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A REVIEW ON COMPARATIVE STUDY OF IN-PROCESS AND FINISHED PRODUCTS QUALITY CONTROL TESTS FOR STERILE AND NON STERILE DOSAGE FORM

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ABSTRACT

In a pharmaceutical organization a quality control is a fundamental segment that refers to a process of striving to produce a product by a series of in process quality control test in order to eliminate or prevent error at any stage of production. The study deals with in process product quality control tests for sterile and non sterile dosage forms taking compendia specifications of IP, BP, USP. Those all quality control test which carried out during the manufacturing of product or before marketing of the product denote as in process quality control test . In process Quality control deals with testing, sampling, specification, documentation which ensure that all tests are actually carried out prior to release of material for sale or use. This is the most ideal approach for determining the pharmaceutical quality of the finished dosage form. This article deals with quality control of sterile dosage form (parenteral and ophthalmic) and non sterile dosage form (tablets, capsules etc.).

INTRODUCTION

Quality is suitability of drugs for their intended use determined by their efficiency weighed against safety, according to label claim, or as promoted or publicized their conformity to specifications regarding identity, purity and other characteristics. The ISO definition states that quality control is "the operational techniques and activities that are used to fulfill requirements for quality". This definition could imply that any activity whether serving the improvement, control, management or assurance of quality could be a quality control activity. Quality control of Pharmaceutical products is a concept that covers all measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that the raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics.

In process quality control (IPQC) is a procedure or set of procedures intended to ensure that a manufactured product or performed service adheres to a defined set of quality criteria or meets the requirements of the client. In process quality control test carried out during the production in the industry or before finishing the product or we can say before marketing the product. These quality control control test carried out in order to maintain the quality, standard and to minimize the error in the finished product.IPQC is concerned with providing accurate, specific & definite descriptions of the procedures to be employed from the receipt of raw materials to the release of the finished dosage forms.It includes operational techniques and individual activities that focus on controlling or regulating processes and materials to fulfill requirements for quality.The focus is on preventing defective products.

The In-Process Quality Control system lays emphasis on the responsibility of manufacturer's processors in ensuring consistency in quality during all stages of production by adopting quality control drills and exercising control on raw materials and bought-out components, manufacturing process, packing and final testing. Finished product is product which has undergone all stages of production including packaging. Quality control test is done for finished product to check the integrity of these products. Different pharmacopoeia gives specific limits according to the regulatory requirements of that particular region.

Methods:

(A) IN PROCESS QUALITY CONTROL (IPQC) FOR STERILE DOSAGE FORM:

Sterile dosage form:- These are the products which are manufactured using sterilization or aseptic processing conditions.

There are two types of sterile dosage forms

1. Parenteral preparation
2. Opthalmic formulations

The in-process quality control test includes the leakage and clarity testing. The quality control of finished product required the pyrogen and sterility testing.

1. Leakage test:

Leakage test is employed to test the package integrity. Package integrity reflects its ability to keep the product in and to keep potential contamination out". It is because leakage occurs when a discontinuity exists in the wall of a package that can allow the passage of gas under pressure or concentration differential existing across the wall. Leakage test can be done by dye bath test.

2.Dye bath test:

The test container is immersed in a dye bath. Vacuum and pressure is applied for some time. The container is removed from the dye bath and washed. The container is then inspected for the presence of dye either visually or by means of uv spectroscopy. The dye used may be of blue, green, yellowish-green color. The dye test can be optimized by use of a surfactant and or a low viscosity fluid in the dye solution to increase the capillary migration through the pores. The dye test is widely accepted in industry and is approved in drug use. The test is inexpensive and is requires no special equipment required for visual dye detection. However, the test is qualitative, destructive and slow. The test is used for ampoules and vials.

3. Clarity test: Clarity testing is carried out to check the particulate matter in the sample.

In this test transparent particles or white particles obserbed against the black background and the black or dark particles obserbed against the white background.

