# Quality Control

By

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# Contents

Course Description	vi
I. General introduction of quality Control	1
II. In process quality control (IPQC)	5
III. Quality Control Tests of Pharmaceutical Dosage	17
Forms جمهورية مصر العربية	
i. Quality Control Tests of powder and granules	17
ii. Tablets	22
iii. Capsules	30
iv. Effervescent granules	32
v. Suppositories	34
vi. Semisolid dosage forms	38
vii. Liquid dosage forms	42
viii. Parenteral products	45
ix. Pharmaceutical aerosols	48
IV. References and Recommended Readings	53

# **Course Description**

	Course Specifications	قسم: التصنيع الدوائي	
		1- بيانات المقرر	
الفرقة /المستوى :الثانية	اسم المقرر :رقابة الجودة	الرمز الكودى :	
ع <i>م</i> لی 2	عدد الوحدات الدراسية : نظرى جدورية مسر 2 ربية	التخصص : التصنيع الدوائي	
2- Overall Aim of Course: 2 هدف المقرر:	of The aim of the course is to describe relations between Quality Assurance (QA), Quality Control (QC) and their relationships to the overall quality management system and responsibilities of quality control unit. The prime objective of this course is to provide students with the basic information of quality control testing of different pharmaceutical dosage forms including solid, liquid semisolid and parenteral as well as them in-process quality control testing		
3- Intended learning outcomes of the course (ILOs): المستهدف من تدريس المقرر - 3			
i. Knowledge and Understanding: ۱. المطومات	<ul> <li>By the end of this course, students</li> <li>1- Understand the scope of Quaversus Quality Control (QC).</li> <li>2- Recognize the in-process quality various dosage forms</li> </ul>	<u>s should be able to:</u> Ility Assurance (QA) ty control testing of	
والمفاهيم :	3- Identify quality control te pharmaceutical dosage form	sting of different	
ii. Intellectual Skills: ب- المهارات الذهنية :	<ul> <li>By the end of this course, students should be able to:</li> <li>1. Select suitable methods for identification and standardization of pharmaceutical products</li> <li>2. Evaluate quality control methods used in identification of pharmaceutical products.</li> </ul>		
III. Professional Skills: ج- المهارات المهنية	By the end of this course, students 1. Apply quality control testing for standardization of drugs	s should be able to: or identification and in pharmaceutical	

الخاصة بالمقرر:	products. 2. Estimate different dosage forms, using various analytical methods, tools and techniques.	
IV. General and Transferable Skills: د- المهارات العامة :	<ul> <li>By the end of this course, students should be able to:</li> <li>1. Work coherently and successfully as a part of a team in pharmaceutical factories.</li> <li>2. Assess problems.</li> </ul>	
4- Course content 4- محتوى المقرر:	<ol> <li>General introduction of quality control (IPQC)</li> <li>IPQC Tests for Various Dosage Forms, (Tablets)</li> <li>IPQC Tests for Syrup and Suspension</li> <li>IPQC Tests for semisolid dosage form.</li> <li>IPQC Tests for Parenteral preparation</li> <li>Quality control tests of powder</li> <li>Quality control tests for solid dosage form (tablets &amp; Capsules)</li> <li>Quality control tests of semisolid dosage form (effervescent granules)</li> <li>Quality control tests of semisolid dosage form.</li> <li>Quality control tests for Parenteral preparation</li> <li>Quality control tests of semisolid dosage form.</li> <li>Quality control tests for solid dosage form.</li> <li>Quality control tests for Parenteral preparation</li> <li>Pharmaceutical aerosols evaluation</li> </ol>	
5- Teaching and Learning Methods: 5- أساايب التعليم والتعلم	<ol> <li>Lectures.</li> <li>Group discussions</li> </ol>	
6- Teaching and learning methods for students with limited abilities 6- أساليب التعليم والتعلم للطلاب ذوى القدرات المحدودة	ป ร ก ร	
7- Student Assessment:		
a- Assessment methods:	a. Class work:	
أ- الأساليب المستخدمة	<ol> <li>Quizzes</li> <li>Midterm theoretical</li> <li>Assignments</li> <li>Participation</li> <li>Final exam:</li> <li>Written theoretical</li> </ol>	

b- Assessment schedule: ب- التوقيت	<ul> <li>a. Class work:</li> <li>1. Quizzes: Quiz I (4<sup>th</sup> week) Quiz II (11<sup>th</sup> week)</li> <li>2. Midterm theoretical (7<sup>th</sup> week)</li> <li>3. Assignments</li> <li>4. Participation</li> <li>b. Final exam written theoretical exam (15<sup>th</sup> week)</li> </ul>	
C-Weight Of Assessments: ج- توزيع الدرجات	<ol> <li>Quizzes and class work (20%), 20 marks</li> <li>Final written theoretical exam (80%), 80 marks.</li> </ol>	
7- List of References		
/ List of Kererences.	8- قائمة الكتب الدراسية والمراجع:	
a- Course notes: أ- مذكرات	Lecture notes for Quality Control of Pharmaceutical dosage form	
b- Essential books (text books) ب- کتب ملزمة	<ol> <li>Ansel, H.C., Popovich, N.G. and Allen, L.V., editors.Pharmaceutical Dosage Forms and Drug Delivery Systems, 10th edition. Philadelphia: Williams &amp; Wilkins. (2014).</li> <li>Aulton's Pharmaceutics: The design and manufacture of medicine, Micheal Aulton, 4th Edition, 2013.</li> </ol>	
c- Recommended books ج- کتب مقترحة	<ol> <li>Modern Pharmaceutics, Editors: G. S. Banker and C. T. Rhodes, Marcel Dekker Inc., New York, 1990.</li> <li>Clark's Analysis of Drugs and Poisons, 3rd edition. London: The Pharmaceutical Press. (2004).</li> </ol>	
d- Periodicals, web sites, ,,,,, د- دوریات علمیة أو نشرات 	<ul> <li>www.pharmaceutical-technology.com</li> <li>www.google.com</li> <li>www.pubmed.com</li> <li>www.biomed.net</li> </ul>	

# General introduction of Quality Control

#### **Objectives**

After reading this chapter, the student will be able to:

- Describe relations between Quality Assurance (QA), Quality Control (QC) and their relationships to the overall quality management system and responsibilities of quality control unit.
- 2. Recognize the role of quality control in pharmaceutical industry.

