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COMPARATIVE STUDY OF IN-PROCESS AND FINISHED PRODUCTS QUALITY CONTROL TESTS OF INDIAN PHARMACOPOEIA, BRITISH PHARMACOPOEIA & UNITED STATES PHARMACOPOEIA FOR CAPSULES AND LIQUID ORALS

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ABSTRACT
Present study deals with a brief overview of the comparative study 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. The concept of total quality control test refers to the process of striving 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. In process product testing is done in order to check the conformance of the final product with the compendial standards as specified in the pharmacopoeias. As the final sample taken for the finished product testing is only a representative of a large batch, a significant difference still remains. The pharmacopoeias have laid down the specified limits within which the value should fall in order to be compliant as per the standards. The official pharmacopoeias in different parts of the world specify the quality requirements for pharmaceutical products. However the parameters and standards differ to some extent from each other. Hence an attempt is being made to compare and bring out the harmonized limits within which a product should fall in order to meet the pharmacopoeial specifications that satisfy quality requirements for many regions. The main aim is to study the quality control tests for capsules and liquid orals and to list down the similarities and differences as per various Pharmacopoeias. The parameters examined for capsules and liquid orals 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.
Keywords: Indian Pharmacopeia, British Pharmacopeia, United States Pharmacopeia, capsules and liquid orals quality control.

INTRODUCTION

In the pharmaceutical industry, total quality of the product must be ensured in order to prevent the kind of product which does not comply with the specifications laid down by the Pharmacopoeias, and at the same time it is also necessary for controlling the errors during the production process. Quality can be defined as the suitability of the goods or service to the determined qualifications. Quality control emphasizes testing of products for defects and reporting to management who makes the decision to investigate or deny the release. Both the in process and finished product quality control tests help to ensure the total quality of the product. The entire dealing process (In process and finished product quality control tests) involves stringent quality control tests to make products totally flawless before they are released into the market.

In-process tests may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal battery of tests which are conducted prior to release.

In process controls (IPC) are checks that are carried out before the manufacturing process is completed. The function of in process controls involves monitoring and if necessary, adaptation of the manufacturing process in order to comply with the specifications. This may include control of equipment and environment too.

In process materials should be tested for their physical parameters and its quality attributes which are later approved or rejected by the quality control department based on the results obtained during the manufacturing process. Rejected In process materials should be identified and controlled under a quarantine system designed to prevent their use in manufacturing.

Standard operating procedures should be established and followed that describe the in process controls and tests. Certain tests conducted during 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.

References to certain procedures are quite similar in pharmacopoeias in each region even though there are minor changes within each of them. Wherever and whichever procedures are appropriate, pharmacopoeial procedures should be utilized. Whereas differences in pharmacopoeial procedures and/or acceptance criteria have existed among the regions, a harmonized specification is possible only if the procedures and acceptance criteria defined are acceptable to regulatory authorities in all regions.

In process controls may be performed at regular intervals during a process or at the end of the process. The objectives of in process control are both quality control and process control. The classic interpretation of the term in process control includes the recording of measured values by members of the in process control group.

Finished product controls (FPC) are checks that are carried out after the manufacturing process is complete with respect to qualitative and quantitative characteristics along with test procedures and their acceptance limits, with which the finished product must comply throughout its valid shelf life.

In order to determine the specifications of the finished product, the quality characteristics related to the manufacturing process should be taken into account. An appropriate specification for each aspect of quality studied during the phase of development and during the validation of the manufacturing process should be determined. At least those aspects considered to be critical should be the object of specifications routinely verified. The specification limits of the finished product at the time of batch release are set by the marketing authorization applicant such that the specifications proposed at the end of shelf life are guaranteed and are established on the basis of a critical detailed review of the data gathered from the batches analyzed.

The concept of total quality control test refers to the process of striving to produce a perfect product by a series of measures requiring an organized effort in order to eliminate errors at every stage in the production. In process product testing is required in order to check the conformance of the product with the compendial standards as specified in the pharmacopoeias. The pharmacopoeias have laid down the specified limits within which the value should fall in order to be compliant as per the standards. As the final samples taken for the finished product testing is only a representative of a large batch, a significant difference still remains

because of minor variation in the specified limits in different pharmacopoeias. Since the markets have opened up due to globalization it is necessary for a product to comply with the standards of the place where it is to be marketed.

As the official pharmacopoeias Indian Pharmacopeia[1-3], British Pharmacopeia[4-6] & United States Pharmacopeia[7] are different in different parts of the globe, there is a need for the harmonized limit within which a product should fall in order to meet the pharmacopoeial specifications of that region. The aim of the study is quality control tests for some conventional dosage forms and to list down the similarities and differences as per various Pharmacopoeias.