4. Pyrogen test: There are two type of test for detecting pyrogen in the formulation.

4.1 LAL test: The LAL (limulus amebocyte lysate) Assay is an *in vitro* assay used to detect the presence and concentration of bacterial endotoxins in drugs and biological products. Endotoxins, which are a type of pyrogen, are lipopolysaccharides present in the cell walls of gram-negative bacteria. Pyrogens as a class are fever-inducing substances that can be harmful or even fatal if administered to humans above certain concentrations. this test is based upon the gelling property of an enzyme, the limulus amebocyte lysate extracted from the horse shoe crab, limulus polyphormus. The enzyme gels in the presence of bacterial endotoxin and the degree of gelling is related to the amount of endotoxin present.a no. of instrument are available for measuring the degree of gelling of enzyme.the test can be used

for quantifying the amount bacterial endotoxin present and provide a better information regarding the quality of a product than rabbit pyrogen test which is more of a qualitative test.

4.2 Rabbit test: The rabbit pyrogen test in an *in vivo* test to detect pyrogens qualitatively. Rabbits have a similar pyrogen tolerance to humans, so by observing a change in body temperature in rabbits it is possible to make a determination of the presence of pyrogens. This method can detect non-bacterial endotoxin pyrogens as well as bacterial endotoxins. It is intended to be used for liquid products that can be tolerated by the test rabbit in a dose of 10 ml per kg, injected intravenously, generally within a period of not more than 4 minutes. For products that require preliminary preparation or are subject to special conditions of administration, additional directions given in the monograph should be followed.

Test animal: Use healthy, adult rabbits, preferably of the same variety. House the animals individually in an area of uniform temperature (±2 °C), possibly with uniform humidity, and free from disturbances likely to excite them. The animals are given **ad libitum** water and food, commonly used for laboratory animals. One to 3 days before using an animal that has not previously been used for a pyrogen test, condition it by conducting a training exercise as described under the recommended procedure, omitting the injection. Do not use animals for pyrogen tests more frequently than once every 48 hours. After a pyrogen test in the course of which a rabbit's temperature has risen by 0.5 °C or more, or after a rabbit has been given a test substance that was adjudged pyrogenic, at least 2 weeks must be allowed to elapse before the animal is used again.

Temperature recording: use an accurate thermometer graduated in 0.1 °c that has been tested to determine the time necessary to reach the maximum reading, or any other temperature-recording device of equal sensitivity. Insert the temperature-sensing device into the rectum of the test animal to a depth of about 6 cm. If the temperature-sensing device is to remain inserted throughout the sensing period, restrain the rabbit with a lightly-fitting neck stock that allows it to assume a natural resting posture. When a thermometer is used, allow sufficient time for it to reach a maximum temperature, as previously determined, before taking the reading.

Procedure: Perform the test in the area where the animals are housed or under similar environmental conditions. For 2 hours before the test and during the test, withhold all food from the animals being used. Access to water may be allowed. The animals should be placed under the conditions of the test at least 1 hour before the injection. Prior to the test, 40 minutes before the injection of the test material, determine the temperature of each animal by

taking 2 measurements at an interval of 30 minutes. The mean of the 2 temperatures serves as the "control temperature" of the animal. The control temperature recorded for each rabbit constitutes the temperature from which any subsequent rise following the injection of the material is calculated.

In any one test, use only those animals the control temperatures of which do not deviate by more than 1.0 °C from each other. Those animals for which the 2 temperatures used to determine the control temperature have deviated by more than ±0.2 °C from the mean should not be used in the test, nor should any animal with a control temperature below 38.0 °C or above 39.8 °C. Render the syringes, needles, and glassware free from pyrogens by heating at 250 °C for not less than 30 minutes or by any other suitable method. Warm the solution to be tested to approximately 38 °C.

