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IN PROCESS QUALITY CONTROL: REVIEW

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ABSTRACT

The drug development is a very tedious process which involves drug discovery, animal studies, laboratory testing, clinical studies and trails and regulatory registration. After approval of drug product several agencies like United States Food and Drug Administration (USFDA) require drug to be tested for its quality, purity, strength, identity and stability before it is released into the market for use. This testing is done to improve the effectiveness and safety of the drug. In this process Pharmaceutical Validation and Process control are the important aspects to encounter the problems of quality, safety and efficacy. Process control involves in inspection of raw materials, in-process control and target for final products. These checks and tests are done before the manufacturing process is completed. Monitoring and if required adaptation of manufacturing process in order to meet the specifications are the functions of in-process quality control. This may also include control of environment and equipment. In-process materials should be tested for quality, purity, strength, identity and stability and should be approved or rejected by quality control unit at the time of production. The rejected in-process materials should be controlled, identified and stored under quarantine in order to prevent the use during manufacturing process.

INTRODUCTION

IPQC stands for In-Process Quality Control. The drug development is a very tedious process which involves drug discovery, animal studies, laboratory testing, clinical studies and trails and regulatory registration. After approval of drug product several agencies like United States Food and Drug Administration (USFDA) require drug to be tested for its quality, purity, strength, identity and stability before it is released into the market for use. This testing is done to improve the effectiveness and safety of the drug. In this process Pharmaceutical Validation

and Process control are the important aspects to encounter the problems of quality, safety and efficacy. Process control involves in inspection of raw materials, in-process control and target for final products. These checks and tests are done before the manufacturing process is completed. Monitoring and if required adaptation of manufacturing process in order to meet the specifications are the functions of in-process quality control. The main purpose is to monitor the on-line and off-line performance of manufacturing process and its validation. Even after validation of the manufacturing process CGMP also require good and well-written procedure to monitor its performance.

DEFINITION OF IPQC

IPQC stands for IN-PROCESS QUALITY CONTROL. These checks are done before the manufacturing process is completed. This testing is done to improve the effectiveness and safety of the drug. In this process Pharmaceutical Validation and Process control are the important aspects to encounter the problems of quality, safety and efficacy. In this process Pharmaceutical Validation and Process control are the important aspects to encounter the problems of quality, safety and efficacy. Process control involves in inspection of raw materials, in-process control and target for final products.

IPQC Tests for Tablets

Un-Official Tests

a) Hardness

b) Friability

c) Thickness

Official Tests

a) Weight variation

b) Content Uniformity

c) Disintegration

d) Dissolution

Un-Official Tests

a) Hardness test

It is laboratory test used determine the breaking point and structural integrity of the tablet. The tablet is placed in between the space of the instrument and is slowly adjusted till the tablet breaks. This breaking point determines the structural integrity and hardness of the

tablet. It is performed using devices Pfizer tester, Monsanto tester, Erwica tester and Strong-Cobb tester.

Factors Affecting Hardness

- ❖ Compressive Forces
- ❖ Binder Amount
- ❖ Method of granulation in tablet preparation

b) Friability test

It is a laboratory test performed to test the durability of tablets using an instrument friabilator. This test is carried out by placing a batch of tablets in a friability apparatus. The total wight of the tablets are initially weighed and is allowed to rotate at 25rpm. The tablets are then re-weighed, and weight loss is calculated. Tablets which broke, crack or cleaves fails the test and with less than 1% weight loss passes the test.

Advantages of Friability testing

- Used regularly in pharmaceutical industries to check the tablet robustness in packaging process and transit.
- Used to determine the quality of the product.
- It determines the uniformity and reproducibility of product in batch-to-batch manufacturing.