IN-PROCESS AND FINISHED PRODUCTS QUALITY CONTROL TESTS FOR CAPSULES

Capsules are solid dosage forms in which medicinal agents and/or inert substances are enclosed in a small shell of gelatin. Gelatin capsule shells may be hard or soft, depending on their composition.

Substances added to official preparations including capsules, to enhance the stability, usefulness or elegance or to facilitate their manufacture may be used only if they

i. Are harmless in the quantities used
ii. Do not exceed the minimum amounts required to provide their intended effect
iii. Do not impair the products bioavailability, therapeutic efficacy or safety.
iv. Do not interfere with requisite compendial assays and tests.

The capsules quality control (CQC) tests (Table 1) are:

- Uniformity of weight
- Content of active ingredients
- Uniformity of content
- Uniformity of mass
- Disintegration test
- Dissolution test

Table 1: Test Procedures for Capsules

<table>
<tr><th>Reference code</th><th>Test Procedure</th></tr>
<tr><td>CQC 1</td><td>Uniformity of weight:
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 odour of the solvent is no longer detectable.
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 weight. Not more than 2 of the individual weights deviate from the average weight by more than the percentage deviation shown in the Table 1(B) and none deviates by more than twice that percentage.</td></tr>
<tr><td>CQC 2</td><td>Content of active ingredients:
Determine the amount of active ingredient by the method described in the assay and calculate the amount of active ingredient in each capsule.
The result lies within the range for the content of active ingredient stated in the monograph. This range is based on the requirement that 20 capsules, or such other number as may be indicated in the monograph, are used in the Assay.
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 the Table 2(A) below.
The requirements of the Table 2(A) 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.
Table 1(A): Limits for content of active ingredients
<table>
<tr><th rowspan="2">Weight of active ingredients in each tablet</th><th colspan="3">Subtract from lower limit for samples of</th><th colspan="3">Add to the upper limit for samples of</th></tr>
<tr><th>15</th><th>10</th><th>5</th><th>15</th><th>10</th><th>5</th></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 But 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>0.3g or more</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>CQC 3</td><td>Uniformity of content:
This test is applicable to capsules that contain less than 10mg or less than 10 percent w/w of active ingredient. For capsules containing more than one active ingredient carry out the test for each active ingredient that corresponds to the before mentioned conditions. The test should be carried out only after the content of active ingredient in a pooled sample of the capsules has been shown to be within accepted limits of the stated content.
Determine the content of the active ingredient in each of 10 capsules taken at random using the method given in the monograph or by any other suitable analytical method of equivalent accuracy and precision.
The 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. 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.</td></tr>
<tr><td>CQC 4</td><td>Uniformity of mass:
Weigh an intact capsule. Open the capsule without losing any part of the shell and remove the contents as completely as possible.
For soft shell capsules, wash the shell with a suitable solvent and allow standing until the odour of the solvent is no longer perceptible. Weigh the shell. The mass of the contents is the difference between the weighing. Repeat the procedure with another 19 capsules.
Table 1(B): Limits for Uniformity of mass
<table>
<tr><th>Pharmaceutical form</th><th>Average mass(mg)</th><th>Percentage deviation (%)</th></tr>
<tr><td>Capsules, granules (uncoated, single dose), powders (single dose)</td><td>Less than 300mg

300mg or more</td><td>10

7.5</td></tr>
</table></td></tr>
<tr><td>CQC 5</td><td>Disintegration test:
Introduce one capsule into each tube and, if directed add a disc to each tube. Suspend the assembly in the beaker containing the specified liquid and operate the apparatus for the specified time. Remove the assembly from the liquid. The capsules pass the test if all of them have disintegrated.
If 1 or 2 capsules fail to disintegrate, repeat the test on 12 additional capsules, not less than 16 of the total of 18 capsules tested disintegrate.
If the capsules adhere to the disc and the preparation under examination fails to comply, repeat the test omitting the disc. The preparation complies with the test if all the capsules in the repeat test disintegrate.</td></tr>
<tr><td>CQC 6</td><td>Dissolution test:</td></tr>
</table>