Inject into a marginal vein of the ear of each of 3 rabbits 10 ml of the solution per kg of body weight or the amount specified in the monograph. The injection should last not longer than 4 minutes, unless otherwise specified in the monograph. When the injection has been completed, record the temperature of the animal during a period of 3 hours, taking the measurements continuously or every 30 minutes. The maximum temperature recorded for each rabbit is considered to be its response; if the temperature readings taken after the injection are all below the control temperature, the response is treated as a zero temperature rise.

Interpretation of result according to IP, BP, USP: Table I

Pharmacopeia	No. of rabbits in a group	Passes if temp. is not more than (°C)	Fails if temp is more than (°C)
IP	3	1.4	Each rabbit temp raise should not be more than 0.6°C
	8	3.7	
USP	3	----	Each rabbit temp raise should not be more than 0.6°C
	8	3.3	
BP	3	1.15	2.65
	6	2.80	4.30
	9	4.45	5.95
	12	6.6	6.6

5.Sterility test: the test for sterility are intended for detecting the presence of viable micro organism in pharmaceutical preparation that are designed to be sterile. The test is based on the principle that if micro oragism are placed in a medium that provide optimum condition of nutrition, moisture, P^H, aeration, temperation, they can grow and their presence will be indicated by the presence of turbidity in clear medium.

Test for sterility may be carried out by one of the following two methods.

5.1 Membrane filtration method:

Use membrane filters having a nominal pore size not greater than 0.45 µm whose effectiveness to retain microorganisms has been established. Cellulose nitrate filters, for example, are used for aqueous, oily, and weakly alcoholic solutions; and cellulose acetate filters, for example, are used for strongly alcoholic solutions. Specially adapted filters may be needed for certain products (e.g., for antibiotics). The technique described below assumes that membranes about 50 mm in diameter will be used. If filters of a different diameter are used, the volumes of the dilutions and the washings should be adjusted accordingly. The filtration apparatus and membrane are sterilized by appropriate means. The apparatus is designed so that the solution to be examined can be introduced and filtered under aseptic conditions: it permits the aseptic removal of the membrane for transfer to the medium, or it is suitable for carrying out the incubation after adding the medium to the apparatus itself. After filtration the preparation membrane is cut into two halves. One halve is transferred in to 100 ml of culture medium meant for the growth of the bacteria and incubated at 30 to 35^0C. for not less than 7 days. The another halve is transferred to 100 ml of culture medium meant for fungi and incubated at 20 to 25^0C. for not less than 7 days.

5.2 Direct inoculation method:

Although international pharmacopoeias recommend using standard membrane filtration for sterility testing, there are certain products that are not filterable or deformable. These products are normally tested using direct inoculation. In this method, the test sample is added directly into the required media, ensuring that the amount of sample is below 10% To comply with your different direct inoculation method requirements, we offer sterility test media in various volumes, from 9 mL tubes up to 750 mL bottles. In this method an aliquot quantity of the material being tested is drawn aseptically from the container and transferred to a vessel containing a measured quantity of a suitable culture medium. The culture is incubated at appropriate temperature for not less than 14 days. The culture medium is observed at periodic intervals during the incubation period and at the end to detect presence of any microbial growth.

(B) IN PROCESS QUALITY CONTROL (IPQC) FOR NON STERILE DOSAGE FORM:

Non sterile dosage form: these are the product which are manufactured without any sterilization technique.

- Most probably solid dossage forms such as tablets, capsules come under this class.

In process quality control (ipqc) test for tablet:

These are the following test for tablet such as:

a) Disintegration Test
b) Dissolution Test
c) Hardness Test
d) Friability Test
e) Weight Variation

a) Disintegration test:

- Disintegration of tablet means to breakdown the tablet into smaller particles after swallowing
- The time required to disintegrate the tablet is called disintegration time
- The rate of disintegration depends upon the type of tablet formulation
- Disintegration time is as short as one minute and in few cases it may as long as 30 mins

Apparatus:

