Review Article **CODEN: AJPCFF** **ISSN: 2321 – 0915**

Asian Journal of Phytomedicine and Clinical Research

Journal home page: www.ajpcrjournal.com

PHARMACEUTICAL SOLID DOSAGE FORMS: IN PROCESS QUALITY CONTROL TESTS

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ABSTRACT

In-process quality control (IPQC) tests was important to remove problems from every stage in production and maintain the quality of the In-process product with standards as specified in the pharmacopoeias. The quality of FP depends on in-process control (IPC) tests because it helps to incorporate excellence within the products. The qualitative and quantitative parameters of pharmaceuticals or biopharmaceuticals products was checked by In-process quality control (IPQC). The aim of this investigation was to provide concise information on the IPQC and FPQC (finished products quality control) tests for pharmaceutical solid dosage as per different pharmacopoeias. In the present investigation we was analyzed the quality control tests for tablets, capsules and other solid dosage forms.

KEYWORDS

IPQC, Tablet, QC, IPC, RM, FP, Solid drugs and FPQC.

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INTRODUCTION

In-Process Quality Control Tests (IPQC) are accurate and specific for testing of raw materials (RM) to the release of the finished dosage (FD) forms (Figure No.1). IPQC tests was performed in production area. Manufacturing practices was include in good quality finished products (FP) and had adequate considerations for safety of the employees is recognized as Good manufacturing practices (GMP). GMP is under with both production and quality control (QC). They should not carry any risk for the quality of product. In process testing enables easier identification of problems.

Instrument used in ipqc department

Number of Instruments which are used in IPQC test such as, Disintegration apparatus, Dissolution apparatus, Analytical balance Muffle furnace, Friability testing apparatus, Bulk density apparatus, Tablet hardness tester, Infra-red moisture content measuring apparatus, U.V Spectroscopy, Abbe Refractometer, T.L.C. kit and Karl fisher Titrimeter.

EVALUATION TESTS OF TABLETS

Official Tests

Weight variation, Disintegration, Dissolution and Drug content.

Non-Official Tests

Hardness and Friability.

Official tests

Weight variation test (uniformity of weight)

- Weigh 20 tablet selected at random, each one individually. X1, X2, X3… Xz
- Determine the average weight X= (X1+X2 +X3+…+ Xz)/20.
- **Formula:** Average Weight of Tablet – Individual Weight of Tablet / Average Weight of Tablet * 100.

Limit

Upper limit = average weight + (average weight *% error), Lower limit = average weight - (average weight * % error), The individual weights are compared with the upper and lower limits, NMT two of the tablets differ from the average weight of tablet. USP XX-NF STANDARDS and IP STANDARDS of Weight variation test was reported in Table No.1 and Table No.2.

CONTENT UNIFORMITY TEST

Randomly select 30 tablets. 10 of these assayed individually, NLT 85 % and NMT 115 %of the labeled drug content and the 10^{th} tablet may not contain less than 75 % and more than125 % of the labeled content. If these conditions are not met, remaining 20 tablet assayed individually and none may fall outside of the 85 to 115 % range.

Disintegration test (U.S.P.)

It is the time required for the tablet to break into particles, the disintegration test is a measure only of the time required under a given set of conditions for a group of tablets to disintegrate into particles. It is performed to identify the disintegration of tablet in particular time period. Disintegration test is not performed for controlled and sustained release tablets. According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass. Disintegration test was performed in disintegration test apparatus (Figure No.2).

Disintegration Media

Disintegrations test was conducted in different disintegration Medias such as, Water, Simulated gastric fluid (pH = 1.2 HCl), or Simulated intestinal fluid (pH = 7.5, KH2PO4 (phosphate buffer) + pancreatic enzyme + NaOH). Disintegration Testing Conditions and Interpretation was reported In Table No.3.

Disintegration Test for Uncoated, Coated and Enteric Coated Tablets

U.S.P. method for uncoated tablets

Disintegration test on 6 tablets. If 1 or 2 tablets from the 6 tablets fail disintegrate completely within 30min repeat the same test on another 12 tablet. (i.e. the whole test will consume 18 tablets). NLT 16 tablets disintegrate completely within the time. If more than two tablets (from the 18) fail to disintegrate, the batch must be rejected.

