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Comparative Study of In-Process and Finished Products Quality Control Tests For Pharmaceutical Dosage Forms: Capsules and Tablets

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Abstract **Review Article**

The study focuses on the comparison of quality requirements for process control(in-process and finished products) quality tests of Indian Pharmacopeia (IP), British Pharmacopeia (BP) & United States Pharmacopeia (USP) for some conventional dosage forms. Total quality control test is defined as the process to produce a quality product by a series of measures, requiring an organized effort in order to eliminate errors at every stage in the production. A quality drug must satisfy certain standards which involve drugs safety, potency, efficacy, stability, patient acceptability as well as regulatory compliance. In process product testing is done in order to check the finished product status which should be similar to the standards as stated in the pharmacopoeias as the final sample taken for the finished product testing tends to be a representative of a large batch, a significant difference still remains. The official pharmacopoeias in different regions determine the quality requirements for pharmaceutical products. However the parameters and standards differ to some extent from each other. So in this, an attempt is being made to compare and bring out the harmonised range within which a product should fall in order to meet the pharmacopoeial specifications of that region. The main aim is to study the quality control tests of tablets and capsules which are the most popular conventional dosage forms and to inscribe the similarities and differences as per various pharmacopoeias. It was noted that except for a few parameters, the quality control tests were broadly similar.

Keywords: Indian Pharmacopoeia (IP), British Pharmacopoeia (BP), United States Pharmacopoeia (USP), Food and Drug Administration (FDA).

INTRODUCTION

Quality can be defined as an extent to which a set of essential properties of drug product fulfils the prespecified regulatory specification, stability, lack of contaminants as well as patient acceptability [1, 2]. Rationale behind federal role in order to manage the quality of pharmaceutical products is that the customers (patients who take the medicines as well as the health care professionals) are often not able to independently assess the quality of the drugs they use. The historical literature of drug management justifies the statement, with the example of tragedies that took place when unaware healthcare professionals treated patients with poor quality drugs or improperly labelled drugs and of the subsequent laws enacted to prevent recurrence which generally brought about the increased federal government surveillance of drug manufacturing activities [3].

Since the world has federated together in order to unite its practices guides and the launching of the Food and Drug Administration (FDA) current good manufacturing practices (cGMP) for the 21st century – there has been an increasing realization for the importance of the standard of the pharmaceutical products [4].

Drug manufactured in compliance with cGMP tends to be a high quality drug. The Federal Food, Drug, and Cosmetic Act (the Act) states that a drug not made in accordance with CGMP is deemed "adulterated." In the pharma industry, it is consequential to manage the errors during each stage of production process since total quality of products must be ensured according to compendia of drugs [5].

The drug product development is an extensive procedure which involves drug discovery, laboratory testing, animal studies, clinical trials as well as regulatory registration. Additionally, for enhancement of effectiveness and safety of drug product after its approval, regulatory agencies like FDA also require that

the product should be tested for its identity, strength, purity, quality as well as stability before its market use. Due to this reason, process controls and validation are essential to counteract the problems [6].

Process controls involves raw materials inspection, in-process controls and target for final product. The motive is to monitor the on-line and off-line performance of the manufacturing process and then validate it. Current good manufacturing practice also requires that a well-written procedure for process controls is established to evaluate its performance even after the validation of manufacturing process. The quality of pharmaceutical oral liquids is strongly related to IPQC and FPQC tests of the pharmaceutical product [7, 8].

The overall procedure (in process and finished product quality control test) includes stringent quality control test to develop error free drug product before its marketing.

In process control (IPC) is an analysis which is performed during the manufacturing procedure or before the manufacturing process is completed. In process control test involves monitoring and if necessary, adaptation of the manufacturing process in order to comply with the specifications. This may include environment as well as equipment control [9].

In process materials need to be tested to check the physical parameters and its quality attributes which are later approved or rejected by the quality control department on the basis of results achieved during the manufacturing process. In process materials in the rejected status should be monitored and controlled under a quarantine system designed to prevent their use in manufacturing [10].

Finished product quality control test is initiated after the completion of manufacturing process with respect to qualitative and quantitative characteristics of the drug product along with its test procedure and their range of acceptance, with which the finished drug product must show its compliance throughout its shelf life [10, 11].