The apparatus consists of a basket-rack assembly, a 1000 ml, low-form beaker, 138-160 mm in height and having an inside diameter of 97-115 mm for the immersion fluid, a thermostatic arrangement for heating the fluid between 35 °C and 39 °C, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute, through a distance of not less than 53 mm and not more than 57 mm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 15 mm below the surface of the fluid and descends to not less than 25 mm from the bottom of the vessel on the downward stroke. At no time should the top of the basket-rack assembly become submerged. The time required for the upward stroke is equal to the time required for the downward stroke and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

Procedure*:*

Place one dosage unit in each of the six tubes of the basket and if specified add a disc. Operate the apparatus using water as the immersion fluid unless another liquid is specified and maintain its temperature at 37 °C. At the end of the specified time, lift the basket from the fluid and observe the dosage units: all of the dosage units have disintegrated completely. If one or two dosage units fail to disintegrate, repeat the test on 12 additional dosage units. The requirements of the test are met if not less than 16 of the 18 dosage units tested are disintegrate.

Table -II

Tablet	Disintegration time
Soluble tab.	3 min.
Sublingual tab.	3 min.
Effervescent tab.	5 min.
Uncoated tab.	15 min.
Film coated tab.	30 min.
Sugar coated tab.	1 hr.
Enteric coated tab.	3 hr.

b) Dissolution test :-

- Dissolution means mass transfer from the solid surface to the liquid medium.
- this test is intended to measure the time required for given drug in oral solid dosage form into solution under a specific set of conditions and all particles to pass through mesh-10 screen
- this test is performed in two ways i.e invivo and invitro
- invivo dissolution test is performed in healthy living subjects
- invitro dissolution test is performed in a dissolution apparatus under stimulated biological conditions
- generally two apparatus used for dissolution test