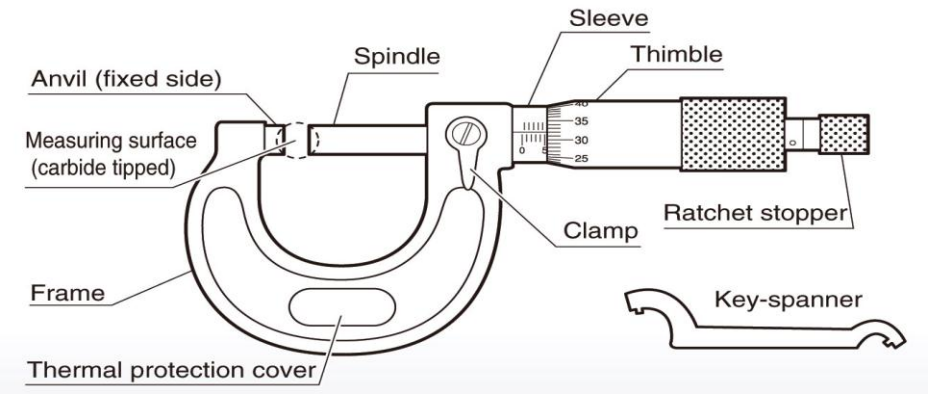
- Repetition is not necessary because a batch of 10/20 tablets are tested at a time, so results are obtained once.
- It is an automated process and no expert supervision required.

Disadvantages of Friability testing

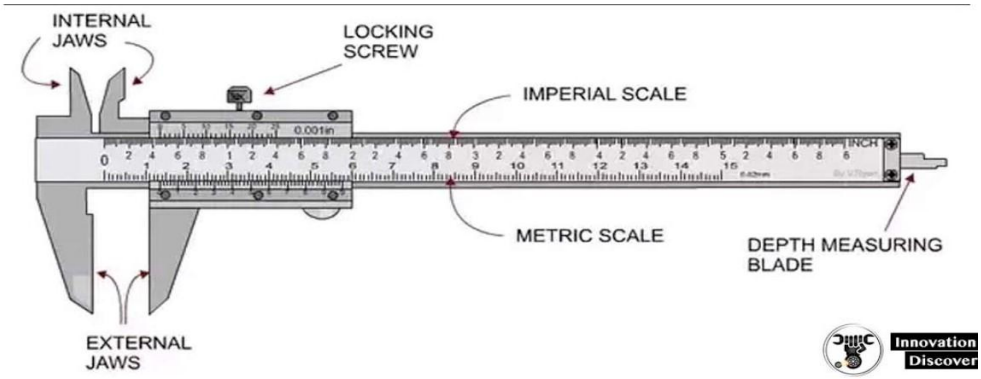
- Moisture content of the tablet or granules, humidity and hardness affect the friability.
- Due to high fragility acryl drums should be very carefully handled.
- Frequent calibration is needed such as drum orientation and numeration.
- Slow process takes more time.

c) Thickness test

Thickness of the tablet depends on the upper and lower clouts at the instant of compression. This is tested using an instruments Vernier calipers and micro-meter. The variation in range is +/- 5.0%.



Micrometer: - The tablet is placed between the two anvils and its thickness is read by scale. It is measured in micrometer (mm).



Vernier Caliper: Here the tablet is placed between the two jaws of the instrument and thickness is measured by reading its scale. It is measured in centimeter (cm).

OFFICIAL TESTS

a) Weight Variation test

Weight variation test is done by weighing 20 tablets individually. The average weight of tablet is calculated and is compared to the individual tablet weight. The value of weight variation is expressed in percentage.

$$\text{Weight Variation} = (IW-AW)/AW \times 100\%$$

Where,

IW- Individual Weight

AW- Average Weight

Factors responsible for weight variation

- Flow Properties
- Degree of segregation

b) Content uniformity test

It is defined as test for tablets containing less than ≤ 25mg and less than ≤ 25% of the tablet weight in case of coated or uncoated tablets.

