

New Approaches for Evaluation Test of Pharmaceutical Dosage Forms

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Abstract: Quality is important in pharmaceutical dosage forms, for that we conduct various tests to ensure quality efficiency and safety of product produced Form process which we have to use in it. So here Qualitative and quantitative parameters of pharmaceuticals products was checked by In-Process quality control (IPQC) as well as finished products quality control tests (FPQC) according USFDA and cGMP guidelines. The aim of this article was to provide updated and new information on the IPQC and FPQC tests for various pharmaceutical solid dosages as per different pharmacopoeias. In the present investigation we was analyzed the quality control tests for solid dosage forms, Liquid dosage forms, and semisolid dosage forms with their acceptance criteria as well as instrument/equipment used. We are giving appropriate relevant accurate information of quality control test of various dosage forms in simple way. It having so much importance in our pharmaceuticals industries as well as others because it helps to build excellence, quality, adding accuracy, provide stability within the products.

Keywords: Solid dosage forms; Semisolid dosage form; liquid dosage forms; IPQC; FPQC.

INTRODUCTION:

We are using various dosage forms in our daily life. It includes tablets, capsules, creams, ointment, pastes, jellies, inhalers and various saltines, injections etc. and many mores. These are the examples of various dosage forms. But these are categorised in broad categories of dosage forms like solid dosage forms, liquid dosage forms, and semisolid dosage forms and it also includes many mores according to our needs. While developing these quality products, we have to ensure its safety efficiency stability by conducting various testing, sampling and specification with required acceptance criteria which are the part of quality control. After passing these products their acceptance criteria, then and then only we can get available these products in market. So here we are discussing about its IPQC and FPQC test for various dosage forms.

SOLID DOSAGE FORM:

- Solid dosage forms are unit dosage forms containing medicaments and API in solid state forms. It mainly includes granules, tablets, and capsules [1-4].
- These dosage forms include various quality control tests which are as follows:

1. General Appearance test:

In that parameter, the physical appearance i.e. colour, odour, test and nature of particles are determined.

2. Bulk density:

- The bulk density is depends on the density of powder particles. Bulk density is a spatial arrangement of particles in the powder bed of a powder. The measurements are made using cylinders so it is expressed in grams per mL (gm/ mL). This density is expressed in grams/cubic centimetre (g/cm³). Kilograms per cubic meter (1 gm/mL = 1000 kg/m³) are the international unit of it.
- The powder bulking properties are varying on the many factors i. e. How it was handled by us, so it including, preparation, treatment as well as it depends onto the storage of the sample. The slightest disturbance of the powder bed may result in a changed bulk density so the particles can be packed to have a range of bulk densities. So we have to measure powder bulk density with good reproducibility. This is done by measuring the volume of a known weight of powder sample, which we have been passed through a sieve. For that various methods are used.
- Method 1 is performed by using graduated cylinder.
- Method 2 includes the known volume mass of powder measuring that has been passed through a volumeter into a cup.
- Method 3 is performed by measuring vessel.
- Calculate the bulk density (gm/ml) using the following formula;

Bulk Density = M/V_0

Where, M is weight of the powder and V_0 is the volume of the cylinder.

3. Tapped density:

- The tapped density is obtained by mechanically tapping a graduated measuring cylinder containing a powder sample, it is an increased bulk density attained after mechanically tapping a graduate container containing sample.
- It is performed after observing the initial powder volume. Final volume readings are taken after measuring cylinder is mechanically tapped.
- It is occurred by raising the cylinder and allowing it to drop under its own weight.
- Calculate the tapped density (gm/ml) using the following formula;

Tapped Density = M/V_t

Where, M is weight of the powder and V_t is the volume measured after tapping the cylinder.

4. Angle of repose:

- The angle of repose can also indicate the cohesiveness, Flowability and friction of the granular material.
- The angle of repose is frequently linked with the Hausner's ratio of sample. This angle separates the transitions between phases of the granular material and the powders will flow at angles greater than the angle of repose in record. The various angles and their flow property of powder are given in following tables.