For Coated tablets

Tablet in distilled water for 5min.put the tablet in the apparatus in water or HCL for 30 min at 37ºC (according to the U.S.P). If not disintegrated, put in intestinal fluid. If one or two tablets fail to disintegrate, repeat on 12 tablets. So 16 tablets from the 18 must completely disintegrate within the time, if two or more not disintegrated the batch is rejected.

U.S.P. and B.P Method for Enteric coated tablets

Tablet in simulated gastric fluid (0.1M HCL) for one hour. Then put in simulated intestinal fluid for two hours. If one or two tablets fail to disintegrate,

repeat this test on another 12 tablets. So 16 tablets from 18 should completely disintegrate. If more than two fail to disintegrate the Batch must be rejected.

DISSOLUTION TEST

Dissolution was conducted to detect the percentage amount of release dosage forms. i.e. Tablet. Small particles of tablet having maximum surface area in dissolving media. Disintegration study was not conform that particles will release drug in solution at an appropriate rate, that's why dissolution tests and its specifications developed for all tablet products. Dissolution is mass transfer process. Dissolution is mainly depend on aqueous solubility of drug. It is process in which solid mass transfer in liquid medium. Dissolution based on four process such as,

1. Wetting
2. Solubility
3. Swelling
4. Diffusion.

Particle size, shape, surface area is important factor can affect the rate of dissolution of drug. The aqueous solubility is increases, increases rate of dissolution drug. Dissolution test was performed in dissolution test apparatus (Figure No.3).

Various terminology related to dissolution test

Dissolution

Solid mass transfer process in to liquid medium.

Diffusion

Diffusion is mass transfer process of individual molecules of atoms having continuous random molecular motion contain in concentration gradient is known has Diffusion.

Dialysis

Separation of easily diffusible particle from poorly diffusible particle through semi permeable Membrane.

Ultra filtration

Separation of colloidal particle from sub colloidal particle through semi permeable membrane.

Osmosis

The passage of solvent molecule into solution through semi permeable membrane.

Semi permeable membrane

Thin layer that can separate two phases.

Steady sate

Mass transfer process is remains constant per unit time.

Osmotic pressure

The pressure is exerted in walls of semi permeable membrane through concentration gradient.

Diffusant (penetrant)

The amount of material transport in semi permeable membrane.

Con. Gradient

Concentration of material transport in region of high con. To region of low con.

Mechanism of Dissolution

Dissolution mechanism based on two concept one is a mass transfer process. Second is the concentration of receptor compartment is maintain lower level as compared to donor compartment is known as sink condition.

Theories of Drug Dissolution

Dissolution concept mainly deepens on three dissolution theories, such as, Diffusion layer model/Film Theory, Danckwert's model/Penetration or surface renewal Theory and Interfacial barrier model/Double barrier or Limited solvation theory.

Factor Affecting Dissolution

Dissolution rate of drug is mainly affected by various factors such as, Physicochemical Properties of Drug, Drug Product Formulation Factors, Processing Factors, Factors Relating Dissolution Apparatus and Factors Relating Dissolution Test Parameters.

Dissolution test apparatus

IP apparatus

First is Paddle apparatus (IP) and second is Basket apparatus (IP).

USP apparatus

Apparatus 1 (rotating basket), Apparatus 2 (paddle assembly), Apparatus 3 (reciprocating cylinder), Apparatus 4 (flow-through cell), Apparatus 5 (paddle over disk), Apparatus 6 (cylinder) and Apparatus 7 (reciprocating holder).

USP Dissolution apparatus I (Basket method)

Tablet was placed in a small wire mesh basket attached to the bottom of the shaft connected to a variable speed motor. The basket is deep in a dissolution medium (as specified in monograph) contained in a 1000 ml flask. The flask is cylindrical with a hemispherical bottom. Constant temperature bath of flask maintained at 37 ± 0.5ºC. The speed of motor is adjusted to turn at the specified and quantity sample withdrawn at intervals at specific interval for determination of concentration of drug (Figure No.5).