Method

- Not less than 30 tablets are selected
- 10 tablets are assayed individually as directed in the monograph
- Calculate the content of active ingredient from assay in each unit
- Calculate Xi = (content / L.C) x100
- Calculate $\bar{X} = \sum Xi / n$ (No. of batches tested)
- Calculate standard deviation $(S) = [(X i- \bar{x})^2 / (n-1)^{1/2}$
- Calculate RSD (Relative Standard Deviation)

$$RSD= (S/\bar{X}) \times 100$$

Acceptance Criteria: The preparation obeys only if each individual content is 85 to 115 % of average content. The preparation fails if more than one individual content is not within these limits and if the contents is outside the limits of 75 and 125% of average content.

c) Disintegration test

It is a process in which the time required by tablet to break into number of particles, it is only a measure of time required by the set of tablets to disintegrate into units. Some of the liquids used in disintegration test are water, simulated gastric fluid (pH=1.2 HCL) or stimulated intestinal fluid (pH=7.5 KH_2PO_4). Disintegration test is done for coated tablets and uncoated tablets.

Method of disintegration for Uncoated Tablets

- The test is started on 6 tablets
- The test is repeated on 12 tablets if two or more tablets from the batch of 6 fail to disintegrate totally within the specified time. Total 18 tablets are consumed for the test.
- Not less than 16 tablets disintegrate totally within the time
- The batch must be rejected if more than two tablets fail to disintegrate

For Coated Tablets

- The tablet must be immersed in distilled water for 5mins to liquify the coat
- The tablet is then placed in the disintegration apparatus filled with water or HCL for 30 mins at 37^oC. Keep in the intestinal fluid if the tablet is not disintegrated.
- The test is repeated on 12 tablets if two or more tablets from the batch of 6 fail to disintegrate totally within the specified time. Total 18 tablets are consumed for the test.
- Not less than 16 tablets disintegrate totally within the time
- The batch must be rejected if more than two tablets fail to disintegrate

For Enteric Coated Tablets

- These enteric coated tablets are kept in distilled water for 5mins to remove the coat
- After this the tablet is placed in simulated gastric fluid (0.1M HCL) for one hour
- For two hours it is placed in stimulated intestinal fluid
- The test is repeated on 12 tablets if two or more tablets from the batch of 6 fail to disintegrate totally within the specified time. Total 18 tablets are consumed for the test.
- Not less than 16 tablets disintegrate totally within the time
- The batch must be rejected if more than two tablets fail to disintegrate

d) Dissolution test

It is defined as the amount of drug substance enter the solution per unit time under standardized conditions of liquid or solid interface. It is the rate determining step for hydrophobic, poorly aqueous soluble drugs.

E.g., Griseofulvin

Several dissolution apparatuses exist to perform dissolution testing studies for tablets.

