve at intervals of not less than 5 s. The total number of deliveries so discharged from the inhaler is not less than the number stated on the label (this test may be combined with the test for uniformity of delivered dose) [36].

3.28 Uniformity of Delivered Dose for Non-pressurized Metered-dose Inhalers

The dose collection apparatus must be capable of quantitatively capturing the delivered dose. The apparatus described in the test for uniformity of delivered dose for pressurized metered-dose preparations may be used [36].

The inhaler is discharged into the apparatus. The procedure is repeated until the numbers of deliveries that constitute the minimum recommended dose have been sampled. Quantitatively the contents of the apparatus are collected and the amount of active substance is determined. The procedure is repeated for a further 2 doses [36].

The inhaler is discharged to waste, until (n/2) + 1 minimum recommended dose remains, where n is the number of minimum recommended deliveries stated on the label. Four doses are collected using the procedure described above. Again the inhaler is discharged to waste until 3 doses remain. These 3 doses are collected using the procedure described above. For preparations containing more than 1 active substance, the test for uniformity of delivered dose for each active substance should be carried out [36].

For this test according to BP unless otherwise justified and authorized, the preparation complies with the test if 9 out of 10 results lie between 75 percent and 125 percent of the average value and all lie between 65 percent and 135 percent. If 2 or 3 values lie outside the limits of 75 percent to 125 percent, the test for 2 more inhalers should be repeated. Not more than 3 of the 30 values lie outside the limits of 75 percent to 125 percent and no value lies outside the limits of 65 percent to 135 percent. Where justified and authorized, another apparatus and procedure may be used [36].

3.29 Number of Deliveries per Inhaler for Non-pressurized Metered-dose Inhalers

For this test according to BP 1 inhaler is taken and then the contents are discharged to waste. The total number of deliveries so discharged from the inhaler is not less than the number stated on the label (this test may be combined with the test for uniformity of delivered dose) [36].

3.30 Uniformity of Delivered Dose for Inhalation Powders

A dose collection apparatus similar to that described for the evaluation of pressurized metered-dose inhalers may be used provided that the dimensions of the tube and the filter can accommodate the measured flow rate [36].

According to BP and IP the preparation complies with the test if 9 out of 10 results lie between 75 percent and 125 percent of the average value and all lie between 65 percent and 135 percent. If 2 or 3 values lie outside the limits of 75 percent to 125 percent, the test for 2 more inhalers should be repeated. Not more than 3 of the 30 values lie outside the limits of 75 percent to 125 percent and no value lies outside the limits of 65 percent to 135 percent. In justified and authorized cases, these ranges may be extended but no value should be greater than 150 percent or less than 50 percent of the average value [36,37].

3.31 Number of Deliveries per Inhaler for Multi-dose Inhalation Powders

For this test according to BP discharge doses from the inhaler until empty, at the predetermined flow rate. The discharged deliveries are recorded. The total number of deliveries so discharged from the inhaler is not less than the number stated on the label (this test may be combined with the test for uniformity of delivered dose) [34].

3.32 Uniformity of Content for Inhalation Powders

The content of active ingredient in each of 10 inhalers taken at random is determined using the method given in the monograph of IP or by any other suitable analytical method of equivalent accuracy and precision [37].

According to IP inhalers comply with the test if not more than one of the individual values, thus obtained is outside the limits 85 to 115 percent of the average value and none is outside the limits 75 to 125 percent. If two or three individual values are outside the limits 85 to 115 percent of the average value the determination is repeated using another 20 inhalers. The inhalers comply with the test if in the total sample of 30 inhalers not more than three individual values are outside the limits 85 to 115 percent and none is outside the limits 75 to 125 percent of the average value [37].

3.33 Microbial Contamination for Inhalation Powders

In this test according to IP total viable aerobic bacterial count is not more than 100 CFU per g of the powder (Table 3).