USP Dissolution apparatus II (Paddle method)

It is same as apparatus-1, except the basket is replaced by a paddle. The dosage form is allowed to sink to the bottom of the flask before stirring. For dissolution test U.S.P. specifies the dissolution test medium and volume, type of apparatus to be used, rpm of the shaft, time limit of the test and assay procedure for. The test tolerance is expressed as a % of the labeled amount of drug dissolved in the time limit (Figure No.6).

Dissolution testing and interpretation IP standards

Dissolution Testing and Interpretation data was reported in Table No.4.

DOSAGE FROM CONDUCTED DISSOLUTION STUDY

IMMEDIATE RELEASE TABLET (CONVENTIONAL TABLET)

a. **Dissolution apparatus** – Type 1 and Type 2 (USP)
b. **Temperature** - 37±0.5˚C
c. **Time** – 30 min
d. **Time of interval** – 5, 10, 15, 20, 25, 30.
e. **Media** – PH 1.2 Acidic Buffer, PH 4.5 Acetate buffer, PH 5.8 Phosphate buffer. (depending upon tablet)
f. **Rpm** – 75 -100 rpm
g. **Volume** – 900 ml
h. **Procedure:** Tablet in cylindrical vessel containing 1000 ml dissolution media having rpm 75 and tem.37±0.5˚C. Dissolution of tablet was conducted 30 min, in 5 min. of interval, after 5 min particular quantity of sample was removed and analyzed by using suitable analytical technique (U.V. spectroscopy and HPLC).

Sustained release tablet

a. **Dissolution apparatus** – Type 2 (USP)
b. **Temperature -**37±0.5˚C
c. **Time** – 7 hrs
d. **Media** – PH 1.2 Acidic Buffer, PH 6.8 Phosphate buffer.
e. **Rpm** – 75 – 100.
f. **Volume** – 900 ml.
g. **Procedure** - Tablet in cylindrical vessel containing PH 1.2 Acidic media (1000ml) having rpm 75 for next two hours and tem. 37±0.5˚C. Dissolution media was changes tablet was added in to PH 6.8 Phosphate buffer for next five hour for 1 hr. of interval. After 1 hr.particular quantity of sample was removed and analyzed by using suitable analytical technique (U.V. spectroscopy and HPLC).

Capsule

a. **Dissolution apparatus** – Type 2 (USP)
b. **Temperature** - 37±0.5˚C
c. **Time** – 5 hrs.
d. **Media** – PH 1.2 Acidic Buffer, PH 6.8 Phosphate buffer.
e. **Rpm** – 75 – 100.
f. **Volume** – 900 ml.
g. **Procedure** - The Capsule was added into cylindrical vessel containing PH 1.2 Acidic media (1000 ml) having rpm 75 for next two hours and tem. 37±0.5˚C. Dissolution media was changes Capsule was added in to PH 6.8 Phosphate buffer for next three hour for 1 hr. of interval. After 1 hr. particular quantity of sample was removed and analyzed by using suitable analytical technique (U.V. spectroscopy and HPLC).

Suppositories

a. **Dissolution apparatus** – Type 1 (USP)
b. **Temperature** - 37±0.5˚C
c. **Time** – 60 min
d. **Time of interval** – 10, 20, 30, 40, 50, 60.

e. **Media** – PH 7.4 Phosphate buffer.
f. **Rpm** – 50 – 75 rpm
g. **Volume** – 900 ml.
h. **Procedure** –Suppository in cylindrical vessel containing dissolution (1000ml) media (PH 7.4 Phosphate buffer) having rpm 75 and tem.37±0.5˚C. Dissolution of Suppository was conducted 60 min, in 10 min. of interval, after 10 min particular quantity of sample was removed and analyzed by using suitable analytical technique (U.V. spectroscopy and HPLC).

NON-OFFICIAL TESTS

Hardness

Tablet having a specific amount of hardness or strength and resistance to friability to withstand mechanical shocks of handling in manufacture, packaging and shipping. Hardness generally measures the tablet crushing strength (Figure No.7).