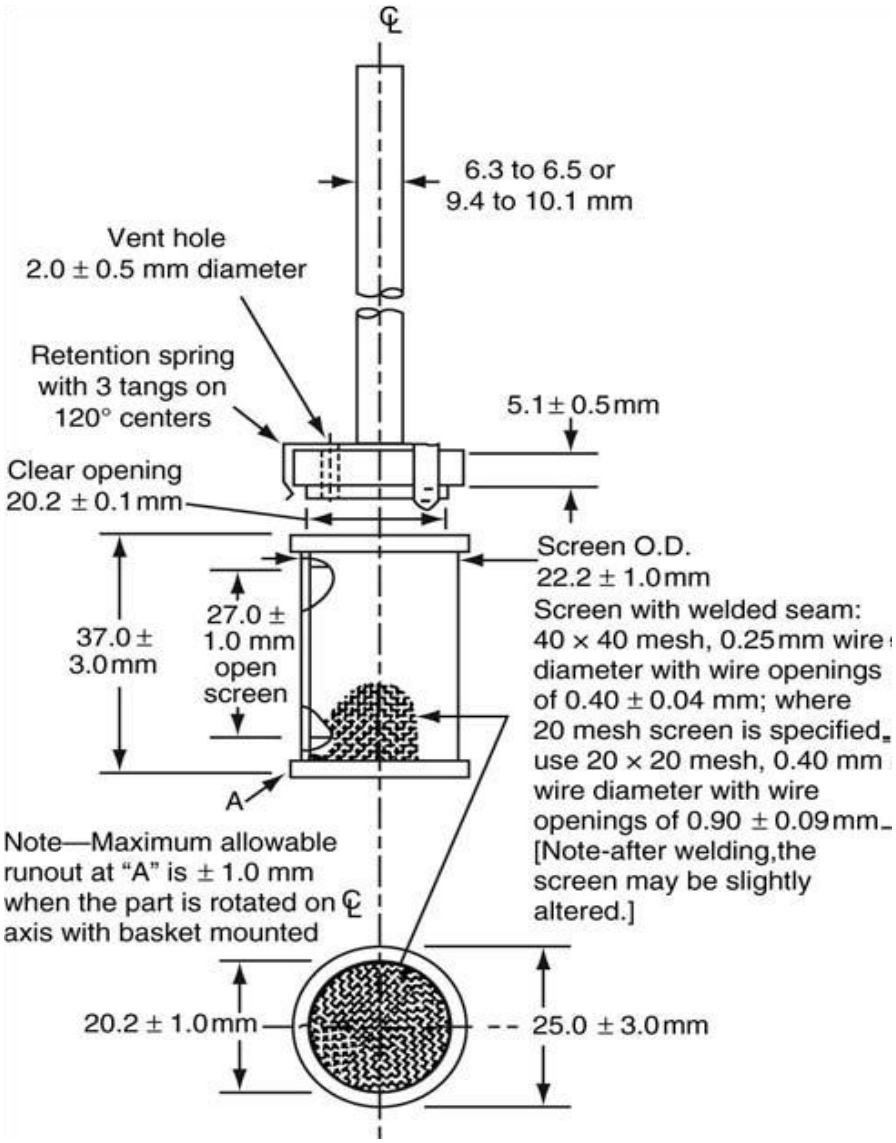
According to IP

Type I - Basket type apparatus

Type II - Paddle type apparatus

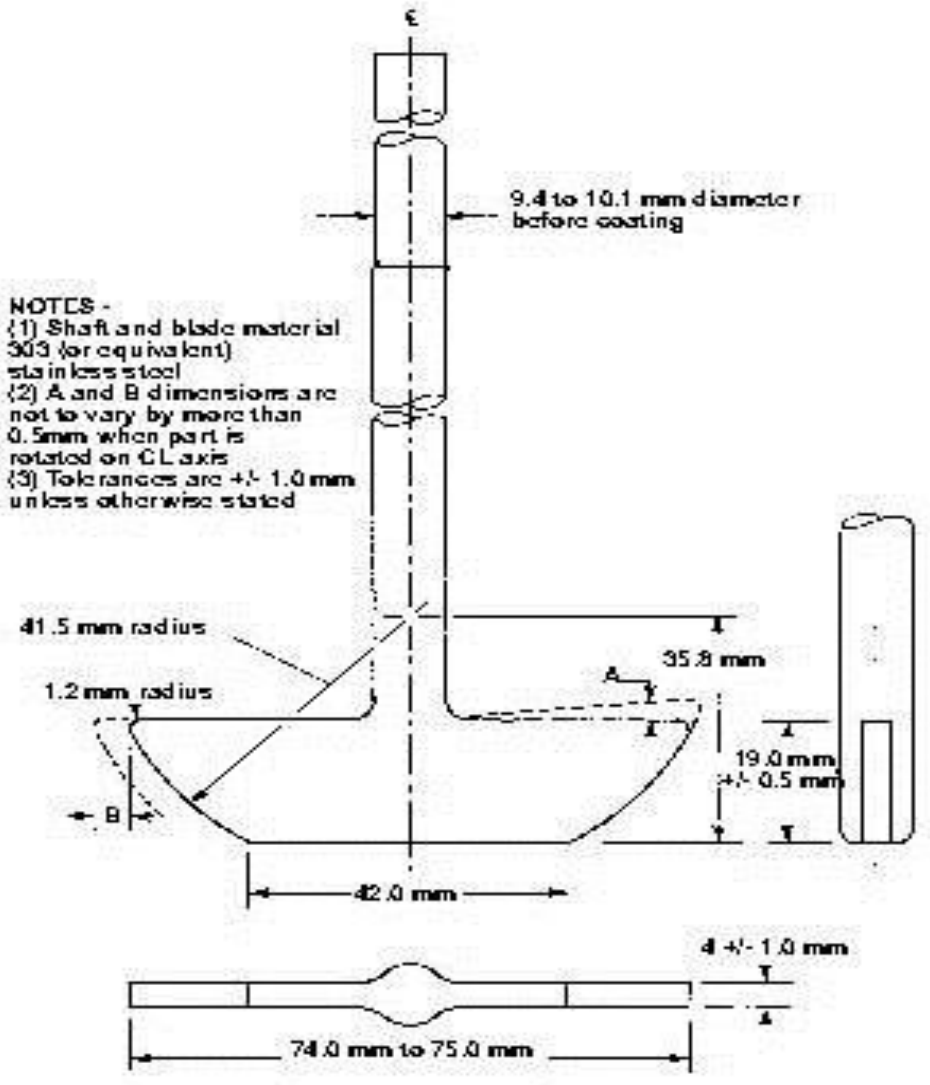
Type I - Basket type apparatus: - This apparatus consists of