#### **Quality Control**

#### **Definition**

Quality as defined by Juran is fitness for purpose or use. It refers to the features and characteristics of a product that bears on its ability to satisfy the needs of the consumer. Features like shape, dimension, composition, strength, workmanship, finish and color.

• According to Broom, quality control is "systematic control of these variables encountered in manufacturing process which affect the excellence of the end product."

• According to Alford and Beatty, quality control is "that technique or group of techniques of industrial management by means of which products of uniform acceptable quality are manufactured."

#### Role of Quality Control in Pharmaceutical Industry

Quality control is an essential operation of the pharmaceutical industry. Drugs must

be marketed as safe and therapeutically active formulations whose performance is consistent and predictable. New and better medicinal agents are being produced at an accelerated rate. At the same time more exacting and sophisticated analytical methods are being developed for their evaluation.

The 4 Main responsibilities of quality control in pharmaceutical industry include

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- > Efficacy
- > Safety
- > Quality
- Compliance



- <u>Raw Materials and API:</u> The techniques used include Raman and IR spectroscopy, Assay (HPLC and Titration), Physical tests.
- Packaging Components: The various packaging components which are in contact with the drug are tested. The techniques include appearance, spectroscopy, loss on drying.
- Finished Products: The techniques include HPLC, Assay, Dissolution, Content uniformity.

#### **Objectives of Quality Control**

- 1. Quick sale of quality goods QC accelerates the sale of the goods by supplying only the quality goods.
- 2. Production of standard quality goods QC aim at manufacturing standard quality products and avoids producing inferior quality goods.
- 3. Improvement in quality Aims at creating quality consciousness at all levels in the organization.

#### Steps in Quality Control

1. DEVISING THE CONTROL OVER RAW MATERIALS:

The quality of the finished products is determined mostly by the quality of raw materials.

- FIXING STANDARDS AND SPECIFICATIONS:
   To make any scheme of quality control successful, it is necessary to predetermine standards and specifications.
- 3. EXERCISING CONTROL OVER PRODUCTION OPERATIONS:

To execute efficient practices, the technical expert of the Quality Control Department must investigate the operating methods.

4. LOCATING INSPECTION POINTS:

When the points at which defects occur are wrongly located or located with delay, it hinders quality control. Hence there should first be inspection of raw material at vendors place, then at company's plant then at various stages during process.

5. MAINTAINING QUALITY OF EQUIPMENTS:

The final quality of the products is conditioned by the quality of the equipment and other devices used.

6. MAINTAINING RECORDS:

The QC department is responsible for setting records related to quality inspection and control and the number rejected

#### **Quality Variation**

When the quality of any drug is given by industry, then it is responsible for any variation from the standard. • Quality Variation may occur due to any mistake during the whole process i.e. from the reception of raw material up to the final product in the packaged form. • The risk of error increases as the material increases and the method become very complicated.

# The general sources causing product Quality Variation during manufacturing are <u>as follows</u>

#### 1. MATERIALS:

- a. Variations among suppliers of same substances.
- b. Variations among batches from same suppliers.
- c. Variations within a batch.

#### 2. METHODS:

- a. Wrong procedure.
- b. Inadequate procedure.
- c. Negligence in procedure by chance.

#### 3. MACHINES:

- a. Variation of equipment of same process.
- b. Difference in adjustments of equipment.
- c. Aging of machines and improper care.

#### 4. <u>MEN:</u>

- a. Improper working conditions.
- b. Inadequate training and understanding.
- c. Lack of interest and emotional upheavals.
- d. Dishonesty, fatigue and carelessness.

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# In process quality control (IPQC)

#### Objectives

After reading this chapter, the student will be able to:

- 1. Know the general introduction of in process quality control
- 2. List IPQC Tests for Various Dosage Forms
- 3. Recognize different Quality Control Equipment's

#### General introduction of in process quality control (IPQC)

#### Definition of IPQC

IPQC stands for in process quality control. These are checks that are carried out before the manufacturing process is completed.

The function of in-process controls is monitoring and if necessary adaption of the manufacturing process to comply with the specifications. This may include control of equipment and environment too. In-process materials should be tested for identity, strength, quality and purity as appropriate and approved or rejected by the quality control unit during the production process.

#### Practical consideration in developing QA/QC SYSTEMS

In practice, the QA/QC system is only part of the inventory development process and inventory agencies do not have unlimited resources. Quality control requirements, improved accuracy and reduced uncertainty need to be balanced against requirements for timeliness and cost effectiveness. A good practice system seeks to achieve that balance and to enable continuous improvement of inventory estimates. Within the QA/QC system, good practice provides for greater effort for key source categories and for those source categories where data and methodological changes have recently occurred, than for another source categories<sup>3</sup>. It is unlikely that inventory agencies will have sufficient resources to conduct all the QA/QC procedures outlined in this review on all source categories. In addition, it is not necessary to conduct all of these procedures every year.

#### Elements of QA/QC System

The following are the major elements to be considered in the development of a QA/QC system to be implemented in tracking inventory compilation:

> An inventory agency responsible for coordinating QA/QC activities;

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- > A QA/QC plan;
- General QC procedures
- Source category-specific QC procedures
- QA review procedures;
- Reporting, documentation, and archiving procedures.

For purposes of the QA/QC system, the QC approach includes all proc<mark>edures in plus</mark> additional

#### Quality Control Equipment's

1. <u>Friabilator</u>

Friabilator is the instrument which is used to detect the friability of the tablets. Friability is the combined effects of shock and abrasions. So to resist shock and abrasions friability test is done for the tablets. In this a no. of tablets are put in the friabilator and revolves at 25rpm, dropping the tablets a distance of six inches with each revolution. Conventional compressed tablets that lose less than 0.5 to 1.0% of their weight are generally considered as acceptable. When capping is considered on friability testing, the tablet should not be considered as for commercial use, regardless of the %age of loss seen.

#### 2. Dissolution test apparatus

The dissolution test is conducted to assure that drug is properly breaks into their parts in a respective medium. Dissolution testing can be continued through three stages.