Importance

To determine the need for pressure adjustments on the tableting machine. Hardness can affect the disintegration and tablet is not too soft, it will not withstand the handling during subsequent processing such as coating or packaging. In general, maximum hardness of tablet, first we conduct disintegration study before rejecting the batch. If the disintegration is in accepted limit then accept the batch.

Factors Affecting the Hardness

1. Compression of the tablet and compressive force.
2. Amount of binder. (More binder à more hardness)
3. Method of granulation in preparing the tablet (wet method gives more hardness than direct method, Slugging method gives the best hardness).

Limits

5 kilograms minimum and 8 kilograms maximum.

FRIABILITY

According to U. S. Pharmacopeia, in friability study of tablet with unit mass equal to or less than 650 mg, take a sample of whole tablet corresponding to 6.5 gm. For tablet with unit mass more than 650 mg, take a sample of 10 tablets. Friability of a tablet can determine in laboratory by friability test apparatus at 25 rpm, for 4 min., dropping the tablets through a Distance of six inches in the friabilator, which is then operate for 100 revolutions (Figure No.8).

Formula

Initial weight of tablet – weight of tablet after friability / Initial weight of tablet * 100.

Limit: less than 1.0 %.

EVALUATION OF PRECOMPRESSIONAL CHARACTERISTICS OF TABLETSOR RHEOLOGICAL CHARACTERISTICS OF GRANULES PARTICLE SIZE AND SHAPE DETERMINATION

Surface area

If required particle size is measured and from this surface area is measured. Most method used is gas absorption and air permeability.

A. In gas absorption method: gas is absorbed as monolayer on particles this is in term of calculated and converted to surface area.
B. In air permeability method: the rate of air permeates a bed of powder, is used to calculate surface area of powder sample.

Angle of repose

It is measured by two methods, one is static angle of repose and second is dynamic angle of repose. Various method for determination of angle of repose shown in Figure 9 and Acceptance limits of angle of repose reported in Table No.5.

Equation is, $\tan \theta = h/r$.

Where, θ - angle of repose, h – height of pile, r – radius of pile.

Hausner's ratio

Hausner's ratio is important to detect interparticulate friction of particles and powder flow characteristics. If powder having low particular friction such as coarse sphere had ratio of approximately 1.2, whereas more as cohesiveness-less free flowing powders such as flaks have Hausner's ratio greater than 1.6.

Formula: Hausner's ratio

Tapped density / Bulk density

Moisture content

Generally the granules contain 2 % moisture. It is required for the binding of the powder or granules during compression in die cavity.Percentage of moisture is calculated by using moisture Balance or IR Balance. The small amount of sample taken from oven to measure moisture content and place in the moisture balance. Initial reading should be note down after that we are initiated the IR Bulb as IR bulb is initiated the moisture is removed from the granules via heating after that note down the reading.

% of moisture is calculated by,

% moisture content = Initial wt. - Final wt. / initial weight X 100

Compressibility index

It is directly related to the relative flow rate cohesiveness and particle size. It is simple fast and popular method of presiding powder flow characters. It can be obtained from bulk density measurements is the % Compressibility index. Acceptance limit Compressibility index was reported in Table No.6.

% Compressibility index = Tapped density - Bulk density / Tapped density X 100.

Table No.1: USP XX-NF Standards

S.No	Average wt. of tablet(mg)	Max. % difference allowed
1	130 or Less	10%
2	130-324	7.5%
3	More than 324	5%

Table No.2: IP Standards

S.No	Average wt. of tablet(mg)	Max. % difference allowed
1	84 or Less	10%
2	84-250	7.5%
3	More than 250	5%

Table No.3: Disintegration Testing Conditions and Interpretation

S.No	Type of tablets	Medium	Temperature	Limit
1	Compressed uncoated	-	37 ± 2^0C	15 minutes or as per individual monograph
2	Sugar coated If 1 or 2 tablets fail	Water 0.1 N HCL	37 ± 2^0C	60 minutes or as per individual monograph
3	Film coated	water	37 ± 2^0C	30 minutes or as per individual monograph
4	Enteric coated	0.1 N HCL and Phosphate buffer pH 6.8	37 ± 2^0C	1 hr or as per individual monograph
5	Dispersible/ Effervescent	water	37 ± 2^0C	LST < 3 minutes or as per individual monograph
6	Buccal	-	37 ± 2^0C	4 hr or as per individual monograph

