Review Article

In-Process and Finished Products Quality Control Tests for Pharmaceutical Capsules According to Pharmacopoeias

ABSTRACT

The quality of pharmaceutical products is essential to assure the maximum level of patient's satisfaction. The most important criteria for quality of any drug in dosage form are its safety, potency, efficacy, stability, patient acceptability and regulatory compliance. Different parameters of quality control of pharmaceutical products can ensure the quality, bioavailability and optimal therapeutic activity. The maintenance of quality with continuous improvement in facilities is very important in pharmaceutical industries because it is directly related to healthcare system. The quality of a pharmaceutical capsule needs to be designed from the product development stage. In process quality control (IPQC) tests are done with a view to remove error from every stage in production and maintain the quality of the final product with the compendial standards as specified in the pharmacopoeias. The quality of final products depends on in-process control (IPC) tests, because it helps to incorporate excellence within the products. The qualitative and quantitative parameters of pharmaceuticals products are performed by finished product quality controls (FPQC) tests. The purpose of this review is to provide concise information on the in-process and finished products quality control tests for pharmaceutical capsules as per different pharmacopoeias.

Key words: Pharmaceutical capsules, Compendia, In-process quality control, finished product quality controls, Specification

1. INTRODUCTION

Quality is the prime issue within the pharmaceutical industry. Quality of pharmaceutical products refers to the fulfilling specification or standardization as per official compendia, without any error. It is the consensus to standards or specifications, fitness for use, accomplishing customer's requirements or satisfaction, hypnotizing the customer etc [1].

In USA, as the Food and Drug Administration (FDA) has a command that the marketed drug product should be safe and effective; the drug product must conform particular criteria for quality and purity [2]. The FDA has issued regulatory guidelines known as current good manufacturing practice (cGMP) and good laboratory practice (GLP) to ensure the public that the marketed drug product has been properly manufactured and clinically tested respectively. A drug product that does not conform the GMP requirements is deliberated unacceptable according to FDA regulations [1,3].

A pharmacopoeia is a lawfully binding collection, prepared by a national or regional authority, of standards and quality specifications for medicines used in that country or region. There are diverse types of pharmacopoeias such as British Pharmacopoeia (BP), United States Pharmacopoeia (USP), European Pharmacopoeia (PhEur), International Pharmacopoeia (PhInt) and Japanese Pharmacopoeia (JP) in different parts of the world and the role of these pharmacopoeias are to embellish quality specifications for active pharmaceutical ingredients (APIs), finished pharmaceutical products (FPPs) and general requisites, e.g. for dosage forms [4].

Quality control (QC) refers to the goodness or excellence of a product [5]. It increases output and reduces breakdown. QC emphasizes testing of products for faults and reporting to regulation that makes the decision to investigate or reject the release. The total quality of the product is assured by both the in process quality control (IPQC) and finished product quality control (FPQC) tests. The total dealing process (IPQC and FPQC tests) represents rigorous QC tests to make products completely indefectible before they are delivered into the market.

QC is the part of GMP that is concerned with sampling, specifications, testing and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, sale or supply, until their quality has been judged to be satisfactory according to specification.

IPQC tests are carried out at regular intervals before the manufacturing process is completed. The function of IPQC involves monitoring and if necessary adaptation of the manufacturing process with a view to comply with pharmacopoeias. During manufacturing process in process materials should be tested for identity, strength, quality and purity as appropriate and approved or rejected by the QC unit during the production process. Rejected in process materials should be identified and controlled under a quarantine system designed to prevent their use in manufacturing [6].

Finished product controls (FPC) are tests that are performed when the manufacturing process is completed in order to check qualitative and quantitative characteristics along with test procedures and their acceptance limits, by which the finished product must comply throughout its valid shelf-life [7]. The aim of this review is to give an overview of the quality parameters for in-process and finished products quality control tests for pharmaceutical capsules according to pharmacopoeias.

2. UNIVERSAL TESTS FOR PHARMACEUTICAL CAPSULES

The capsule dosage form accounts for approximately 10 % of all dosage forms on the market. There are four tests that are generally applicable to pharmaceutical capsules and other drug products:

2.1. Description

This test is often called appearance on a specification and is a qualitative description of the pharmaceutical capsules. For example, the description of a capsule on a specification may read: white cap, red body, imprinted with "R_x" on cap [8].