Standard operating procedures should be established and followed that describe the in process controls and tests. Certain tests performed at the manufacturing process, where the acceptance criterion is identical to or narrower than the release requirement, (e.g., pH of a solution) which may satisfy requirements when the test is included in the specification [11].

Pharmacopoeias are called drugs standard [12]. In different parts of the world there are various types of pharmacopoeias such as Indian Pharmacopoeia (IP), British Pharmacopoeia (BP), United States Pharmacopoeia (USP), European Pharmacopoeia (PhEur), International Pharmacopoeia (PhInt) and Japanese Pharmacopoeia (JP) and they have laid down the specified limits within which the value should fall in order to be compliant as per the standards.

This article intends to establish a comparison of quality requirements for in-process and finished products quality control tests of Indian Pharmacopeia (IP), British Pharmacopeia (BP) & United States Pharmacopeia (USP) for some conventional dosage forms (tablets and capsules). The official pharmacopoeias in different regions determine the quality requirements for pharmaceutical products. However the parameters and standards differ to some extent from each other. So in this, an attempt is being made to compare and bring out the harmonised range within which a product should fall in order to meet the pharmacopoeial specifications of that region. The main aim is to study the quality control tests of tablets and capsules which are the most popular conventional dosage forms and to inscribe the similarities and differences as per various pharmacopoeias. The parameters examined for conventional dosage forms as per the Pharmacopoeias were compared and certain similarities and differences were observed. It was noted that except for a few parameters, the quality control tests were broadly similar.

IN PROCESS AND FINISHED PRODUCTS QUALITY CONTROL TESTS FOR CAPSULES

Capsules are solid dosage forms of various shapes and sizes with hard or soft shells made up of gelatin and have one or more active medicaments enclosed in it intended for oral administration. Capsule shell may contain various excipients like diluents, solvents, sweetening agents, coloring matter and many other substances which are capable of improving the activity of active ingredient in the gastrointestinal tract. The contents in it should not cause deterioration of the shell [13]. The quality control test for capsules is given in Table 1[14-16].

Table-1: Capsules quality control (CQC) test procedure

<table>
<tr><th>Code</th><th>Test Procedure</th></tr>
<tr><td>CQC1.</td><td>Uniformity of weight
Weigh an intact capsule. Open the capsule without losing any part of the shell and completely remove as much as possible. In the case of soft gelatin shells, it is continued by washing the shell with an appropriate solvent and keep aside until the odour of the solvent is vanished completely. Weigh the shell, the content weight is determined by the difference in weighing. This procedure is done for 20 such capsules.

Not more than 2 of the individual weight deviate from the average weight by more than percent deviation shown in table 1(a).

Table-1(a): Limit for uniformity of weight
<table>
<tr><th>Dosage form</th><th>Average mass (mg)</th><th>% Deviation</th></tr>
<tr><td rowspan="2">Capsule (single dose)</td><td>Less than 300mg</td><td>10%</td></tr>
<tr><td>300mg or more</td><td>7.5%</td></tr>
</table></td></tr>
<tr><td>CQC2.</td><td>Content of active ingredients
The content of active ingredient uniformity depends on the assay of an individual content of active substance in each capsule. According to Indian Pharmacopoeia the variable range for the content of active ingredient in the monograph depends upon the requirement of 20 capsules or such other numerical ranges are indicated in the monograph, are applicable for the assay. In some conditions where 20 capsules cannot be made available, a smaller number of capsules which can be used should be more than 5, but in the case of sampling errors the tolerances are widened which is shown in table 1(b)