STAGE (1-3)-Six tablets are tested and are acceptable if all the tablets are not less than monograph tolerance limit plus 5%. if the tablet fails ,an additional six tablets are tested. The tablets are acceptable if average of the twelve tablets are greater than or equal to tolerance limit and no unit less than tolerance limit minus 15%, if tablet still fails the test, an additional 12 tablets are tested. The tablets are acceptable if the average of all 24 tablets is greater than or equal to tolerance limit and if not more than 2 tablets are less than tolerance limit minus 15%. Industrial pharmacists routinely test their formulations for dissolution.

#### 3. Digital pH meter

Digital pH meter is used in pharmaceutical industries to assure the pH of the solutions which is needed for the preparation of the drug, pH is very important to make assure the stability of the product. Solutions stability investigation usually commence with probing experiments to confirm decay at the extremes of pH for an e.g 0.1N HCL, Water, and 0.1N NaOH). These intentionally degraded samples may be used to confirm assay specificity as well as to provide estimates for maximum rates of degradation. This initial experiment should be followed by the generation of a complete pH rate profile to identify the pH of maximum stability. Aqueous buffers are used to produce solutions over a wide range of ph values with constant levels of drug, cosolvent and ionic strength. Since most solution pharmaceuticals are intended for parenterals routes of administration, this initial ph Rte study should be conducted at a constant ionic strength that is compatible with physiologic media. Ionic strength of an isotonic 0.9% NaCl solution is 0.15. Moisture analyzer A moisture analyzer indicating by its name as to analyze moisture in a drug content. The formula which is used to detect moisture is

as follows:

% moisture content (M.C) = (wt. of water in sample/wt. of dry sample)\*100

#### 4. Drying of solids

The moisture content in a solid can be expressed on a wet-weight or dry weight basis. On a wet weight weight basis, the water content of a material is calculated as a % age of the weight of the wet solid, whereas on the dry weight basis, the water is expressed as a % age of the weight of the dry solid. In pharmacy loss on drying is commonly referred as L.O.D, is an expression of moisture content on a wet weight basis which is calculated as follows

#### 5. Process viscometer

This instrument is capable for performing the rheologic studies of most pharmaceutical preparations such as semi-solid preparations or formulations: pastes, ointments and creams.

#### 6. Digital refractometer

Digital refractometer is used for those products which are sensitive to light refraction, so it is simply used to check the refraction spectrum of drug product.

#### 7. Leak test apparatus

A leak test apparatus is used for checking the crimping of the valve which must be available to prevent defective containers due to leakage. For metal containers, this is accomplished by measuring the "crimp" dimensions and ensuring that they meet specifications. Final testing of the efficiency of the valve closure is accomplished by passing the filled containers through the water bath. Periodic checks are made of the temperature of the water bath, these results are recorded.

#### A. IPQC Tests for Various Dosage Forms

- 1. Tablets:
  - a. Drug contents determination.
  - b. Moisture contents of granules.
  - c. Assay of active ingredients.
  - d. Weight variation of uncoated tablets.
  - e. Hardness test.
  - f. Disintegration test.

#### a. Drug Content Determination

A physically sound tablet may not produce the desired effects. To evaluate a tablet potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet and batch to batch, and a measure of the tablets ability to release the drug needs to be ascertained.

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#### **b**. <u>Moisture Content of granules</u>

Granules should possess sufficient strength to withstand normal handling and mixing processes without breaking down and producing large amounts of fine powder. On the other hand, some size reduction during compaction into tablets is desirable to expose the areas of clean surface necessary for optimum bonding to take place so moisture content is the very important factor for producing god pharmaceutical product.

c. Assay of active ingredient

In a tablet an active ingredient is present which is called active pharmaceutical ingredient (A.P.I). So to prepare the tablet assay has to be done to produce good finished product.

#### d. <u>Hardness test</u>

The monitoring of tablet hardness is especially important for drug products that possess real or potential bioavailability problems that are sensitive to altered dissolution release profiles as a function of the compressive force employed. One of the earliest testers to evaluate tablet hardness was the Monsanto hardness tester to evaluate tablet hardness tester.

#### e. Disintegration test

A generally accepted maximum is that drug to be readily available to the body, it must be in solution. For most tablets, the first important step towards solution is break down of the tablet into smaller particles or granules, a process known as disintegration. The U.S.P device to test disintegration uses 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 tablet is placed in each tube, and the basket rack is positioned in a 1-L beaker of water simulated gastric fluid and at  $37\pm^{0}$  c, such that tablet remains 2.5 cm below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker. A standard motor driven device is used to move the basket assembly containing the tablets up and down through distance of 5 to 6cm at a frequency of 28 to 32 cycles per minute.

#### 2. Syrup and Suspension

- a. Drug contents determination. ealth & Populatic
- b. Assay of active ingredients.
- c. Determination of pH
- d. particle size
- e. Viscosity and specific gravity test
- a. Drug content determination

Determination of drug content in suspension and syrups are important because their concentration has to be sufficient itself that it produce the pharmacological action. A suspension is much prescribed to pediatrics, so their concentration has to be sufficient not to less not to large. Assay of

#### b. active ingredient

Active ingredient means pure drug present in the product. An assay of active ingredient must be done because it is the only which is responsible for pharmacological action and in syrups and suspension a small and fine particles are included in syrups and suspension

#### c. pH of the product

pH affects the stability of the product so before filling and after filling of suspension and syrups pH has to be checked out for consistency of the product.

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#### d. <u>Particle size</u>

In suspension and syrups a solute particle is dispersed in a suitable solvent so particle size becomes the important factor for the suitability of the product and all the particles has to be of same size and shape for proper dispersing in the solvent.

#### e. <u>Viscosity and specific gravity test</u>

Once the desired semi-solid preparation have been chosen, a consistency that provides the desired stability and has appropriate flow characteristics must be attained. For emulsion it is routinely observed that the building up of viscosity in a freshly prepared emulsion requires some time. The is recommended, therefore that newly formulation emulsion be allowed to rest undisturbed for 24 to 48 hours before it is determined whether its rheologic properties correspond to those that are required. The viscosity of emulsions responds to changes in composition in accordance with the following generalizations.

- ✓ There is a linear relationship between emulsion viscosity and viscosity of continuous phase.
- The greater the volume of the internal phase, the greater is the apparent viscosity.
- $\checkmark$  To control emulsion viscosity, three interacting effects must be balanced

- > The viscosity of o/w and w/o emulsions can be increased by the reducing the particle size of the dispersed phase.
- > Emulsion stability is improved by a reduction in particle in particle size.
- Flocculation or clumping which tends to structure the internal phase, can be stabilizing effect, it increases the viscosity.