  1) rotating basket apparatus

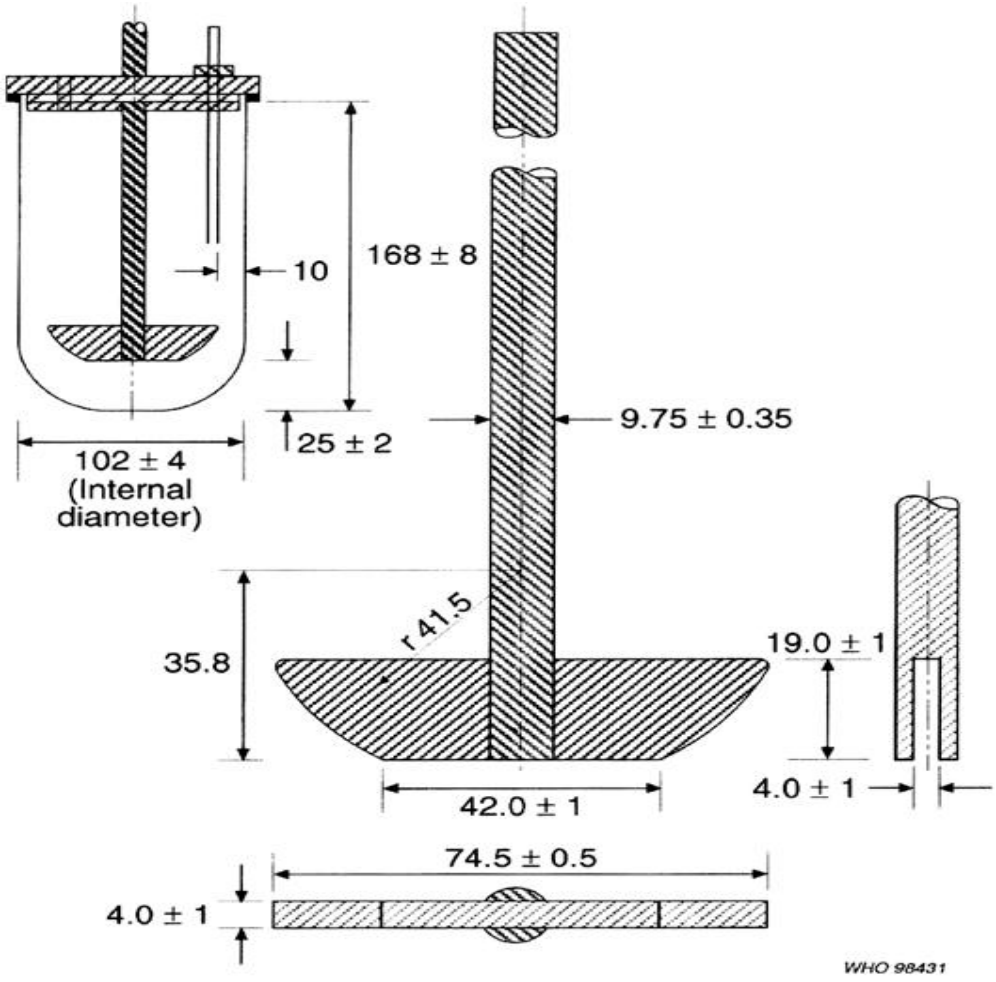
  2) rotating paddle apparatus

Apparatus:

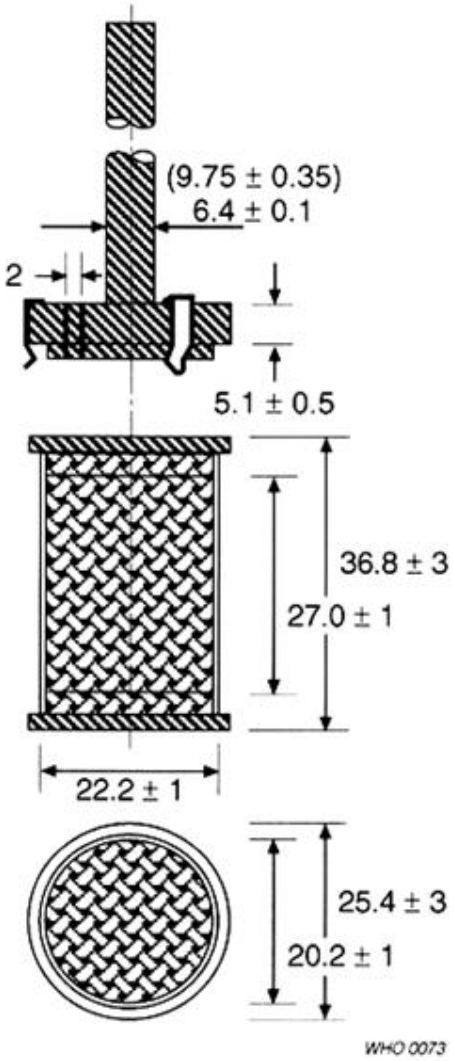
All parts of the apparatus, including any metal that may come into contact with the sample to be tested or the dissolution medium, should be made from a chemically inert material and should not adsorb, react or interfere with the preparation or the dissolution medium. the dissolution assembly should be constructed in such a way that any vibration is reduced to a minimum. The apparatus "paddle" consists of a cylindrical vessel of suitable glass or other suitable transparent material with a hemispherical bottom and a nominal capacity of 1000 ml. the vessel is covered to prevent evaporation of the medium with a cover that has a central hole to accommodate the shaft of the stirrer and other holes for the thermometer and for devices for withdrawal of liquid. the stirrer consists of a vertical shaft with a blade at the lower end. the blade is constructed around the shaft so that it is flush with the bottom of the shaft. when placed inside the vessel, the shaft's axis is within 2mm of the axis of the vessel and the bottom of the blade is 25 ± 2mm from the inner bottom of the vessel. the upper part of the shaft is connected to a motor provided with a speed regulator so that smooth rotation of

the stirrer can be maintained without any significant wobble. the apparatus is placed in a water-bath that maintains the dissolution medium in the vessel at 37 ± 0.5 °c.