2.2. Identification

The purpose of an identification or identity test is to verify the identity of the active pharmaceutical ingredient (API) in the pharmaceutical capsule. This test should be able to discriminate between compounds of closely related structure that are likely to be present [8].

2.3. Assay

This test determines the strength or content of the API in the pharmaceutical capsule and is sometimes called a content test [8].

2.4. Impurities

This test determines the presence of any component that is not the API or an excipient of pharmaceutical capsule. The most common type of impurities that are measured is related substances, which are process impurities from the new drug substance synthesis, degradation products of the API, or both [8].

3. IPQC AND FPQC TEST FOR PHARMACEUTICAL CAPSULES

Physical parameters of pharmaceutical capsules that are controlled by IPQC tests are temperature, pressure, relative humidity, time, weight, particle size, color, fill weight, shell weight, softgel ribbon thickness, softgel seal thickness, softgel shell moisture level, softgel hardness, disintegration time etc. FPQC test for pharmaceutical capsules are assay, fill weight, uniformity of content, uniformity of mass, weight variation, microbiological test, disintegration test, dissolution test, stability test etc [9]. IPQC and FPQC test for pharmaceutical capsules according to pharmacopoeias are listed below:

3.1. Appearance

Capsules produced on a small or a large scale should be uniform in appearance. Visual or electronic inspection should be undertaken to detect any flaws in the integrity and appearance of the capsule. Evidence of physical instability is demonstrated by gross changes in appearance, including hardening or softening, cracking, swelling, mottling, printing mistake or discoloration of the shell. Defective capsules should be rejected [10].

3.2. Size and Shape

Hard capsules are made in a range of sizes, the standard industrial ones in use today for human medicines range from size from 000 (the largest, 1.40 ml) to 5 (the smallest, 0.13 ml) are commercially available. Soft gel capsules are available in variety of shapes such as spherical (0.05–5 ml), ovoid (0.05–7 ml), cylindrical (0.15–25 ml), tubes (0.5–0 ml), pear (0.3–5 ml) etc [10].

3.3. Unique Identification Markings

Capsule surfaces may bear symbols or other unique identification markings for better identification.

3.4. Assay

In a capsule an active ingredient is present which is called API. So to prepare the capsule assay has to be done by using suitable analytical method to produce good finished product.

3.5. Content of Active Ingredients

For this test a sample of the contents is assayed as described in individual monographs and calculates the amount of active ingredient in each capsule. According to BP the range for the content of active ingredient stated in the monograph is based on the requirement that 20 capsules, or such other number as may be indicated in the monograph, are used in the assay. In the circumstances where 20 capsules cannot be obtained, a smaller number, which must not be less than 5, may be used, but to allow for sampling errors the tolerances are widened in accordance with Table 1.

Table 1. BP limits for content of active ingredients

Weight of active ingredients in each capsule	Subtract from lower limit for samples of			Add to the upper limit for samples of		
	15	10	5	15	10	5
0.12 g or less	0.2	0.7	1.6	0.3	0.8	1.8
More than 0.12 g But less than 0.3 g	0.2	0.5	1.2	0.3	0.6	1.5
0.3 g or more	0.1	0.2	0.8	0.2	0.4	1.0

The requirements of the Table 1 apply when the stated limits are between 90 and 110 percent. For limits other than 90 to 110 percent, proportionately smaller or larger allowances should be made [11].

3.6. Content Uniformity Test

For this test according to BP determine the content of the active ingredient in each of 10 capsules (hard or soft) taken at random using the method given in the monograph or by any other suitable analytical method of equivalent accuracy and precision. Calculate the acceptance value (AV) using the following formula:

$$|M - X| + KS$$

Where,

M = Reference value, X = Mean of individual content (x_1, x_2,..., x_n) expressed as percentage of the label claim, K = Acceptability constant, S = Sample standard deviation.

According to BP capsules comply with the test if not more than one of the individual values thus obtained is outside the limits 85 to 115 percent of the average value and none is outside the limits 75 to 125 percent. The capsules fails to comply with the test if more than 3 individual contents are outside the limits of 85 percent to 115 percent of the average content or if one or more individual contents are outside the limits of 75 percent to 125 per cent of the average content. If 2 or 3 individual values are outside the limits 85 to 115 percent of the average values, repeat the determination using another 20 capsules. The capsules comply with the test if in the total sample of 30 capsules not more than 3 individual values are outside the limits 85 to 115 percent and none is outside the limits 75 to 125 percent of the average value.