Table 1: Classification of flowability of powder based on repose angle

Sr. no.	Description	Repose Angle
1	Very free flowing	<30°
2	Free flowing	30-38°
3	Fair to passable flow	38-45°
4	Cohesive	45-55°
5	Very cohesive (non-flowing)	>55°

- To find out Angle of repose various methods are used. Which are mentioned below:
 - a. Tilting box method
 - b. Fixed funnel method
 - c. Revolving cylinder/drum method
 - d. Hollow cylinder method
 - e. State-of-the-art methods
 - f. Tilting cylinder method
 - g. State-of-the practice methods

- Formula for Calculating Angle of repose:

Formula for Angle of repose = $\tan^{-1}(h/r)$

Where, is angle of repose, h is height of heap and r is radius of heap.

5. Compressibility Index & Hausner's ratio:

- A measure of the relative importance of these interactions in a given powder by comparative study of the tapped and bulk densities give. That comparison is used as an index of the ability of the powder to flow freely.
- For example the compressibility index and hausner's ratio are measures of the powder's propensity, ability to settle, and they permit an assessment of the real flowing powder. But those interactions are less significant as well as the bulk density and tapped densities will be closer in reading value.
- If material having poorer flowing ability then there are frequently greater interparticle interactions occurred and results has a greater difference between the bulk and tapped densities observed. These differences we can get by finding the compressibility index and the hausner's ratio.
- Compressibility Index is calculating by the following formula:

Index of Compressibility = $100(V_0 - V_f)/V_0$

Where, V_0 is unsettled apparent volume and V_f is final tapped volume.

- Hausner's Ratio is calculated by the following formula;

Hausner's Ratio = V_0/V_f **6. Hardness test:**

- It matches with friability testing but they are not the same thing. The breaking point of a tablet is based on its shape so it is mainly performed on tablets to find out how it changes under different conditions of storage, transportation, packaging and handling before usage.
- So we can say that it is a laboratory technique used by the pharmaceutical industry to determine the breaking point and structural integrity of a tablet.
- We are using 2 main processes to test tablet hardness:
 - a. Compression testing

b. 3 point bend testing

The tablet breaking point we have to measure by using these methods and different apparatus.

- The units of measurement of tablet hardness mostly follow standards used in materials testing. The International System of Units i. e. The kilogram (Kg) is recognized by the SI system as the primary unit of mass and the Newton (N) is the SI unit of force and it is the standard for tablet hardness testing.

9.807 Newtons = 1 Kg (at one G, earth surface gravity).

- The following are the different apparatus used into Hardness testing.
 - The Monsanto tester
 - The Strong-Cobb tester
 - The Pfizer tester
 - The Erweka tester
 - The Dr. Schleuniger Pharmatron tester
 - Kraemer Elektronik's tablet testing system

7. Friability test:

- Friability testing is used to test the durability, crushing strength, capping & lamination of tablets before and after to packing processes and during a transit.
- Dropping a sample of tablets over a fixed time repeatedly involves in it. By using a rotating drum with a baffle attached on it. The result is inspected for broken tablets, and the percentage of tablet mass lost through chipping is calculated by using following formula;

$$\text{Friability of Sample} = \left(\frac{W_i - W_f}{W_i} \right) * 100$$

Where, W_i is the total initial weight of the tablets and W_f is the total final weight of tablets.

- we take a sample of whole tablets corresponding to 6.5 gm if tablets which having a unit mass equal to or less than 650 mg and we take a sample of 10 whole tablets for friability testing for tablets with a unit mass of more than 650 mg.
- In that firstly accurately weigh the tablet sample, and then place the tablets in the drum. Rotate the drum at 25 rpm or 100 rotations in 4 min. and lastly remove the tablets and calculate result by putting required values. Remove any loose dust from the tablets carefully dedusted prior to testing.
- If more amounts of cracked, cleaved, or broken tablets are present in the Tablet sample after performing this test then we can say that the sample fails the test. A maximum mean weight loss from the three samples of not more than 1.0 % is considered, if the results are doubtful or if the weight loss is Greater than the targeted value, the test should be repeated twice and the mean of the three tests was considered for evaluation.