- Covered vessel
- Metallic drive shaft
- Stainless steel paddle
- Motor
- Sinker to prevent floating of tablet
- Water batch of holding temperature 37°C ± 5°C
- Acidic or alkaline media



Type II - Paddle type apparatus: - This apparatus consists of

- Covered Vessel
- Metallic drive shaft
- Cylindrical basket
- Motor
- Sample
- Water batch of holding temperature 37^{o}C ± 5^{o}C
- Acidic or alkaline media



Method of determination

Warm the dissolution medium to 36.5° to 37.5°. Place one dosage unit in the apparatus, cover the vessel and operate the apparatus at the specified rate. After two hours of operation in the

acid medium, extract an aliquot of the liquid and progress immediately as directed under buffer stage.

IPQC Tests for Capsules

a) Density

b) Angle of Repose

c) Particle Size Distribution

d) Appearance

e) Gel strength of Gelatin

f) Viscosity

g) Uniformity of Content

h) Content of active ingredients

a) Density

Density is determined by taking the ratio of mass to the volume.

Density = Mass / Volume

- **Bulk Density**

Bulk density is determined by measurement of the volume of identified mass of residue sample which is passed over screen into a graduated cylinder.

Bulk Density = Mass of Granules / Bulk volume of Granules

- **Tapped Density**

Tapped density is determined by tapping the measuring cylinder in which the powder or drug sample is placed. The initial volume of the sample was recorded and the cylinder is again tapped mechanically and the volume readings are recorded until the minor change in volume of sample is detected.

b) Angle of Repose

It is determined by the measurement of the angle between the sample (drug/powder) mass and the bottom surface on which the sample is placed.

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

Procedure

- The funnel is fixed to a stand at a suitable height from the surface
- The powder or sample is then placed in the funnel and tapped with minimal force
- The sample then passes through the funnel forming a heap of mass like a hill
- Then the height of heap formed by tapping is measured and recorded.