According to BP, USP and PhEur limits for content uniformity (CU) and weight variation (WV) tests of capsules are given in Table 2 [11,12,13]:

Table 2. BP, USP and PhEur limits for content uniformity (CU) and weight variation (WV) tests

Dosage form	Subtype	Dose and ratio of active substance	
		≥ 25 mg and ≥ 25%	< 25 mg or < 25%
Hard		WV	CU
Soft	Suspensions Emulsions Gels	CU	CU
	Solutions	WV	WV

3.7. Uniformity of Mass

For this test weigh an intact capsule. Open the capsule without losing any part of the shell and remove the contents as completely as possible. To remove the contents of a soft capsule the shell may be washed with ether or other suitable solvent and the shell allowed to stand until the odor of the solvent is no longer perceptible. Weigh the shell. The weight of the contents is the difference between the weighing. Repeat the procedure with a further 19 capsules. Determine the average mass. According to BP, PhEur and PhInt capsules not more than 2 of the individual masses deviate from the average mass by more than the percentage deviation shown in the Table 3 and none deviates by more than twice that percentage [11,13,14].

Table 3. BP, PhEur and PhInt limits for uniformity of mass

Average mass (mg)	Percentage deviation (%)
Less than 300	10
300 or more	7.5

3.8. Mass Variation Test

For hard capsules according to BP accurately weigh 10 capsules individually, taking care to preserve the identity of each capsule. Remove the contents of each capsule by suitable means. Accurately weigh the emptied shells individually, and calculate for each capsule the net mass of its contents by subtracting the mass of the shell from the respective gross mass. Calculate the active substance content in each capsule from the mass of product removed from the individual capsules and the result of the assay. Calculate the AV using the following formula:

$$X_i = W_i \times A/W$$

Where,

$x_1, x_2, ..., x_n$ = Individual estimated contents of the dosage units tested, $w_1, w_2, ..., w_n$ = Individual masses of the dosage units tested, A = Content of active substance (percentage of label claim) obtained using an appropriate analytical method (assay), W = Mean of individual weights ($w_1, w_2, ..., w_n$).

For soft capsules according to BP accurately weigh 10 intact capsules individually to obtain their gross masses, taking care to preserve the identity of each capsule. Then cut open the capsules by means of a suitable clean, dry cutting instrument such as scissors or a sharp open blade, and remove the contents by washing with a suitable

solvent. Allow the occluded solvent to evaporate from the shells at room temperature over a period of about 30 min, taking precautions to avoid uptake or loss of moisture. Weigh the individual shells, and calculate the net contents. Calculate the active substance content in each capsule from the mass of product removed from the individual capsules and the result of the assay. Calculate the AV using the following formula given above [11].

According to BP and USP, the requirement is met if the acceptance value of 10 capsules is less than or equal to 15%. If acceptance value is greater than 15%, test the next 20 capsule and calculate the acceptance value. The requirements are met if the final acceptance value of the 30 capsule is less than or equal to 15 percent and no individual content of the capsule is less than $(1 - 25 \times 0.01)M$ or more than $(1 + 25 \times 0.01)M$ in calculation of acceptance value under mass variation or content uniformity [11,12].

3.9. Disintegration Test

The USP disintegration apparatus consist of 6 glass tubes that are 3 inches long, open at the top, and held against a 10-mesh screen at the bottom end of the basket rack assembly. To test for disintegration time, one capsule is placed in each tube and the basket rack is positioned in specified medium at 37 ± 2 ºC such that capsule remains 2.5 cm below the surface of the liquid on their upward movement and descend not closer than 2.5 cm from the bottom of the beaker. A standard motor driven device is used to move the basket assembly containing the capsules up and down through distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute. Perforated plastic discs may also be used in the test. These are placed on the top of capsules and impart an abrasive action to the capsules. The discs may or may not be meaningful or impart more sensitivity to the test, but they are useful for capsules that float. Operate the apparatus for the specified time. The capsule complies with the test, if the capsules disintegrate, and all particles pass through the 10-mesh screen in the time specified. If any residue remains, it must have a soft mass with no palpably firm core.