Table-1(b): Limits for Content of active ingredients
<table>
<tr><td rowspan="2">Weight of active constituent in each capsule</td><td colspan="3">Subtract from lower limit for samples of</td><td colspan="3">Add to the upper limits for samples of</td></tr>
<tr><td>15</td><td>10</td><td>5</td><td>15</td><td>10</td><td>5</td></tr>
<tr><td>0.12g or less</td><td>0.2</td><td>0.7</td><td>1.6</td><td>0.3</td><td>0.8</td><td>1.8</td></tr>
<tr><td>More than 0.12g and less than 0.3g</td><td>0.2</td><td>0.5</td><td>1.2</td><td>0.3</td><td>0.6</td><td>1.5</td></tr>
<tr><td>More than or equivalent to 0.3g</td><td>0.1</td><td>0.2</td><td>0.8</td><td>0.2</td><td>0.4</td><td>1.0</td></tr>
</table></td></tr>
<tr><td>CQC3.</td><td>Uniformity of Content
According to IP, the dosage form (capsule) complies with the test if not more than one single content is outside the range of 85 to 115% of the average content and no content exceeds the limit of 75 to 125% of the average content. The capsules fails to comply with the test if more than three individual contents exceeds the limits of 85 to 115% of the average content or one or more exceeds the limit of 75 to 125% of the average content.
IP states that if two or three single contents exceeds the range of 85 to 115% of the average content but passes for the range of 75 to 125%, the test is performed again by another 20 dosage units.
If total sample of capsules are 30; then not more than 3 individual contents should be outside the limit of 85 to 115% of the average content and none should exceeds the limit of 75 to 125% of the average content.</td></tr>
<tr><td>CQC4.</td><td>Uniformity of mass:
Accurately weigh intact capsules, open the capsule without dropping any part of the shell and remove the contents from shell as much as possible. In the case of soft gelatin capsules, wash the shell with a suitable solvent and kept aside until the odour is completely vanished. Weigh the shell. Difference between the weighing represents the mass of the contents. Repeat the similar procedure with another 19 capsules. The limits for uniformity of mass is shown in table 1(c)
Table 1(c): Limits for uniformity of mass
<table>
<tr><td>Dosage form</td><td>Average mass (mg)</td><td>% Deviation</td></tr>
<tr><td rowspan="2">Capsule (single dose)</td><td>Less than 300mg</td><td>10%</td></tr>
<tr><td>300mg or more</td><td>7.5%</td></tr>
</table></td></tr>
<tr><td>CQC5.</td><td>Dissolution Test
Dissolution vessel apparatus contain the mentioned volume of the dissolution medium which is free from dissolved air. Unite the apparatus and the temperature is maintained at 36.5°C to 37.5°C. Unless otherwise stated, add one capsule in the apparatus, without formation of any air bubbles from the surface of the capsule.</td></tr>
</table>

	In the paddle type system, prior to the rotation of paddle capsule is allowed to sink to the bottom of the vessel. Device such as a wire of glass helix can be implemented to keep horizontal at the bottom of the vessel in the case of floating capsules. In the case of basket type system, at the initial stage of the test place the capsule in a dry basket. Before rotation lower the basket into position. As specified in the monograph, immediately operate the apparatus at the speed of rotation. Within the specified time interval or at the time stated withdraw sample during the process in-between the dissolution medium surface and the top of rotating blade or basket, not less than 10mm from the wall of the vessel. Except in the case of single sampling, add the volume of dissolution which must be equivalent to the volume of sample withdrawn. Repeat the whole testing procedure. In the case where 2 or more capsules are mentioned to be placed together in the apparatus, carry out 6 replicate tests. For each of the tested capsule calculate the amount of dissolved active constituent in solution as a percentage of the stated amount.
CQC6.	**Disintegration test:** This test is initiated in order to determine whether capsules disintegrate within the stipulated time when placed in a liquid medium at the experimental conditions. According to USP, the apparatus consists of 6 glass tubes that are 3 inches long, open at the top, and held against a 10 mesh- screen at the bottom of the basket rack assembly. In order to analyse the disintegration time, one capsule is placed in each tube and the basket rack is placed in such a way in the specified liquid medium (temperature 37 ±2°C with the help of thermostatic device) so that the capsule remains 2.5cm below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker. A device is used for raising and lowering the basket in the medium at a frequency rate between 29 and 32 cycles per minute, the basket rack assembly moves vertically and if required plastic discs can also be used in the case of floating capsules. If all the capsules disintegrates completely then it complies with the test in accordance of the procedure described. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules: not fewer than 16 of the total of 18 capsules tested disintegrate completely.
CQC7.	**Moisture Permeation Test** According to USP, moisture permeation property of single and unit dose containers is essential to test in order to assure their suitability for capsules packaging. The degree and extent of moisture penetration are determined by packaging the dosage unit together with a color revealing desiccant pellet, exposing the packaged dosage unit to known condition of relative humidity over a specified time, observing the desiccant pellet for color change. Any change in color indicates absorption of moisture. Pretest and protest weight of pellet is measured and amount is calculated.