#### 3. Semi-Solid

- a. Drug contents determination.
- b. Assay of active ingredients.
- c. Uniformity and homogeneity test.
- d. Viscosity and specific gravity test.

#### a. Drug content determination

As all have discussed earlier drug content becomes important factor for active pharmaceutical product. Drug content has to be of very suitable ratio that it can give the pharmacological action.

#### b. active ingredient

Active ingredient means pure drug present in the product. An assay of active ingredient must be done because it is the only which is responsible for pharmacological action and in syrups and suspension a small and fine particles are included in syrups and suspension

#### c. Homogenecity test

The semi-solid preparations require further treatment are transferred or pumped to the proper homogenizer, the selection of which is governed by the degree and rate of shear stress required.

#### d. Viscosity and Specific gravity test

Once the desired semi-solid preparation have been chosen, a consistency that provides the desired stability and has appropriate flow characteristics

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must be attained. For emulsion it is routinely observed that the building up of viscosity in a freshly prepared emulsion requires some time. The is recommended, therefore that newly formulation emulsion be allowed to rest undisturbed for 24 to 48 hours before it is determined whether its rheologic properties correspond to those that are required. The viscosity of emulsions responds to changes in composition in accordance with the following generalizations.

- There is a linear relationship between emulsion viscosity and viscosity of continuous phase.
- The greater the volume of the internal phase, the greater is the apparent viscosity.
- To control emulsion viscosity, three interacting effects must be balanced by the formulator.
  - The viscosity of o/w and w/o emulsions can be increased by the reducing the particle size of the dispersed phase.
  - Emulsion stability is improved by a reduction in particle in particle size.
  - Flocculation or clumping which tends to structure the internal phase, c a n be stabilizing effect, it increases the viscosity.

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#### 4. Parenteral preparation

- 1. Drug contents determination.
- 2. Clarity test.
- 3. Determination of pH
- 4. Pyrogen test.
- 5. Stability test.
- 6. Leakage test.
- 7. Checkup of particulate matters.

#### a. Drug content determination

As all have discussed earlier drug content becomes important factor for

active pharmaceutical product. Drug content has to be of very suitable ratio that it can give the pharmacological action

#### b. Pyrogen test

The presence of pyrogenic substance in parenteral is determined by a qualitative biologic test based on the fever response of the rabbits. Rabbits are used as test animal because they show a physiologic response to pyrogens similar to that of human beings. If a pyrogenic substance is injected into the vein of a rabbit, an elevation of temperature occurs in a period of three hours.

#### c. pH of the product

pH affects the stability of the product so before filling and after filling of suspension and syrups pH has to be checked out for consistency of the product.

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#### d. Sterility test

All products labeled "sterile" must pass through sterility test, having been subjected to an effective process of sterilization. The traditional concept of sterilization is the absolute condition of total elimination of all the microorganisms. With a terminal method of sterilization of a parenteral product, particularly steam under pressure, a probability of no more than one sterile unit in a million is readily achievable. The term aseptic indicates a controlled process in which the level of microbial contamination is reduced to the degree that microorganisms can be excluded from a product during processing. It describes apparently sterile state.

#### e. Leaking test

Ampules are intended to provide hermetically sealed container for a single dose of a product, thereby completely barring any interchange between the contents of the sealed ampule and its environment. Should capillary pores or tiny cracks be present, microorganisms or other dangerous contaminants may enter the ampule, or the contents may lead to the outside and spoil the appearance of the package. Changes in temperature during storage cause expansion and contraction of the ampule and contents, thereby accentuating interchange if an opening exists. Leakers usually detected by producing a negative pressure with an incompletely sealed ampule, usually in a vaccum chamber, while the ampule is entirely submerged in a deeply coloured dye solution, usually 0.5 to 0.1% methylene blue. Subsuequent atmospheric pressure then causes dye to penetrate an opening, being visible after the ampule has been washed externally to clear it of dye. The vaccum (27 inches Hg or more) should be sharply released after 30 min. Only a tiny drop of dye may penetrate a small opening. Vials and bottles are not subjected to such a leaker test because the rubber closure is not rigid; however, bottles are often sealed while a vacuum is

#### f. Clarity test

Clarity is the relative term, the meaning of which is markedly affected by the subjective evaluation of the observer. Unquestionly a clean solution having a high polish conveys to the observer that the product is of exceptional quality and purity. It is practically impossible, however, to prepare a lot of a sterile product so that every unit of that lot is perfectly free from visible particulate matter, that is, from particles that are 30 to 40 micrometer and larger in size. Consequently, it is the responsibility of the quality control department to detect and discard individual containers of a product that the ultimate user would consider to be unclean.

being pulled so that the bottle remains evacuated during its shelf life.

This clarity test is performed in industry by visual inspection machine by the light baffles against reflection into the eyes, and views against a black and white background, with the contents set in motion with a swirling action

#### g. <u>Stability</u>

To enhance the assurance of successful manufacturing operations, all process steps must be carefully reduced to writing after being shown to be effective. These process steps are often called standard operating procedures(SOPs). No extemporaneous changes are permitted to be made in these procedures; any change must go through the same approval steps as the original written SOP. Further external records must be kept to give assurance at the end of the production process that all steps have been performed as prescribed. Such in-process control is essential to assuring the quality of the product, since these assurances are even more significant than those from product release testing.

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## Quality Control Tests of Pharmaceutical Dosage Forms

#### **Objectives**

After reading this chapter, the student will be able to:

- 1. Describe QC tests for powder and granules
- 2. Know different methods for Particle Size Measurement
- 3. Determine the Uniformity of powder.