8. Dissolution test:

- Meaning of Dissolution is rate and extends of drug release.
- In-vitro dissolution data are supportive regarding biopharmaceutical aspects also in the evaluation and interpretation of possible risks in the case of controlled/modified-release dosage forms mainly into the dose dumping, food effects on bioavailability or interaction with other drugs, which influence gastrointestinal environmental conditions also it having great importance when assessing changes in production site, manufacturing process or formulation and assist in decisions concerning the need for bioavailability studies and as a important for Stability concerns.
 - By suitable analytical technique (UV-Spectrophotometry or HPLC) and standard plot of your drug in the dissolution medium you can find the release studies.
 - During dissolution studies by your method you will be withdrawing different aliquots and analysing the content of drug in them.
 - From calibration/ Standard plot find out amount in the withdrawn aliquots.
 - By applying simple mathematics we can calculate the amount in total dissolution medium i.e. 900 ml.
- Large numbers of different dissolution apparatuses are described in the following table

Table 2: Apparatus used for solid dosage form

Sr. no.	Apparatus	Name	Drug product
1	Apparatus I	Rotating Basket	Tablets
2	Apparatus II	Paddle	Tablets, capsules modified release drug products
3	Apparatus III	Reciprocating cylinder	Cylinder Extended release drug products
4	Apparatus IV	Flow cell	Drug containing low water soluble drugs
5	Apparatus V	Paddle over disk	Transdermal drug products
6	Apparatus VI	Cylinder	Transdermal drug products
7	Apparatus VII	Reciprocating disc	Extended release drug products
8	Apparatus VIII	(Non-USP-NF)	Extended release drug products (beads)
9	Apparatus IX	(Non-USP-NF)	Ointments, Creams, Suppository, Transdermal drug products

9. Disintegration test:

- In simple way disintegration test is a process in which solutes dissolve in a solvent.

- This test determines whether dosage forms disintegrate within a prescribed time i. e. disintegration time when placed in a liquid medium under the prescribed experimental conditions of various dosage forms such as tablets, capsules and suppositories
- Disintegration is a process of breaking down a substance into small/tiny fragments to improve its solubility in a solvent also it is used to check how much drug is soluble in the body.
- In disintegration test we have to find out how much dosage form is dispersed as well as how a drug in pellet form will disintegrate in solution.
- It consists of a 1000 mL low-form beaker 138–160 mm height basket rack assembly which having an inside 97-115 mm diameter for the immersion fluid, with a thermostatic arrangement for 35 °C to 39 °C heating the fluid. A device for raising and lowering the basket in the immersion fluid at a constant frequency rate 29-32 cycles/min with a distance of NLT 53 mm and NMT 57 mm.
- The required upward stroke time is equal to the downward stroke required time.
- The assembly of basket-rack moves vertically along its axis.

Table 3: disintegration limits for tablets

Sr. no.	Dosage Type	Time
1	Uncoated	15 minutes
2	Plain coated tablet	60 minutes
3	Enteric coated tablet	3 hours
4	Dispersible tablet	3 minutes
5	Effervescent tablet	<3 minutes
6	Sublingual tablets	4 hours
7	Buccal tablet	4 hours
8	Vaginal tablet	60 minutes
9	Chewable tablet	Not required

10. Weight Variation test (USP):

- Tablet weight is mainly affected by factors such as tooling of the compression machine, head pressure, machine speed and flow properties of the powder.
- Inconsistent powder or granulate density and particle size distribution are common sources of weight variation during compression.
- Variation between tablet with respect to dose and weight must be reduced to a minimum. Uniformity of weight is an in process test parameter which ensures consistency of dosage units during compression.
- Take 20 tablets and weighed individually. Calculate average weight and compare the Individual tablet weight to the average. The tablet pass the U.S.P. test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Table 4: I.P Limits for Weight Variation of Tablets

Sr. no.	IP/BP	Limit	USP
1	80 mg or less	10 %	130 mg or less
2	More than 80 mg or less than 250 mg	7.5 %	130 mg to 324 mg
3	250 mg or more	5 %	More than 324 mg

11. Content Uniformity Test:

- The content uniformity test is used to ensure that every tablet contains the amount of drug substance Intended with little variation among tablets within a batch. Due to increase awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated Tablets and al capsules intended for oral administration.
- Randomly select 30 tablets 10 of these assayed individually. The tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labelled drug content and the 10th Tablet may not contain less than 75% and more than 125% of the labelled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

Table 5: Drug content uniformity and release

Sr. no.	Dosage form	Average weight (mg)		Maximum % difference allowed
		As per USP	As per IP	
1	Uncoated tablet	80 or less	130 or less	10
		80-250	130-324	7.5
2	Film coated tablet	>250	>324	05
	Capsules, granules	<300	<300	10
3	Powder	>300	>300	7.5
	Powders for parenteral use	More than 40	-	10
	Pessaries and Suppositories	All weights	-	05

SEMI-SOLID DOSAGE FORMS

- Semisolid dosage forms are the intermediate of both solid and liquid dosage forms. It includes creams pastes jellies ointments and many mores. We are discussing about their various quality control test including official and unofficial test.
- It is a dermatological product of semisolid consistency which is applied to the skin. This gives therapeutic cosmetic protective actions ^[4-7].