In process and finished products quality control tests for tablets

Tablets are defined as a compressed solid dosage form containing active pharmaceutical ingredient with or without excipient. According to Indian Pharmacopeia tablets are solid, flat or biconvex unit dosage form which is prepared by compression of a drug or mixture of drugs to which diluents may or may not be added [14].

Tablets are considered as most important and commonly used dosage form and statistically 70% of the total medicines are dispensed in the form of tablets. The quality control test for tablets are described in Table 2[14-16].

Table-2: Tablets quality control (TQC) test procedure

Code	Test Procedure
TQC1.	**Size and Shape** The size and shape of the tablet can be determined, monitored and controlled dimensionally which can be done by the tooling at the time of compression process.
TQC2.	**Color and Odor** For ease of identification, consumer acceptance and sometimes to maintain the stability of the drug; many pharmaceutical tablets use color which must be uniform within a single tablet, from tablet to tablet and from batch to batch. In the case of chewable tablet taste is important factor for consumer acceptance.
TQC3.	**Uniformity of content** Content uniformity analysis is done to assure the consistency of active drug within a range around the

label claim in dosage forms. According to BP, the test for content uniformity is based on the assay of the individual contents of active substances of a number of single dose units to determine whether the individual contents are within the range set with reference to the average content of the sample. The dosage form complies with the test if each content is in the range of 85% and 115% of the average content. The preparation fails to comply if more than one individual content is outside the above stated limit or if one of the individual content is outside the limit of 75% to 125% of the average content. If one individual content is outside the limits of 85% to 115% as compared to average content but within the limits of 75 to 125 percent, repeat the determination using another 20 tablets. The preparation complies with the test if not more than one of the individual dosage contents of the total drug sample of 30 tablets is outside 85 to 115 % of the average content and no content lies in the range of 75 to 125% of the average content.

TQC4. **Uniformity of weight (For film coated and uncoated tablets)**

Uniformity of weight is an analysis to test the granulation quality, granulation flow as well as the machine performance. According to IP, weigh 20 tablets individually and determine the average mass. The tablets pass the test if not more than 2 of the individual masses deviates from the average mass by more than the percent deviation as represented in table 2(a).

Table-2(a): Limits for uniformity of weight

Average Mass (mg)	Percentage Deviation (%)
80 or less	10
More than 80 and less than 250	7.5
250 or more	5

TQC5. **Disintegration Test**

This test is done to determine whether tablets disintegrate within the prescribed time when placed in a liquid medium under the specified experimental conditions. Disintegration is defined as that condition in which any residue of the unit, remaining on the screen of the test apparatus or adhering to the lower surface of the discs, if used, is a soft mass having no palpably firm core except fragments of insoluble coating or capsule shell. According to USP, the apparatus consists of 6 glass tubes that are 3 inches long, open at the top, and held against a 10 mesh- screen at the bottom of the basket rack assembly. In order to analyse the disintegration time, one tablet is placed in each tube and the basket rack is placed in such a way in the specified liquid medium (temperature 37 ±2°C with the help of thermostatic device) so that the tablet remains 2.5cm below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

A device is used for raising and lowering the basket in the medium at a frequency rate between 29 and 32 cycles per minute, the basket rack assembly moves vertically and if required plastic discs can also be used in the case of floating tablets. According to USP if all the tablets disintegrate completely then the sample passes the test criteria. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets and the requirement is fulfilled if not less than 16 of the total of 18 tablets tested are Disintegrated.

TQC6. **Dissolution Test**

According to BP dissolution apparatus (Basket type) comprises of a cylindrical vessel having hemispherical bottom, which may be covered, made of glass or other transparent material; a motor; a metallic drive shaft; and a cylindrical basket. The basket is immersed partially in a suitable water bath of convenient size or heated by a suitable device to maintain the temperature of 37 ±0.5°C during the test. For the test place the specified volume of the medium in the vessel, assemble the apparatus stabilize the temperature at 37 ±0.5°C and place a tablet in the apparatus, continue the test for defined period of time at specified rate, 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 time is commanded, replace the aliquots withdrawn for analysis with similar volumes of fresh dissolution medium at 37 °C or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Execute the analysis by suitable assay method as stated in the monograph.