	Place the stated volume of the dissolution medium, free from dissolved air, into the vessel of the apparatus. Assemble the apparatus and warm the dissolution medium to 36.5° to 37.5° C. Unless otherwise stated, place one capsule in the apparatus, taking care to exclude air bubbles from the surface of the capsule. When paddle is used, allow the capsule to sink to the bottom of the vessel prior to the rotation of the paddle. A suitable device such as a wire of glass helix may be used to keep horizontal at the bottom of the vessel capsules that would otherwise float. When basket type is used, place the capsule in a dry basket at the beginning of each test. Lower the basket into position before rotation. Operate the apparatus immediately at the speed of rotation specified in the individual monograph. 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 blade or basket, not less than 10 mm from the wall of the vessel. Except in the case of single sampling, add a volume of dissolution medium equal to the volume of the samples withdrawn. Perform the analysis as directed in the individual monograph. Repeat the whole operation 5 times. Where 2 or more capsules are directed to be placed together in the apparatus, carry out 6 replicate tests. For each of the capsule tested, calculate the amount of dissolved active ingredient in solution as a percentage of the stated amount where 2 or more capsules are placed together, determine for each test the amount of active ingredient in solution per capsule and calculate as a percentage of the stated amount.
CQC 7	**Hard capsules:** **Disintegration test:** Use water as the dissolution medium. If the capsules float on the surface of the medium, a disc may be added. If the capsules adhere to the discs, attach a removable piece of stainless steel woven gauze with mesh aperture of 2.00 mm to the upper plate of the basket rack assembly and carry out the test omitting the discs. Operate the apparatus for 30 minutes. Remove the assembly from the liquid. The capsules pass the test if all of them have disintegrated. If 1 or 2 capsules fail to disintegrate, repeat the test on 12 additional capsules, not less than 16 of the total of 18 capsules tested disintegrate.
CQC 8	**Soft capsules:** **Disintegration test:** Use water as the medium and add a disc to each tube. Operate the apparatus for 60 minutes. Remove the assembly from the liquid. The capsules pass the test if all of them have disintegrated. If 1 or 2 capsules fail to disintegrate, repeat the test on 12 additional capsules, not less than 16 of the total of 18 capsules tested disintegrate.
CQC 9	**Enteric capsules:** **Disintegration test:** Place one capsule in each tube. Operate the apparatus for 2 hours without the discs in 0.1M hydrochloric acid. No capsule shows signs of disintegration or rupture permitting the escape of the contents. Replace the medium in the vessel with mixed phosphate buffer pH 6.8. Add a disc to each tube and operate the apparatus for a further 60 minutes. Remove the apparatus from the medium and examine the capsules. They pass the test if no residue remains on the screen or on the underside of the discs, or if the residue remains, it consists of fragments of shell or of a soft mass with no palpable, unmoistened core.
CQC 10	**Gastro-resistant capsules:** **Disintegration test:** Place one capsule in each tube. Operate the apparatus for 2 hours without the discs in 0.1M hydrochloric acid. Examine the state of the capsules and the time of resistance varies according to the formulation of the capsules to be examined. It is typically 2h to 3h but even with deviations it must not be less than 1h. No capsules show signs of disintegration or rupture permitting the escape of the content. Replace the acid by phosphate buffer solution of pH 6.8. Add a disc to each tube; operate the apparatus for 60 min. If the capsules fail to comply because of adherence to the discs, the results are invalid. Repeat the tests on further 6 capsules omitting the discs **Dissolution test:** Similar as that of CQC 6

IN-PROCESS AND FINISHED PRODUCTS QUALITY CONTROL TESTS FOR LIQUID ORALS

The oral use of liquid pharmaceuticals has generally been justified on the basis of ease of administration to those individuals who have difficulty in swallowing solid dosage forms. A more positive argument can be made for the use of homogenous liquids (systems in which the drug or drugs are in solution) with rare exceptions, a drug must be in solution in order to be absorbed. A dug administered in solution is immediately available for absorption and in most cases, is more rapidly and efficiently absorbed than the same amount of dug administered in the tablet or capsule.