1. Appearance:

- Formulations without any active ingredients or preservatives and drug loaded formulations were tested for physical appearance, texture, colour, phase separation, and homogeneity.
- These parameters were evaluated by visual observation.

2. Spreadability:

- Spreadability of semisolid formulations plays a necessary role in the administration of medicated formulation a std. dose into the skin. And the efficacy of a topical therapy spreadability of the formulations was identified by measuring the spreading diameter of 1 gm of sample between two horizontal glass plates 10 cm × 20 cm after 1 min.
- 25 gm the standard weight was applied to the upper plate. Each formulation was tested three times.

3. pH Values:

- 1 gm of each formulation including the blank formulation was dispersed in 25 mL of deionized water, and the pH was determined with triplicate measurements.
- With prepared standard buffer solutions pH 4, 7, and 10 before each use the pH meter was calibrated.

4. Rate of absorption:

- The evaluation should be performed of diadermatic ointment for the rate of absorption of drug into the blood stream. The rate of absorption test can be run in-vivo only.
- Definite amount of ointments should be rubbed through the skin under std. conditions as well as medicaments are estimated in the blood plasma or urine.

5. Test of non-irritancy:

- Draize skin irritation test
- Test substance (A known amount) is introduced under 1 square inch gauge patch.
- The patch was applied to 12 albino rabbit's skin, (6 with intact skin) and (6 with abraded skin).
- This patches was secured in place with adhesive tape and furthermore, The entire trunk of the animal was wrapped for a 24 hr. period with an impervious material,
- The patches are removed after 24 hr and resulting reaction is evaluated for erythema and edema formation.
- The reaction is again scored at the end of 72 hr. and the two readings are averaged.

Table 6: Category Draize and skin reaction

Sr. no.	Category Draize	Skin reaction
1	Mild	Well defined erythema and slight Edema (edges of area well defined by definite raising)
2	Moderate	Moderate to severe erythema and moderate Edema (area raised approximately 1 mm)
3	Severe	Severe erythema raised more than the 1 mm and extending beyond area of exposure

6. Test of rate of penetration:

- For a given period of time the weighed ointment quantity is rubbed over skin and unabsorbed quantity ointment is collected and weighed. Amount absorbed represented by the differences in weights.
- In *Vitro* skin penetration
 - Flow through cell
 - Franz diffusion cell
- They mainly have two compartments
 - Donor
 - Receptor
- Method:
 - Mouse skin or human cadaver skin.
 - Placed in between the two compartments.
 - By flow through type detector the passage of semisolid preparation through the epidermal surface to receptor compartment is measured and sampling conducted by Franz diffusion cell.

7. Consistency Test:

Preparation of test sample: 3 methods A, B and C

- **Method A:** Carefully and completely fill three containers without forming air bubbles. Level it if necessary to obtain a flat surface.

- **Method B:** This method involves application of a suitable shear to the samples for 5 min carefully and completely fills three containers without forming air bubbles. Level it if necessary to obtain a flat surface.
- **Method C:** Take 3 samples and melt it carefully and completely fill three containers without forming an air bubbles. Level it if necessary to obtain a flat surface.
- **Caution:** Store the samples at 25 ± 0.5 °C for 24 hr. unless otherwise prescribed.

8. Sensitivity test:

- In this, when we use various types of ingredients with occasional use of antiseptics hormones etc. there is a possibility of occurrence of sensitization or photosensitization of the skin.
- This should be tested before hand. This test is generally done by patch test.
- At different places the test sample is applied along with a standard market product and after a period of time effect is compared.

9. Drug content determination:

- Drug content determination involves the ointment having known weight is taken and assayed for amount of the drug.

10. Rheology & Viscosity:

- Creams are marketed in tubes or containers so rheology is very important. The rheology or viscosity should remain constant. The viscosity can be measured using viscometers for non-Newtonian products. With a concentric cylinder spindle #29 A brookfield viscometer can be used to identify the viscosity of the different topical formulations. The tests were carried out at 21°C. The spindle was rotated at various rpm such as on 0, 0.5, 1, 2, 2.5, 4, 5, 10, 20, 50, and 100 rpm values. All measurements were made in triplicate.
- Rheological measurements are used to the ease of bottle pouring, squeezing from a tube container, and maintaining product shape in a jar.