TQC7. **Weight Variation Test**

According to USP, the test is performed on 20 tablets, by comparing the calculated average weight of the tablets with the individual weight of the tablet. The value of the weight variation test is expressed in percentage which is calculated by the formula given below

Weight Variation = (Iw - Aw)/Aw X 100%

Where,

Iw = Individual weight of tablet

	Aw = Average weight of tablet. **Table-2(b): Limits for weight variation test** **Average Mass (mg)** / **Percentage Deviation (%)** 130 or less / 10 More than 130 and less than 324 / 7.5 324 or more / 5
TQC8.	**Hardness Test** Earlier, the hardness measuring devices like Monsanto hardness tester, Pfizer hardness tester manually operated but this encounters certain problem like operator variability in rates of loading and difficulties in proper setup and calibration. Modern testers employ mechanical drives, strain gauge based load cells for force measurements, and electronic signal processing. Modern breaking force testers are usually calibrated in kiloponds or newtons. Breaking forces should be readable to be within 1 N.
TQC9.	**Friability Test** Roche friabilator is used for the determination of friability of tablet (like compressed, uncoated tablets), the measurement supplement other physical strength measurements such as breaking force of tablet. Test is initiated by weighing 20 tablets and place the tablets in the friabilator. The device operates at 25rpm for 4 minutes. The tablets are then dedusted and weighed. The difference between the initial weight and the final weight expresses the value of friability which is shown in percentage. According to USP, if obviously cracked, cleaved or broken tablets are present in the tablet sample after tumbling then the sample fails the test. A maximum mean weight loss from the three samples of not more than 1% is considered acceptable for most products. * In the case of hygroscopic tablets friability testing in humidity controlled environment is needed.

Comparison of Specifications and Parameters

The comparative study of Quality control parameters and specifications for capsules and tablets as per IP, BP and USP are shown in table 3 and table 4.

Table-3: Specifications for Capsules

Tests	Reference code	IP	BP	USP
Uniformity of weight	CQC1	90-110%	NS	NS
Content of active ingredients	CQC2	NS	<10%	NS
Uniformity of content	CQC3	85-115%	85-115%	85-115%
Uniformity of mass	CQC4	<10%	<10%	<10%
Disintegration test	CQC6	Disintegration time		
Hard capsules		<30 min	< 30 min	< 30 min
Soft capsules		<60 min	<60 min	<60 min
Enteric capsules		3 hrs	NS	NS
Gastro-resistant capsules		3 hrs	NS	NS

Table-4: Specifications for tablets

Tests	Reference Code	IP	BP	USP
Uniformity of content	TQC3	85-115%	85-115%	85-115%
Uniformity of weight	TQC4	<10%	<10%	<10%
Dissolution test	TQC6	>70%	>70%	>70%
Weight variation test	TQC7	<10%	<10%	<10%
Disintegration test		Disintegration Time		
Uncoated	TQC5	15	15	5-30
Coated		60	60	60-120
Enteric coated		60	-	60 or as per individual monograph
Film Coated		30	-	30min
Effervescent		5	5	Less than 3min or as stated in monograph
Soluble		3	3	-
Dispersible		3	3	Less than 3min or as stated in monograph
Orodispersible		-	3	-
Gastro-resistant		-	60	-
Friability test	TQC9	<1%	<1%	<1%

CONCLUSION

From the above review it can be summarized that though British Pharmacopeia, Indian Pharmacopeia and Unites States Pharmacopoeia encompasses most of in process and finished products QC tests for capsules and tablets. However dissimilarities were observed. Some tests are mentioned only in some pharmacopeias. The differences in the tests and their acceptance range as stated in the pharmacopeias needs to be harmonized and streamlined in such a way that if the test meets the acceptable range as per harmonized one, it meets all the requirements of the pharmacopeias and further the regulatory requirements of the concerned country. This is essential for the products marketed globally as it will be time saving.

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