#### I. Quality control tests for powder and granules

#### Why Flow Properties Testing?

A thorough understanding of a bulk material's flow properties and its flowability are crucial for identifying the cause of poor flow, powder flooding or rate limitations, segregation, or product non-uniformity. Flow properties tests are also critical when designing a new silo/bin/hopper, stockpile, feeder, chute, conveyor or other material handling equipment. Issues can arise or be compounded when powder and bulk solids flow properties have not been measured, the test results may be limited, or the data are non-representative of the application

#### Flow Properties Tests

Key bulk material flow properties that should be measured for troubleshooting problems, assessing powder flowability, or designing a bulk material handling system are:

#### 1. Angle of repose $(\theta)$

The frictional forces or resistance to movement between particles in the loose

powder can be measured by the angle of repose ( $\theta$ ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

 $\theta$  = tan-1 (h / r)

Where,  $\theta$  is the angle of repose; h is the height in cm; r is the radius in cm.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. The value of angle of repose between 25-30° indicates good flow property, 36-40° indicates fair flow property (aid not needed), 41-45° indicates passable flow property, 46-55° indicates poor flow property (must agitate, vibrate), 56-66° indicates very poor flow property and value >66° indicates very very poor flow property.

#### 2. Powder density

#### a. Bulk density

Apparent bulk density (p bulk) was determined by pouring a weighed quantity of blend (100g) into a graduated cylinder (250 mL) and measuring the volume of this weight (B.P. 2009).

 $\rho_{\text{bulk}}$  = weight of the powder/initial volume

#### b. <u>Tapped density</u>

Tapped density (**ptap**) was determined by tapping the cylinder containing the powder blend until no further volume changes occur (B.P. 2009).

 $\rho_{tap}$  = weight of the powder/finial volume

Further evaluation of the prepared powders was carried out by calculating

Hausner ratio (HR) and Carr's index (CI). Hausner ratio (HR) was calculated according to the following equation:

#### c. <u>Hausner Ratio = P<sub>tap</sub>/ P<sub>bulk</sub></u>

Where (**ptap**) is the tapped density and (**pbulk**) is the bulk density. The value of the HR between 1.00-1.11 indicates excellent flowability, 1.12-1.18 indicates good flowability, 1.19-

1.25 indicates fair flowability, 1.26-1.34 indicated poor flowability, 1.46-1.59 indicates very poor flowability and value >1.6 indicates very very poor flowability. Carr's index (compressibility index) was calculated according to the following equation:

#### <u>d. Carr's Index = (P<sub>tap</sub> - P<sub>bulk</sub>/ P<sub>tap</sub>) x 100</u>

There is a relationship between compressibility index and flowability where compressibility index between 1-10 % indicates excellent flowability, 10-15 % indicates good flowability, 16-20 % indicates fair flowability, 21-25 % indicates passable flowability, 26-31 % indicates poor flowability, 32-37 % indicates very poor flowability and value >38 % indicates very very poor flowability.

#### 3. Particle size and size distribution

Any collection of particles is heterogeneous i.e., particles of more than one size are present.

- ✓ We must know size of particle & how many particles of the same size exist in the sample.
- ✓ This is the <u>particle size distribution</u> and from this we calculate average particle size for the sample.

#### Methods of Particle Size Measurement

#### a. Sieving Method

- Common & Simple method.
- Size range: 50 to 5000 microns.

Principle:

Powder is placed on the coarsest mesh (larger) of a series of standard sieves with the finest mesh (smaller) at the bottom.

Fractionation done by shaking & tapping.

Each fraction is weighed.

Results expressed in term of sieve size.

#### N.B.

- 1. Standard sieves must never be mishandled: Forcing a powder through the sieve distort openings size, particularly in finer mesh screens,  $\rightarrow$  wrong results.
- Sieves are used to break up granulation mass, but this is not the purpose for standard sieves. (Less expensive sieves may be used for size reduction operations).

11311

#### Determination of the Uniformity of Fineness

For Very Coarse, Coarse, and Moderately Coarse Powders.

- 1. Place 25 to 100 gm powder on the proper standard testing sieve with receiving pan & cover.
- 2. Shake sieves in rotary horizontal direction & vertically by tapping on hard surface for not less than 20 minutes or until no particles pass through sieves.
- 3. Weigh amount remaining on each sieve and the receiving pan.
- In case of fine or very fine powders, shake the sieve for at least 30 minutes or until no particles pass through sieves.



#### > In the case of oily or other powders, which tend to clog the openings:

(a) Brush the screen at intervals during the test.

(b) Break up lumps, which form during the sifting but do not increase the fineness of the powder during the sieve testing.

#### Mechanical Sieve Shaker

Screening through standard sieves in a mechanical sieve shaker which reproduces the circular and tapping action with a uniform mechanical action.

b. The Microscope Method

Direct method for substances, which below sieve size.

✓ Ordinary optical microscope used for particles 0.5 to 100 microns.

**C**lectron microscope is used for sizes 0.001 to 10 microns.

Only one dimension is measured, usually is the longest axis of each particle.

#### Method:

- 1- Powder is suspended in suitable diluent (water, oil).
- 2- The eye piece of microscope is fitted with a calibrated micrometer to determine the particle size.
- 3- To obtain valid results the diameters of 1000 or more particles should be measured.
- s usually histogram of size distribution curve take the form of symmetric curve
- Sometimes particle size distribution curve skewed to left, indicating greater numbers of finer particles than coarse, or skewed to the right indicating the opposite.

This method is exceedingly useful in defining degree fineness:

- 1) For comparing fineness of different lots of solids.
- 2) Used as a control procedure in milling operation.

# **Quality Control Tests of Tablets**

#### **Objectives**

After reading this chapter, the student will be able to:

- 1. Know different tests for tablet evaluation.
- 2. Define and differentiate weight variation from content uniformity
- 3. Distinguish between different equipment's used in QC tests for tablets

### II. <u>Tablets</u>

#### Evaluation of tablets includes:

- 1- General appearance
- 2- Weight variation
- 3- Content uniformity
- 4- Disintegration time
- 5- Dissolution rate
- 6- Tablet hardness
- 7- Friability
- 8- Thickness

#### 1- General Appearance

The general appearance of a tablet is essential for consumer acceptance, for control lot to lot uniformity, tablet to tablet uniformity and to monitor trouble-free manufacturing. The control of the general appearance of a tablet involves the measurement of a number of attributes such as: tablet's size, shape, color, odor, taste, surface texture,

Population

physical defect, consistency and legibility of any identifying markings.

#### 2- Weight variation

The weight of the tablet is routinely measured to ensure that a tablet contains the proper amount of the drug. In practice samples of tablets are taken and weighed throughout the compression process. The volumetric fill of the die cavity of the tablet machine determines the weight of the compressed tablet.