Table 3. Microbial limits for inhalation powders [37]

Microorganisms	Absent in per gram (g) of the powder
Salmonella	50
Escherichia coli	10
Staphylococcus aureus	10
Pseudomonas aeruginosa	10

4. CONCLUSION

Quality is the key issue within the pharmaceutical industry. Controlling the quality of pharmaceutical products is a relentless concern of WHO. Efforts have been made around the world to assure the practice of quality along with effective medicines. As, among the drug products, pharmaceutical aerosols are pressurized dosage form, it's in-process and finished product quality must be maintained under rigorous quality control tests to ensure proper performance of the package, active ingredients and safety during use and storage. Any deviations from each and every test mentioned in this study will hamper the finished product quality. So tests mentioned in pharmacopoeias for the pharmaceutical aerosols must strictly be performed to ensure the proper quality. Therefore, human health safety can be secured with pharmaceutical aerosols.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENTS

The authors wish to thank the Department of Pharmacy, Southeast University, Dhaka-1213, Bangladesh.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Anonymous. In-process revision. Available:http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/pharmaceuticalDosageForms.pdf (Accessed 28 September 2015)
2. Ashurst I, Malton A, Prime D, Sumby B. Latest advances in the development of dry powder inhalers. Pharmaceutical Science and Technology Today. 2000;3(7):246-256.
3. Anonymous. Aerosol therapy Available:https://quizlet.com/13012403/egans-chapter-36-aerosol-therapy-flash-cards/ (Accessed 28 September 2015)
4. Anonymous. EudraLex: The rules governing medicinal products in the European Union. Available:http://ec.europa.eu/health/files/eudralex/vol-4/2014-03_gmp_chapter_6.pdf (Accessed 28 September 2015)

5. Mostafa H. Good Manufacturing Practices (GMP) and its role in quality control. Available:https://www.linkedin.com/pulse/20140423234120-45122425-good-manufacturing-practices-gmp-and-its-role-in-quality-control (Accessed 28 September 2015)
6. Dewan SMR, Alam A, Ahamed SK. A comparative quality control study on conventional ibuprofen tablets available in Bangladeshi pharma market. Int Res J Pharm. 2013;4:96-98.
7. Uddin MS, Mamun AA, Tasnu T, Asaduzzaman M. In-process and finished products quality control tests for pharmaceutical tablets according to pharmacopoeias. J of Chemi and Pharmace Res. 2015;7(7):180-181.
8. Srujana N, Balachandra PM, Venkatesh MP, Balamuralidhara V, Kumar TMP. A comparative study of in-process and finished products quality control tests for ophthalmic products in different pharmacopoeias. Int J of Pharma Teach & Prac. 2012;3(2):261-262.
9. Teja CH, Balamuralidhara V, Vinay S, Sudeendra BR, Kumar TMP. Comparative study of in-process and finished products quality control tests of Indian pharmacopoeia, British pharmacopoeia and United States pharmacopoeia for capsules and liquid orals. Int Res J of Pharma. 2011;2(9):65-66.
10. Anonymous. Quality solutions for inhaler testing. Available:http://www.mspcorp.com/images/pproducts/copley-inhaler-testing-catalog-2015.pdf (Accessed 28 September 2015)
11. Anonymous. Food and drug administration. Available:https://en.wikipedia.org/wiki/Food_and_Drug_Administration (Accessed 28 September 2015)
12. Anonymous. European medicines agency. Available:https://en.wikipedia.org/wiki/European_Medicines_Agency (Accessed 28 September 2015)
13. Anonymous. Medicines and healthcare products regulatory agency. Available:https://en.wikipedia.org/wiki/Medicines_and_Healthcare_Products_Regulatory_Agenc (Accessed 28 September 2015)
14. Mazumder B, Bhattacharya S, Yadav A. Total quality management in pharmaceuticals: A review. Int J of PharmTech Rese. 2011;3(1):365-366.
15. Anonymous. Pharmaceutical cGMPS for the 21st Century-A risk-based approach: Second progress report and implementation plan. Available:http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/UCM071836 (Accessed 28 September 2015)
16. Brambilla G, Ganderton D, Garzia R, Lewis D, Meakin B, Ventura P. Modulation of aerosol clouds produced by pressurized inhalation aerosols. International Journal of Pharmaceutics. 1999;186:53-61.
17. Jr LVA. Remington: An introduction to pharmacy. 1st ed. UK: Pharmaceutical Press; 2013.
18. Uddin MS, Mamun AA, Rashid M, Asaduzzaman M. In-process and finished products quality control tests for pharmaceutical capsules according to Pharmacopoeias. Bri J of Pharmace Res. 2016;9(2). (In Press).
19. Brambilla G, Ganderton D, Garzia R, Lewis D, Meakin B, Ventura P. Modulation of aerosol clouds produced by pressurised inhalation aerosols. Int J of Pharmaceu. 1999;186:53-61.
20. Anonymous. A review of the European Pharmaceutical Aerosol Group (EPAG) technical subteam. Available:http://www.inhalationmag.com/dynamic/CrossIndustryOrg/crossind_epag_review.pdf (Accessed 5 November 2015)
21. Anonymous. An introduction to the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS). Available:http://www.inhalationmag.com/dynamic/CrossIndustryOrg/crossind_ipac-rs.pdf (Accessed 5 November 2015)
22. Nichols SC. European Pharmaceutical Aerosol Group (EPAG); History, aims and successes. Available:https://www.google.com.bd/url?sa=t&rct=j&q=&esrc=s&source=web&cd=4&cad=rja&uact=8&ved=0CDIQFjADahUKEwjHhISt2pbJAhUBCY4KHVWkBpM&url=http%3A%2F%2Fepag.co.uk%2FDownload2.asp%3FDID%3D850&usg=AFQjCNHxp8QRM_YEpIkn_bJOt4HrfQHK-g&sig2=CnnrdzRU9Ik3aitSKjXHLQ&bvm=bv.107467506,d.c2E (Accessed 17 November 2015)
23. Dundon A, Wallace R, Mannerstrale F. Collaborative IPAC-RS initiatives to advance device development. Available:http://ddl-conference.com/files/DDL24Abstracts/37.D