The capsule complies with the test according to USP, if all of the capsules have disintegrated completely. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules. The requirement is met if not less than 16 of the total of 18 capsules tested are disintegrated [12]. The disintegration time of various capsules is given in Table 4:

Table 4. Disintegration time of various capsules according to BP

Capsule	Disintegration time (min)
Hard capsule	30
Soft capsule	30
Gastro resistance capsule	60
Rectal capsules	30
Vaginal capsules	30

According to BP apparatus A is used for capsules that are not greater than 18 mm long and for larger capsules apparatus B is used [11].

3.10. Dissolution Test

The BP or USP dissolution apparatus (Basket apparatus) consist of a cylindrical vessel with a hemispherical bottom, which may be covered, made of glass or other inert, transparent material; a motor; a metallic drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size or heated by a suitable device such as a heating jacket. The water bath or heating device permits holding the temperature inside the vessel at 37 ± 0.5 ℃ during the test and keeping the bath fluid in constant, smooth motion [11,12].

For this test according to BP and PhEur place the stated volume of the dissolution medium (± 1 %) in the vessel of the specified apparatus. Assemble the apparatus, equilibrate the dissolution medium to 37 ± 0.5 ℃. Place 1 capsules in the apparatus, taking care to exclude air bubbles from the surface of the capsules. Operate the apparatus at the specified rate. Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the dissolution medium and the top of the rotating basket or blade, not less than 1 cm from the vessel wall. Where multiple sampling times are specified, replace the

aliquots withdrawn for analysis with equal volumes of fresh dissolution medium at 37 ℃ or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test and verify the temperature of the medium at suitable times. Perform the analysis using a suitable assay method as directed in the individual monograph. Repeat the test with additional capsules. Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the capsules tested conform to the following acceptance criteria as shown in Table 5:

Table 5. BP, PhEur, PhInt and JP acceptance criteria for dissolution test of capsule

Stage	Number of capsule tested	Acceptance criteria
S1	6	Each unit is not less than Q + 5 %.
S2	6	Average of 12 units (S1 + S2) is equal to or greater than Q, and no unit is less than Q – 15 %.
S3	12	Average of 24 units (S1 + S2 + S3) is equal to or greater than Q, not more than 2 units are less than Q – 15 %, and no unit is less than Q – 25 %.

Continue testing through the 3 stages unless the results conform at either S1 or S2. The quantity Q, is the specified amount of dissolved active substance, expressed as a percentage of the labeled content; the 5 percent, 15 percent, and 25 percent values in the capsule are percentages of the labeled content so that these values and Q are in the same terms.

For those hard or soft capsules for which a requirement for dissolution is included in the individual monograph, the requirement for disintegration does not apply [11,13,14,15].

3.11. Moisture Permeation Test

The USP requires determination of the moisture permeation characteristics of single-unit and unit-dose containers to ensure their suitability for packaging capsules. The degree and rate of moisture penetration are determined by packaging the dosage unit together with a color-revealing desiccant pellet, exposing the packaged unit to known relative humidity over a specified time, observing the desiccant pellet for color change. Any change in color indicates absorption of moisture. By measuring pretest weight and protest weight of pellet, amount can be calculated [10,12].

3.12. Stability Test

The capsule manufacturers routinely conduct accelerated physical stability tests on all new capsule products as an integral part of the product development program. The following tests have proved adequate for determining the effect of the capsule shell content on the gelatin shell. The tests are strictly relevant to the integrity of the gelatin shell and should not be confused as stability tests for the active ingredients in the capsule content. The results of such tests are used as a guide for the reformulation of the capsule content or the capsule shell, or for the selection of the proper retail package. The test conditions for such accelerated stability tests are shown in Table 6. The capsules at these stations are observed periodically for 2 weeks. Both gross and subtle effects of the storage conditions on the capsule shell are noted and recorded. The control capsule should not be affected except at the 80 % RH (relative humidity) station, where the capsule would react as described under the effects of high humidity [10].

Table 6: Test conditions for accelerated stability tests for capsule dosage forms

Test conditions	Observation
80 % RH at room temperature in an open container.	Capsules are observed periodically for 2 weeks, both gross and subtle effects of the storage conditions are noted and recorded. The control capsule should not be affected except at the 80 % RH station.
40 °C in an open container.	
40 °C in a closed container (glass bottle with tight screw-cap).	

CONCLUSION

From the present review it is clearly reveals though various pharmacopoeias suggest different types of IPQC and FPQC tests for pharmaceutical capsules with different specification, but the main function of the all pharmacopoeia is to produce better quality pharmaceuticals for human health.

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