Table No.4: Dissolution Testing and Interpretation IP Standards

S.No	Quantity Stage/level	Number of tablets tested	Acceptance criteria
1	S1	6	Each unit is < D* + 5 percent**
2	S2	6	Average of 12 units (S1 +S2) is equal to or greater than (>)D, and no unit is less than D - 15 percent**
3	S3	12	Average of 24 units (S1+S2+S3) is equal to or greater than (>)D, not more than 2 units are less than d-15 percent** and no unit is less than d-25 percent**

*D is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labelled content.

** Percentages of the labelled content.

Table No.5: Acceptance limits of angle of repose

S.No	Angle of repose (º)	Type of flow
1	< 25	Excellent
2	25-30	Good
3	30-40	passable
4	> 40	Poor

Table No.6: Acceptance limit Compressibility index

S.No	% Compressibility index	Type of flow
1	5-15	Excellent
2	12-16	Very good
3	18-21	Good
4	23-25	Passable
5	33-38	Poor
6	> 40	Very poor

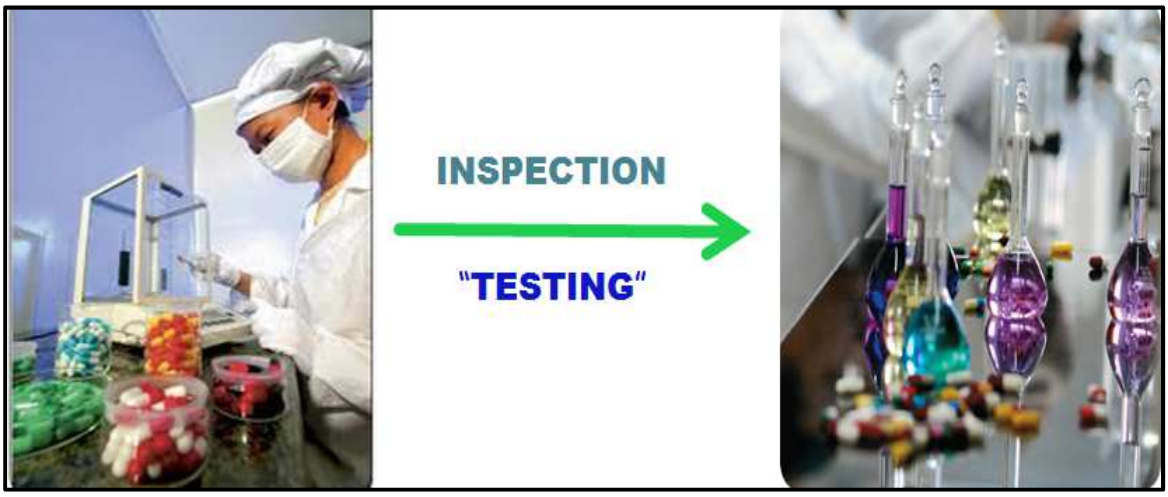

Figure No.1: In-process Quality Control Test

Figure No.2: Disintegration Test Apparatus

Figure No.3: Dissolution Test Apparatus

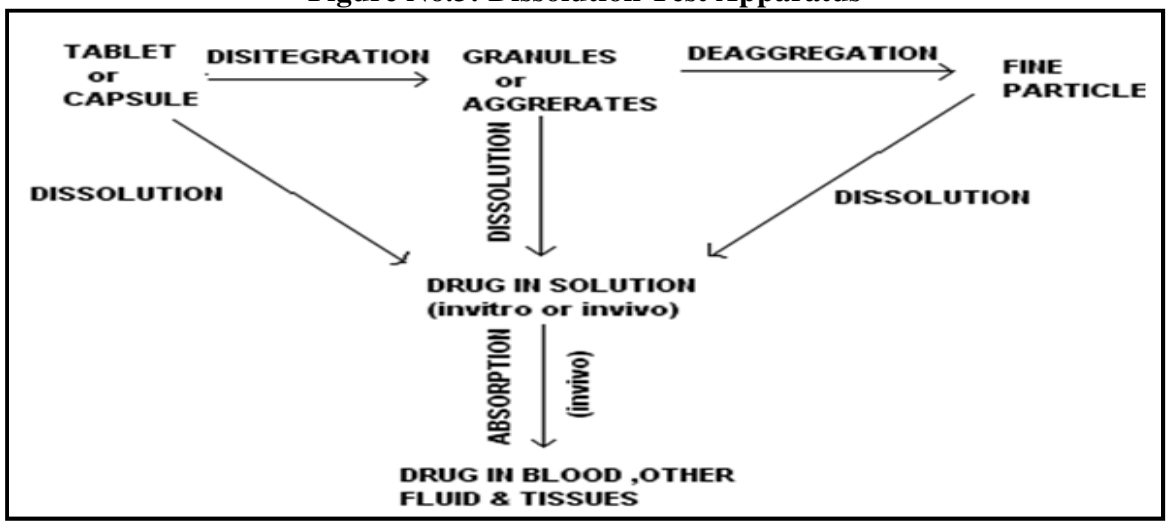

Figure No.4: Dissolution Process of Solid Dosage Forms

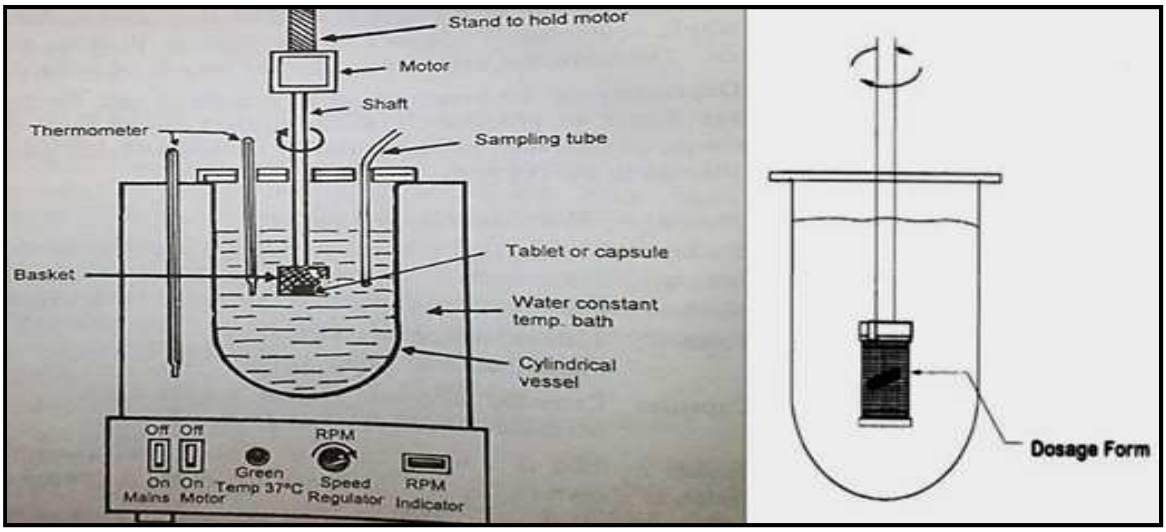

Figure No.5: USP Dissolution apparatus I (Basket method)