the apparatus "basket" consists of the same apparatus as described for "paddle", except that the paddle stirrer is replaced by a basket stirrer. the basket consists of two parts. the top part, with a vent, is attached to the shaft. it is fitted with three spring clips, or other suitable attachments, that allow removal of the lower part so that the preparation being examined can be placed in the basket. these three spring clips firmly hold the lower part of the basket concentric with the axis of the vessel during rotation. the lower detachable part of the basket is made of welded-seam cloth, with a wire thickness of 0.254 mm diameter and with 0.381 mm square openings, formed into a cylinder with a narrow rim of sheet metal around the top and the bottom. if the basket is to be used with acidic media, it may be plated with a 2.5-µm layer of gold. when placed inside the vessel, the distance between the inner bottom of the vessel and the basket is 25 ± 2mm



“Figure I” paddle apparatus



"Figure II" basket apparatus

Procedure*:* ensure that the equipment has been calibrated within the past 6-12 months. place the volume of dissolution medium, as stipulated in the individual monograph, in the vessel; assemble the apparatus and place it in the water-bath; allow the temperature of the dissolution medium to reach 37±0.5°c and remove the thermometer. When apparatus "paddle" is used, allow one tablet of the preparation to be tested to sink to the bottom of the vessel before starting the rotation of the blade, taking care that no air bubbles are present on the surface of the dosage form. in order to stop the dosage form from floating, anchor it to the bottom of the vessel using a suitable device such as a wire or glass helix. when apparatus "basket" is used, place one tablet of the preparation to be tested in a dry basket at the beginning of each test. lower the basket into position before rotation. immediately start rotation of the blade or

basket at the rate specified in the individual monograph. withdraw a sample from a zone midway between the surface of the dissolution medium and the top of the rotating blade or basket, not less than 10 mm below the surface[1] and at least 10 mm from the vessel wall, at the time or time intervals specified. either replace the volume of dissolution medium with a volume equal to that of the liquid removed, or compensate for the loss of liquid by calculation, except where continuous measurement is used.

acceptance criteria*:* the requirements are met if the quantities of active ingredient(s) dissolved from the dosage forms tested conform to the following table, unless otherwise specified in the individual monograph.

stage	samples tested	acceptance criteria
S1	6	each unit is not less than q+5%
S2	6	average of 12 units (s_1+s_2) is equal to or greater than q, and no unit is less than q-15%
S3	12	average of 24 units (s_1 + s_2 + s_3) is equal to or greater than q; not more than 2 units are less than q-15%; no unit is less than q-25%

continue testing through the three stages unless the results conform at either s_1 or s_2. the quantity, q, is the released labelled content of active ingredient as a percentage as specified in the individual monograph; both the 5% and 15% values in the acceptance table are percentages of the labelled content so that these values and q are in the same terms.

c) Hardness test:

The tablets must be hard enough to withstand mechanical stress during packaging, shipment, and handling by the consumer. there are several hand operated tablet hardness testers that might be useful. examples of devices are the strong cobb, pfizer, and stokes hardness testers. the principle of measurement involves subjecting the tablet to an increasing load until the tablet breaks or fractures. the load is applied along the radial axis of the tablet. oral tablets normally have a hardness of 4 to 8 or 10 kg; however, hypodermic and chewable tablets are much softer (3 kg) and some sustained release tablets are much harder (10-20 kg).

d) Friability test*:*

Tablets are constantly subjected to mechanical shocks & aberration during the manufacturing, packing and transportation process. such stress can lead to capping, aberration or eve breakage of the tablets it is there fore important that the tablet is formulated to withstand such

stress in order to monitor the resistance of tablets to such stress and to decide on their suitability for further processing such as coating, tablets are routinely subjected to friability test. friability is defined as the % of weight loss by tablets due to mechanical action during the test. tablets are weighing before and after testing and friability is expressed as a percentage loss on pre test tablet weight. friability refers the ability of the compressed tablet to avoid fracture and breaking during transport. a number of tablets (20 nos.) are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. after 4 minutes of this treatment or 100 revolutions the tablets are weighed and the weight compared with initial weight. the loss due to abrasion is a measure of tablet friability. the value is expressed in percentage.