undon/37.Dundon.pdf (Accessed 17 November 2015)
24. Shaik NB. Quality control tests for pharmaceutical aerosols. Available:http://www.pharmainfo.net/aerosols/quality-control-tests-pharmaceutical-aerosols (Accessed 28 September 2015)
25. Lachman L, Lieberman H, Kanig JL. The theory and practice of industrial pharmacy. 3rd ed. Philadelphia: Lea & Febiger; 1986.
26. Pokar HG, Patel KR, Patel NM. Review on: Pharmaceutical aerosol. Inter Pharma Sciencia. 2012;2:63-64.
27. Benjamin EJ, Korten J, Shek E. Characterization of spray patterns of inhalation aerosols using thin-layer chromatography. J Pharm Sci 1983;72: 380-5.
28. Haywood PA, Martin-Smith M, Smith IJ. Establishing more meaningful specifications and tests for metered dose pressurised inhalers formulated as suspensions. Pharm Forum. 1989;15: 5193-202.
29. Anonymous. Aerosols. Available:http://www.authorstream.com/Presentation/sreekanth0339-1127092-aerosols/ (Accessed 28 September 2015)
30. Anonymous. Andersen cascade impactor. Available:http://www.copleyscientific.com/home/inhaler-testing/aerodynamic-particle-size/andersen-cascade-impactor-aci (Accessed 17 November 2015)
31. Sunita L. An overview on: pharmaceutical aerosols. Iner Res Jour of Phar. 2012; 3(9):72.
32. Maheshraje. Quality control & evaluation of pharmaceutical aerosols. Available:http://www.authorstream.com/Presentation/Maheshraje-812238-quality-control-evaluation-of-pharmaceutical-aerosols/ (Accessed 28 September 2015)
33. Anonymous. Guideline on the pharmaceutical quality of inhalation and nasal products. Available:http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003568.pd (Accessed 28 September 2015)
34. United States Pharmacopeial Convention. United States Pharmacopoeia 33-National Formulary 28. USA: Stationery Office; 2010.
35. Anonymous. Aerosols, nasal spray, metered-dose inhalers and dry power inhalers. Available:http://www.pharmacopeia.cn/v29240/usp29nf24s0_c601_viewall.html (Accessed 28 September 2015)
36. British Pharmacopoeia Commission. British Pharmacopoeia. 8th ed. Great Britain: Stationery Office; 2014.
37. Indian Pharmacopoeia Commission. Indian Pharmacopoeia. Ghaziabad: Indian Pharmacopoeia Commission; 2007.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/12834