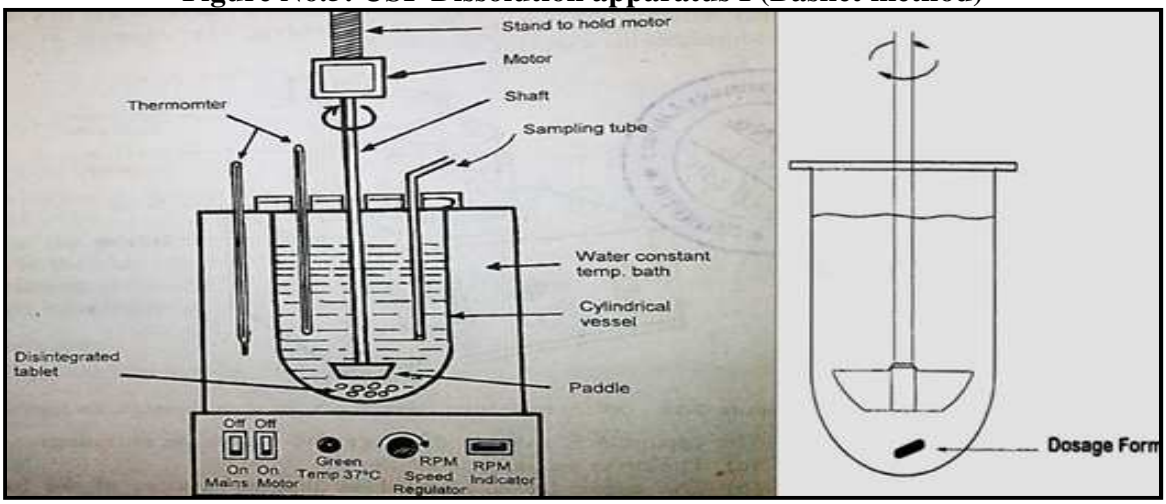

Figure No.6: USP Dissolution apparatus II (Paddle method)

Figure No.7: Hardness Test Apparatus

Figure No.8: Friability Test Apparatus

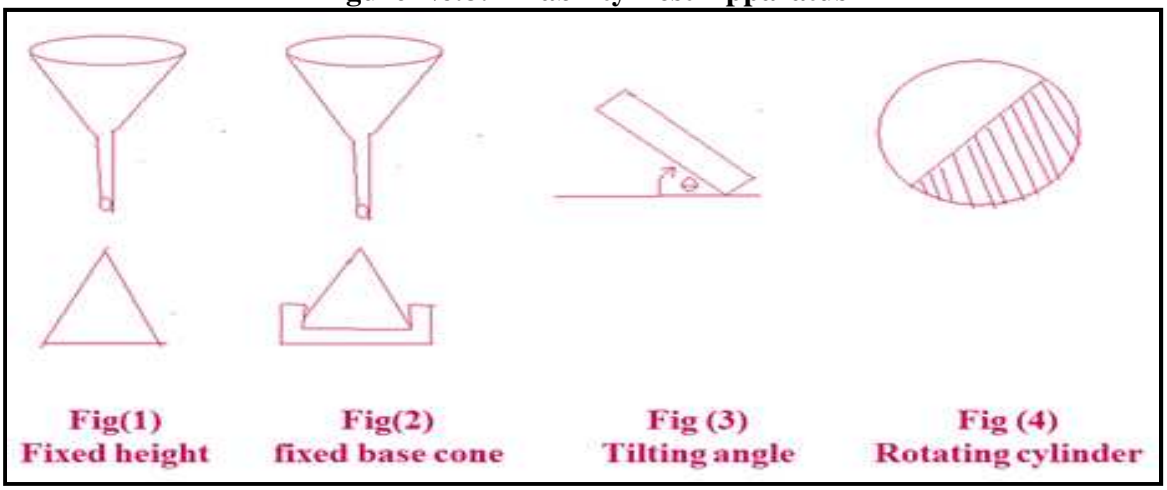

Figure No.9: Method for Determination of Angle of Repose

CONCLUSION

The QC testing was assigned to production or QC depending on the company base of large scale and small scale. The QC executive was determined the quality tests of the tablets or solid dosage to pass the products into market. They was regularly checked by the RA (Regulatory Affairs) and FDA (Food Drug Administration) bodies.

ACKNOWLEDGEMENT

I wish to acknowledge all those who are involved directly or indirectly for compilation of this article. It has been a great honor to work with such a professional.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Sagar Kishor Savale. Pharmaceutical solid dosage forms: in process quality control tests, *Asian Journal of Phytomedicine and Clinical Research,* 6(1), 2018, 44-54.