The liquid orals quality control (LQC) tests (Table 2) are

- Uniformity of content
- Uniformity of weight
- Uniformity of mass

Table 2: Test Procedures for Liquid Orals

Reference code	Test Procedure
LQC 1	**Uniformity of content** Determine the content of active ingredient of each of 10 containers taken at random using the method given in the monograph. The preparation complies with the test if the individual values thus obtained are all between 85 to 115 percent of the average value. The preparation fails to comply with the test if more than one individual value is outside the limits 85 to 115 percent of the average value or if any one individual value is outside the limits 75 to 125 percent of the average value. If one individual value is outside the limits 85 to 115 percent but within the limits 75 to 125 percent of the average value, repeat the determination using another 20 containers taken at random. The preparation complies with the test if in the total sample of 30 containers not more than 3 individual values are outside the limits 85 to 115 percent and not more than 1 is outside the limits 75 to 125 percent of the average value.
LQC 2	**Uniformity of weight:** Select a sample of 10 filled containers and remove the label on the containers. Clean and dry the outer surfaces of the container and weigh each container. Remove the contents from each container. If necessary, cut open the container and wash each empty container with a suitable solvent, taking care to ensure that the closure and other parts of the container are retained. Dry and again weigh each empty container together with its parts which may have been removed. The difference between the two weights is the net weight of the contents of the container. The average net weight of the contents of the 10 containers is not less than the labelled amount and the net weight of the contents of any single containers is not less than 91 percent and not more than 109 percent of the labelled amount where the labelled amount is 50 g or less, or not less than 95.5 percent and not more than 104.5 percent of the labelled amount where the labelled is more than 50 g but not more than 100g. If this requirement is not met, determine the net weight of the contents of 10 additional containers. The average net weight of the contents of the 20 containers is not less than the labelled amount, and the net weight of the contents not more than 1 of the 20 containers is less than 91 percent or more than 109 percent of the labelled amount, where the labelled amount is 50 g or less than 95 percent or more than 104.5 percent of the labelled amount is more than 50 g but not more than 100 g.
LQC 3	**Uniformity of mass:** Weigh individually the contents of 20 containers, emptied as completely as possible, and determine the average the average mass. Not more than 2 of the individual masses deviate by more than 10 percent from the average mass and none deviate by more than 20 percent.

The comparative study of Quality control parameters and specifications for capsules as per IP, BP and USP is given in the table3

Table 3: Specifications for Capsules.

Tests	Reference code	IP	BP	USP
Uniformity of weight	CQC 1	90-110%	NS	NS
Content of active ingredients	CQC 2	NS	< 10%	NS
Uniformity of content	CQC 3	85-115%	85-115%	85-115%
Uniformity of mass	CQC 4	< 10%	< 10%	< 10%
Disintegration test		Disintegration time		
Hard Capsules	CQC 5	< 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

The comparative study of Quality control parameters and specifications for liquid orals as per IP, BP and USP is given in the table 4

Table 4: Specifications for Liquid orals

Tests	Reference code	IP	BP	USP
Uniformity of content	LQC 1	85-115 %	85-115 %	85-115 %
Uniformity of weight	LQC 2	91-109 %	91-109 %	91-109 %
Uniformity of mass	LQC 3	NS	10 %	NS

SUMMARY

The objective of the present work was to compare various in process and finished product Quality Control tests as per Indian Pharmacopoeia, British Pharmacopoeia and United States Pharmacopoeia. The formulations for which the comparison was made included are Capsules and Liquid orals. The available Quality Control tests from various pharmacopoeias supplement each other and each pharmacopoeia gives more details on a special issue than the other. Each pharmacopeia has its own specifications for each test.

Following are the tables specifying the tests included for Capsules and Liquid orals as per Indian Pharmacopoeia, British Pharmacopoeia and United States Pharmacopoeia .

Table 5: Quality control tests for Capsules as per Indian Pharmacopoeia, British Pharmacopoeia and United States Pharmacopoeia

Tests	Indian Pharmacopoeia	British Pharmacopoeia	United States Pharmacopoeia
Uniformity of weight	✓	✓	✓
Content of active ingredients	✓	✓	✓
Uniformity of content	✓	✓	✓
Uniformity of mass	NS	✓	NS
Disintegration test	✓	✓	✓
Dissolution test	✓	✓	✓
Hard capsules Disintegration test	✓	✓	✓
Soft capsules Disintegration test	✓	✓	✓
Enteric capsules Disintegration test	✓	NS	NS
Gastro- resistant capsules Disintegration test Dissolution test	NS	✓	NS

Table 6: Quality control tests for Liquid Orals as per Indian Pharmacopoeia, British Pharmacopoeia and United States Pharmacopoeia

Tests	Indian Pharmacopoeia	British Pharmacopoeia	United States Pharmacopoeia
Uniformity of content	✓	✓	✓
Uniformity of weight	✓	✓	✓
Uniformity of mass	NS	✓	NS

CONCLUSION

From the above review it can be concluded that though Indian Pharmacopoeia, British Pharmacopoeia and United States Pharmacopoeia included most of the in process and finished products QC tests for Capsules and Liquid Orals. However some difference was observed. Some of the tests are available only in some pharmacopoeia. The differences in the tests and their limits as specified in the different pharmacopoeias needs to be harmonized and streamlined in such a way that if the test meets the specified limit as per harmonized one, it meets all the requirements of all the pharmacopoeias and later the regulatory requirements of that particular country. This is important for the products which are marketed globally. Because of this a huge amount of time, money and man power can be minimized.

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