The angle of repose is then calculated by using the formulae

$$\Theta = \tan\text{-}1(h/r)$$

Where,

Θ = angle of repose

h = height of pile

r = radius of base

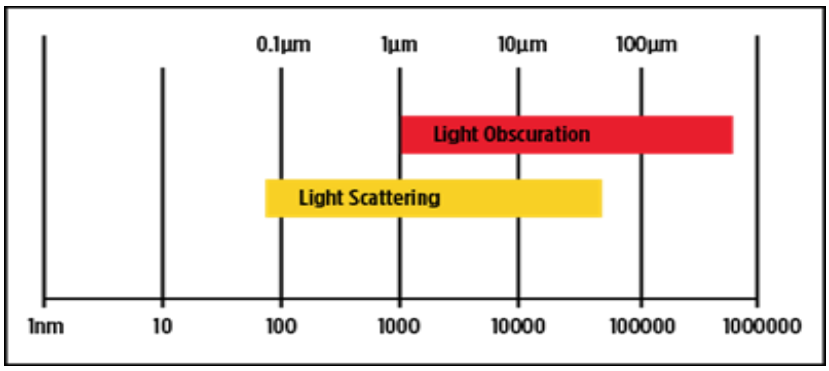
c) Particle Size Distribution

There are different methods to determine the particle size of the sample. Sieving is the oldest and easy method to determine particle size of powder and granules.

- Sieving Method
- Light Obscuration Particle Count Test
- Microscopic Particle Count Test

Light Obscuration Particle Count Test

Light obscuration functions by fleeting a diluted stream of elements in a liquid suspension among a light source and a detector. Laser diode is the light source in HIAC 9703+ liquid particle counter, which irradiates specific particles in the stream to produce a shadow or impasse of light on the detector. This impasse is called ‘obscuration’. The detector measures the decrease in light intensity, and by using a calibration curve it progressions the signal to determine unit size.



d) Appearance

The capsules should be of uniform size and appearance produced on large gauge or small gauge. To detect any fault or errors in size and appearance of capsule pictorial or electronic review must be carried out. Physical variability in the capsule can be determined by hardening or softening, appearance, change in shape and size, inflammation and staining or change in colour of the capsule. Capsules which are defected or damaged should be rejected.

e) Gel strength of Gelatin

Procedure

- 105 ml of water is pipetted out at 10-15^{o} C into a standard flask
- Add 7.5 gm of Gelatin to the water sample and stir continuously
- Allow it to stand for 1 hour
- Then adjust the temperature to 62^{o}C gradually in 15 minutes by heating it in a water bath maintained at a of temperature 65^{o}C.
- The sample is finally mixed by inversion and is allowed to stand for 15 mins
- Then it is placed in a water bath of temperature 10±0.10 and is cooled without disturbing the sample for more than 17 hours
- The gel strength is determined by Bloom Gelometer an instrument which is specially developed to determine the gel strength under specific standard conditions

f) Viscosity

Viscosity is a basic property of liquids or gels which is related systematically to the confrontation to flow. The basic unit is “POISE”. Viscosity is measured by the determination of the time taken by the volume of liquid or gel to pass through the capillary.

There are different instruments to determine viscosity of liquids or gels

- Ostwald-Type Viscometer,

- Brookfield viscometer,
- Rotouisco meter,
- Stormer viscometer

g) Uniformity of Content

It is one of the pharmaceutical parameters in quality control testing of capsules. Various capsules are selected and analysed by employing preferable analytical method and the individual content in each capsule is assayed.

Acceptance Criteria

The preparation obeys only if each individual content is 85 to 115 % of average content. The preparation fails if more than three individual contents are not within the limits of 85 to115% of average content and if one or more individual contents is outside the limits of 75 and 125% of average content.

Calculation of Acceptance Value by formula

$$|M-X| + ks$$

h) Content of active ingredients

For this test determine the amount of active ingredient by the method described in the assay and calculate the amount of active ingredient per capsule.

The capsule complies with the test if content of active ingredient lies within the stated range. The range is based on the requirement that 20 capsules, or such other number indicated in the monograph Where 20 capsules are not available a smaller number not less than 5 can be used, for this smaller number tolerances are widened in accordance with given capsule.

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