11. Rate of Release of Medicament:

- Small amount of the ointment can be placed on the surface of nutrient agar contained to assess rate of release of medicament in a Petri dish.
- The agar plate is previously seeded with a suitable organism if the medicament is bactericidal. The zone of inhibition is measured and correlated with the rate of release after a suitable period of incubation.

LIQUID DOSAGE FORMS

- Liquid dosage forms are pourable pharmaceutical formulations which contain a mixture of active drug components and nondrug components (excipients) dissolved or suspended in a suitable solvent or mixtures of solvents.
- These preparations designed to give the max. therapeutic response and produce rapid therapeutic effects ^[7-10].

1. Homogeneity test:

- By pressing a small quantity of the formulated cream and gels between the thumb and index finger homogeneity and texture were tested.
- The semi-solid preparations pumped to the proper homogenizer, the selection of which is based on the degree and rate of shear stress required.

2. Consistency test:

- To evaluate the texture and homogeneity of the formulations the consistency of the formulations and presence of coarse particles were used. Skin feels immediate grittiness, greasiness and stiffness.

3. Viscosity and Specific gravity test:

- Once the desired semi-solid preparation has been chosen, a consistency that provides the desired stability and has appropriate flow characteristics must be attained.
- It is observed that the building up of viscosity in a freshly prepared emulsion requires for emulsion some times. Before it is determined the newly formulation emulsion be allowed to rest undisturbed for 24 to 48 hrs.
- With the following generalizations the viscosity of emulsions responds to changes in composition in accordance.
 - a. Between emulsion viscosity and viscosity of continuous phase there is a linear relationship.
 - b. The greater the volume of the internal phase, the greater is the apparent viscosity.
 - c. To control emulsion viscosity, three interacting effects must be balanced by the formulator.
 - d. The viscosity of o/w and w/o emulsions can be increased by the reducing the particle size of the dispersed phase.
 - e. Emulsion stability is improved by a reduction in particle in particle size.

4. pH:

- Before filling for drug content checking of pH is required. From following standpoint the pH of a formulation must be considered:
 - a. The effect on the body when the solution is administered
 - b. The effect on stability of the product
 - c. The effect on container-closure system pH measurement
 - d. pH is measured by using a pH meter

e. pH meter is initially calibrated with respective buffer capsule then the pH of the preparation is measured.

5. Leakage test:

- To test the package integrity leakage test is employed. Package integrity reflects its ability to keep to keep potential contamination out and the product in. It is because leakage occur 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 the test container is immersed in a dye bath. Pressure and vacuum is applied for some time. From the dye bath the container is removed and washed. The container is then analyzed for the presence of dye either by means of UV-Spectroscopy or visually. The dye used may be of blue, yellowish-green, green colour. To increase the capillary migration through the pores the dye test can be optimized by use of a low viscosity fluid in the dye solution. The dye test is mostly accepted in industry and is approved in use of drug. The test is cheap and is requires no special equipment. For ampoules and vials this test is used.

6. Clarity test:

- To check the particulate matter in the sample clarity testing is carried out.
- In this test against the black background white particles observed and against the white background the black particles observed.

7. Check-up of particulate matters:

- The preparations should be free from particulate matter and should be clear intended for parenteral use when inspected visually.
- To the filled volume of the product to be tested 2 methods are described by USP. Microscopically examination procedure is used for LVP's (large volume parenterals).
- A light obscuration based sensor containing electronic liquid borne particle counter system is used for SVP's (small volume parenterals).

Table 7: As per IP, BP, EP and JP limits for particle number

Sr. no.	Volume of solution	≥ 10 µm Particle size	≥25 µm Particle size
1	Small volume injections (< 100 ml)	3000 per container	300 per container
2	Large volume injections (> 100 ml)	12 per ml	2 per ml

CONCLUSION:

This reviews articles presented the new updated information regarding IPQC as well as FPQC test of solid, semi-solid and liquid dosage forms. This article gives details about the various types of quality control test of various dosage forms. It having so much importance in our pharmaceuticals industries as well as others because it helps to build excellence, quality, adding accuracy, provide stability within the products.

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