Twenty tablets are dusted and weighed on an analytical balance and the average weight is calculated. Each tablet is then weighed individually and the weight of each tablet is compared with the average weight already calculated. According to the USP, not more than two tablets are permitted to differ from the mean weight by greater than the permissible deviation listed below and no tablet is permitted to differ by more than double that deviation.

Average Weight	Percentage Deviation
130 mg or less	10
More than 130 mg and less than 324 mg	7.5
more than 324	5

#### 3- Content uniformity

The control of weight variation may be a sufficient control over the uniformity of drug content if the dose of the drug is large and there is relatively little diluent or excipient present. In case of more potent, low-dose drugs, in which excipients make up the bulk of the tablet weight, the control of weight variation does not offer sufficient assurance of the uniformity of drug content. Therefore, in order to ensure that every tablet contains the labeled amount of the drug within the prescribed limits, the USP includes the content uniformity test.

Twenty tablets are powdered together and an aliquot of the mixture is analyzed for its drug content. The results obtained must be within the prescribed limits stated in the pharmacopeia.

Factors affecting content uniformity:

a- Non-uniform distribution of the drug substance throughout the powder mixture or granulation.

b- Segregation of the powder mixture or granulation during the various manufacturing processes.

c- Tablet weight variation.

#### 4- Disintegration time

The disintegration time test is carried out to determine the time required for the tablet to disintegrate. This test is very important because the dissolution rate of the drug depends upon the disintegration time of the tablets which ultimately affects the rate of absorption of the drug. The apparatus used for this test is known as the disintegration test apparatus which consists of a rack holding 6 glass or plastic tubes each having a 10-mesh screen at its bottom. The tubes are raised and lowered at a fixed rate in a water bath maintained at  $37\pm2^{\circ}$ C. Six tablets are placed one in each tube along with a plastic disk over each tablet. The tubes are allowed to move up and down and the time required for each tablet to disintegrate and pass through the screen is recorded. The plastic disks do not allow the tablets to float and impart a slight pressure on the tablets to force any soft mass through the screen. Generally, the disintegration time for uncoated tablets is 30 minutes and for coated tablets 1 hour. There are, however, a number of exceptions in this test:

- a) Soluble tablets and effervescent tablets should disintegrate within 3 minutes.
- b) Enteric-coated tablets should not disintegrate in simulated gastric fluid, but should disintegrate in simulated intestinal fluid in 2hours.
- c) Chewable tablets are not subjected to the disintegration time test.



**Disintegration Tester** 

#### 5- Dissolution rate

The purpose of dissolution testing is to see how much of the drug goes into solution after a given period of time. Determination of dissolution rate of the drug is necessary because the rate of dissolution of the drug plays an important role in the absorption of the drug into the blood stream.

Three types of apparatuses are officially recognized for determining the tablet dissolution rate:

a) Apparatus 1 (rotating basket apparatus): It consists of a 40-mesh stainless steel basket fixed to a shaft which is rotated by a motor. The basket containing the tablet or capsule is immersed in the specified dissolution medium contained in a 1000 ml vessel and maintained at  $37 \pm 0.5$  <sup>0</sup>C by a constant temperature water bath. The dissolution medium is allowed to rotate at a specified speed by the motor.

b) Apparatus 2 (rotating paddle apparatus): It is the same as apparatus 1 except that the basket is replaced by a paddle which acts as the stirring element.

c) Apparatus 3 (modified disintegration test apparatus): in which the 10-mesh screen at the bottom of the tubes is replaced with a 40-mesh screen and no plastic disks are used. One tablet is placed in the basket in apparatus 1 or in the tube in apparatus 3 or dropped directly in the dissolution medium in case of apparatus 2. The motor is adjusted to turn at the specified speed, and samples of the dissolution medium are withdrawn at time intervals to determine the amount of the drug in solution. Six tablets are tested, and the batch will be accepted if not less than 70% of the labeled drug content of each tablet have dissolved within 45 minutes. If 1 or 2 tablets fail the test, 6 more tablets are tested. At least 10 of the 12 tablets must meet the requirements. The dissolution results are plotted as concentration versus time.



#### 6- Tablet hardness

Tablets hardness describes its strength and resistance of tablets to breakage during handling, packaging, storage and transportation. Tablet hardness (or tablet crushing strength) is the force required to break a tablet. The relationship of hardness to tablet disintegration, and perhaps more significantly, to the drug dissolution rate, has become apparent. If the tablet is too hard, it may not disintegrate in the required period of time; and if it is too soft, it will not withstand the handling during packaging and transportation. Therefore, it is very necessary to check the hardness of the tablets when they are being compressed and the pressure is adjusted accordingly on the tablet machine.

The tablet hardness test consists of breaking or crushing the tablet by application of a compression force. Tablet hardness devices are of two types:

#### I. Hand-operated: e.g.:

a) Monsanto or Stokes hardness tester: It is a small and portable hardness tester which was manufactured and introduced in the mid-thirties by the Monsanto Chemical Co. it is now distributed by the Stokes Div. and may be designated as either the Monsanto or Stokes hardness tester. In this instrument, the force required to break the tablet is applied by a screw-driven spring and recorded on a scale in kilograms. Hardness of 4 - 6 kg is considered satisfactory to the tablet.

b) Pfizer hardness tester which operates on the same mechanical principle as ordinary

pliers. The force required to break the tablet is recorded on a dial and may be expressed in kilograms or pounds.



#### II. Electrically-operated:

These are digital instruments in which the force is applied electrically. They give more reproducible results e.g. Erweka and Vankel hardness testers.

Using forceps, 10 tablets are individually placed between the plates of the hardness tester. The test button was pushed, and the instrument gave a visual reading of tablet hardness.



Vankel hardness tester

#### 7- Tablet friability

Tablet hardness is not an absolute indicator of strength since some formulations, when compressed into very hard tablets, tend to "cap" on attrition. Therefore, another measure of a tablet's strength is its friability. Friability test determines the ability of the tablets to withstand abrasion during packaging, handling and shipping. Tablets that tend to powder, chip and fragment when handled lack elegance and consumer acceptance, and can create excessively dirty processes in such areas of manufacturing as coating and packaging. They can also lead to a tablet's weight variation or content uniformity Problems. The laboratory friability tester is known as the Roche friabilator. It consists of a plastic chamber divided into two parts and revolves at a speed of 25 rpm.