Minimum weight loss of the tablet should not be NMT 1%.

e) Weight variation test*:*

Weight variation test is performed to check that the manufactured tablets have an uniform weight. As per USP twenty tablets are weighed individually and an compendia weight is taken, the average weight is obtained by dividing the compendia weight by 20, now the average weight is compared to the individual weight of the tablet, For a tablet to pass the test not more than 2 tablets should lie out of the specified percentage and if no tablet differs by more than two times the percentage limit.

Table III

S.N.	Average weight (mg)		Maximum percentage difference allowed
	USP	IP	
1	130 or less	80 or less	10%
2	130-324	80- 250	7.5%
3	More than 324	More than 250	15%

In process quality control (IPQC) test for capsule:

1. Uniformity of Weight of capsules:

It is to be done on 20 capsules.

Limit:

Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in the table,none deviates by more than twice that percentage.

Table IV

Average weight of capsule	Percentage deviation
less than 300 mg	10%
300 mg or more	7.5%

2. Disintegration test:

Apparatus

The apparatus consists of a basket-rack assembly, a 1000 ml, low-form beaker, 138-160 mm in height and having an inside diameter of 97-115 mm for the immersion fluid, a thermostatic arrangement for heating the fluid between 35 °C and 39 °C, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute, through a distance of not less than 53 mm and not more than 57 mm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 15 mm below the surface of the fluid and descends to not less than 25 mm from the bottom of the vessel on the downward stroke. At no time should the top of the basket-rack assembly become submerged. The time required for the upward stroke is equal to the time required for the downward stroke and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

Procedure

Place one dosage unit in each of the six tubes of the basket and if specified add a disc. Operate the apparatus using water as the immersion fluid unless another liquid is specified and maintain its temperature at 37 °C. At the end of the specified time, lift the basket from the fluid and observe the dosage units: all of the dosage units have disintegrated completely. If one or two dosage units fail to disintegrate, repeat the test on 12 additional dosage units. The requirements of the test are met if not less than 16 of the 18 dosage units tested are disintegrated.

Table V

Capsule type	Disintegration time
Soft gelation capsule	1 hr.
Hard gelation capsule	30 min.

RESULT AND DISCUSSION

Quality control should be a fundamental segment of sterile and non sterile products manufacturing. All of the basic tests which are performed are essential and have its own importance in production. All of these tests ensure that product meet its quality which has been judged to satisfactory also. Each test is unique and provide detailed assement of quality control for pharmaceutical products.

REFERENCES

1. Atkers M.J, Larrimor D.S, Guazzao morton D; "Parenteral Quality control" New York, Marcel Deckker; 2006. 180-183.
2. Indian Pharmacopoeia (2007) "Ministry of Health and Family Welfare, Government of India", Indian Pharmacopoeial Commission, Ghaziabad (3) :1651-1654.
3. Lachman.L, Liberman H.A, Kaniz J.L; "The Theory and practice of industrial pharmacy" Bombay, Varghese publication House; 1986.(3) 673-675.
4. Hanna S.A, Avis K.E, Lieberman H.A, Lachman L;"Pharmaceutical dosage forms: Parenteral Medications".2nd ed. (1.) Newyork: Marcel Dekker; 1996: 60-65.
5. Sastry S.V, Nyshadham J.R, Fix J.A; (2000) "Recent technological advances in oral drug delivery: A review". Pharm Sci Technol Today, (3):138-145.
6. Chaudhari P.D, Chaudhari S.P, Lanke S.D, Patel N; (2007) "Formulation and in vitro evaluation of taste masked orodispersible dosage form of Levocetirizine", Indian J Pharm Educ Res., (41):319-328.
7. United State Pharmacopoeia; Published by the national formulary. 2008,vol. (1) 590-660.