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#### **Roche Friabilator**

Ten tablets are dusted, weighed then placed in the drum of the friabilator which is allowed to rotate for 4 miutes or for 100 revolutions. During each revolution, the tablets fall from a distance of 6 inches to undergo repeated shocks. The tablets are then redusted and re-weighed and the % loss in weight is calculated to indicate the friability. According to USP, the weight loss should not be more than 0.8%.

#### 8- Tablet thickness

The thickness of the tablet from production - run to production - run must be carefully controlled. Control of tablet thickness is important in reproducing tablets identical in

appearance. Moreover, variation in tablet thickness leads to counting and packaging problems. The thickness of a tablet often is directly related to tablet hardness and can, therefore, be used as an initial control of this parameter. Thickness of the tablets depends on the density of the granulation, the pressure applied to the tablets and the speed of tablet compression. Tablet thickness is determined with a micrometer. Ten tablets are dusted then individually placed between the calipers of the micrometer using forceps. The instrument gave a visual reading of tablet thickness. The allowed limit of thickness variation is  $\pm 5\%$  of the size of the tablet.

Micrometer

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8 Population

# **Quality Control Tests of Capsules**

#### Objectives

After reading this chapter, the student will be able to:

- 1. Know different QC tests for capsules.
- 2. Distinguish between different equipment's used in QC tests for capsules

#### III. Capsules

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#### Evaluation of capsules includes:

- 1- Weight variation
- 2- Content uniformity
- 3- Disintegration time
- 4- Dissolution rate

#### 1- Weight variation

Twenty capsules are weighed, and the average weight is determined. Each capsule is then weighed individually, and its weight is compared with the average weight. The requirements are met if each of the individual weights is within 90 - 110 % of the average weight.

#### 2- Content uniformity

This test to ensure that every capsule contains the labeled amount of the drug within the prescribed limits (generally 15%).

In the official test 30 capsules are selected and 10 of these are assayed individually. At least 9 of these fall within 85-115% of specified dose, and none may fall below 75% or above 125% of that dose. If 1 to 3 of them falls outside of the 85 and 115 % limits, the remaining 20 capsules are individually assayed, and the requirements are said to be met

if no few than 27 falls within the 85 % and 115% limits and none fall outside the 75% and 125% limits.

#### 3- Disintegration time

The disintegration test is usually not required for capsules because of the rapidity with which the gelatin shell dissolves in the stomach. However, the test is applied in case of enteric-coated capsules which have been treated to resist gastric fluid. In this case, they must meet the requirements for disintegration of enteric-coated tablets.

#### 4- Dissolution rate

Procedures used in these tests are like those employed in the case of compressedtablets.

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# **Quality Control Tests of Effervescent Granules**

#### Objectives

After reading this chapter, the student will be able to:

- 1. Describe different methods used to evaluate effervescent granules.
- 2. Differentiate between lag time and froth time

#### IV. Effervescent Granules

Granules are solid dosage forms that consist of particles ranging from about 4 to 10 mesh in size (4.76 mm to 2 mm), formed by moistening blended powders and passing through a screen or a special granulator. These moist granules are then either air or oven dried. A special form of granules can be used to provide a pleasant vehicle for drugs with either a bitter or salty taste. This special formulation is the "effervescent granules" which consist of a mixture of citric and tartaric acids combined with sodium bicarbonate. Effervescent granules are prepared by one of two methods: the fusion method and the wet method.

Evaluation of effervescent granules includes:

- 1- Lag time
- 2- Froth time
- 3- Froth height
- 4- Clarity
- 5- Flowability test
- 6- Compressibility test

#### 1- Lag time

Put 15 ml water in 100 ml cylindrical measure, and then add 5 g of the prepared effervescent granules. Record the time till the effervescence starts in second (lag time).

#### 2- Froth time

It is the time required until the effervescence cease. Add 5 g of the granules to 15 ml of distilled water contained in a measuring cylinder of 100 ml capacity. Record the time taken for complete cessation of effervescence.

#### 3- Froth height

The froth height test measures the power of effervescence of the granules as follows: Determine the power of effervescence of sodium citrotartarate effervescent granules by measuring the froth height obtained by adding 5 g of the granules to 15 ml of distilled water contained in a measuring cylinder of 50 ml capacity.

This test is performed on the following batches to study the effect of both the method of preparation and granule size:

- 1. Granules prepared by the fusion method.
- 2. Granules prepared by the wet method.
- 3. Granules of 2000 µm size prepared by passing through sieve No. 10.
- 4. Granules of 840 μm size prepared by passing through sieve No. 20.
- 5. Granules of 420 µm size prepared by passing through sieve No. 40.

#### 4- Clarity

Record the clarity of solution after effervescence completely ceases.

#### 5- Flowability test

Flowability is done using the angle of repose method as previously described using either funnel or open-ended cylinder methods.

#### 6- Compressibility test

Compressibility test is done by determining the bulk density before and after tapping using the method described before.

(33)

# Quality Control Tests of Suppositories

#### **Objectives**

After reading this chapter, the student will be able to:

- 1. Know different quality control tests to evaluate suppositories
- 2. Differentiate between liquefaction time and melting range of suppositories

### V. <u>Suppositories</u>

Suppositories are molded solid dosage forms intended for insertion into the rectum, vagina, or urethra where they melt, dissolve or disperse and exert either a local or systemic effect. Suppositories are suited particularly for administration of drugs to the very young (pediatric) and very old (geriatric) patients.

Population

#### Evaluation of suppositories includes:

- 1- Visual examination
- 2- Weight variation
- 3- Liquefaction (or softening) time test
- 4- Melting Range Test
- 5- Breaking test
- 6- Content uniformity
- 7- In-vitro drug release

#### 1- Visual examination

Finished suppositories are inspected for:

a) Appearance: they should have uniform shape and color and smooth surface devoid of fissures or pores.

b) Uniformity of mix: the suppository is sliced longitudinally to determine uniform distribution of the medicament throughout the suppository.

#### 2- Weight variation

All the suppositories should be uniform in weight. Weight variation may result if some of the mould cavities are underfilled and others are overfilled.

To perform this test, 20 suppositories are weighed, and the average weight is calculated. Then each suppository is weighed individually. No suppository should deviate from the average weight by more than 5% except two that should not deviate by more than 7.5%.

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#### 3- Liquefaction (or softening) time test

This test measures the time required for a suppository to liquefy under conditions that simulate in vivo conditions. Liquefaction time should be no longer than 30 minutes. A dialysis membrane (cellophane tube) is tied to both ends of a condenser with each end of the tube open. Water at 37°C is circulated through the condenser at such a rate that the lower half of the cellophane tube collapses and the upper half gapes (as in the fig.). The hydrostatic pressure of the water in the apparatus is about zero when the tube starts to collapse. When the water temperature is stabilized at 37°C, the suppository is dropped into it so that it sits at a specific level and the time is measured for the suppository to completely melt in the tube. This method is designed upon the combined effects of heat and pressure, so that to imitate the natural conditions as possible.

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Apparatus for measuring the liquefaction time of rectal suppositories. The dimensions are in millimeters.



#### 4- Melting Range Test

Melting range tests are performed to check the physical and absorption characteristics of each batch of the suppositories. The melting range test is performed for suppositories containing fatty bases only. The melting range test has two types:

a) The macro-melting range test which measures the time taken for the entire suppository to melt when immersed in a constant temperature (37°C) water bath. The apparatus used is a U.S.P Tablet disintegration test Apparatus. The suppository is completely immersed in the constant temperature water bath and the time for the entire suppository to melt or disperse in the surrounding water is measured.

b) The micro-melting range test which measures the melting range in capillary tubes.

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#### 5- Breaking Test

The breaking test is designed as a method for measuring the fragility or brittleness of suppositories to ascertain that they can withstand breakage during handling, packaging, storage and transportation.

The apparatus used for this test (Erweka hardness tester) consists of a double wall chamber in which the test suppository is placed. Water at 37°C is pumped through the double walls of the chamber, and the suppository contained in the dry inner chamber, supports by a disc to which a rod is attached. The other end of the rod consists of another disc to which weights are applied. The test is conducted by placing 600 g on the platform. At one-minute intervals, 200 g weights are added, and the weight at which the suppository collapses is the breaking point. Differently shaped suppositories have different breaking points.

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#### Breaking test apparatus

double-wall chamber, (2) test suppository, (3) constant temperature water bath and pump, (4) rod, (5) disc for weights; (6) 200-g weights.



#### 6- Content uniformity

Assays of active ingredients must be carried out to ensure that the suppositories contain the labeled amount of the drug.

#### 7- In-vitro drug release

It is used for in-vitro assessment of product efficacy. The rate of drug release from suppositories can be determined by using the same apparatus used for determination of dissolution rate of compressed tables (Apparatus 1, 2 or 3). The test can also be carried out by simple placement of the suppository in a beaker containing the dissolution medium.

Ministry of

Population

# **Quality Control Tests of Semisolid Dosage Forms**

#### Objectives

After reading this chapter, the student will be able to:

- 1. Identify QC tests of semisolid dosage forms.
- 2. Differentiate between average filling weight and content uniformity of semisolid dosage form.
- 3. Measure the degree of spreading of the semisolid preparation.
- 4. Know special evaluation tests for cream and ophthalmic ointment

### VI. Semisolid Dosage Forms Evaluation

Pharmaceutical semisolid preparations for external application include ointments, pastes, creams and gels. They are retained to the surface of application for a reasonable duration before they are washed. Such products are referred to as topicals or dermatologicals.

A topical can be defined as a formulation that is applied directly to an external body surface including skin, scalp or epithelial membrane as buccal mucosa or nasal mucosa. A dermatological is limited to products that are applied to the skin or scalp only.

#### Evaluation of Semisolid Dosage Forms includes:

- 1- Visual examination (organoleptic properties)
- 2- Average filling weight
- 3- Content uniformity
- 4- Homogeneity
- 5- Rheological studies
- 6- Spreadability
- 7- Determination of pH

- 8- Microbial content
- 9- In-vitro drug release
- 10-Accelerated stability studies

#### 1- Visual examination (Organoleptic properties)

The color, odor and other physical characteristics of the product are noted by visual examination.

#### 2- Average filling weight

In this test, the net weight or volume of the contents of the filled containers is determined. It is carried out to ensure that the product contains the proper content when compared with the labeled amount.

Weigh the intact container at the beginning of the analysis. After the analysis is completed, remove any remaining sample and weigh the empty container. Calculate the weight of the product by difference.

#### 3- Content uniformity

Assay of the active ingredients must be carried out to ensure that the semisolid product contain the labeled amount of the drug.

#### 4- Homogeneity

Test for homogeneity of semisolid preparations is done to assure the absence of gritty particles in the preparation upon its application to the skin.

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#### 5- Rheological studies

The viscosity of the semisolid preparation is measured using a Brookfield viscometer.

#### 6- Spreadability

Spreadability is the degree of spreading of the semisolid preparation upon its application to the skin. A sample of 1 g of semisolid was placed at the center of the glass plate ( $10 \times 10 \text{ cm}$ ) ad another glass plate was placed over it carefully above the glass plates 2 kilogram weight was placed at the center of the plate avoid sliding of the plate. The

diameter of the semisolid in centimeters was measured after 30 minutes. The experiment was repeated three times and the average was calculated.

#### 7- pH determination

pH of the semisolid preparation should be measured to avoid irritation upon its application to the skin. One gm of the preparation is mixed with 9 ml of distilled water and the pH of the resulting mixture is determined using a glass electrode instrument (pH meter).

#### 8- Microbial content

Semisolid preparations containing water tend to support microbial growth to a greater extent than water-free preparations. Therefore, those preparations should be examined for *P. aeruginosa* and *S. aureus*. Preparations intended for rectal, vaginal or urethral use should be tested for yeasts and molds which are common offenders at these sites of application.

#### 8- In-vitro drug release

A dialysis membrane is loaded with 2 g of the medicated semisolid, suspended in a beaker containing 100 ml of dissolution medium of pH 6.8, maintained at a temperature of 32°C and stirred at 100 rpm for one hour. Samples of the dissolution medium are withdrawn at time intervals to determine the amount of the drug in solution. The release results are plotted as concentration versus time.

#### 9- Accelerated stability studies

It is based on stressing the system, either by temperature or centrifugation.

#### a- Effect of centrifugation

Centrifugation can be used to predict long-term behavior of semisolids. Centrifugation at 3750 rpm for 5 hours is equivalent to the effect of gravity for one year.

#### b- Effect of freeze-thaw cycling

Semisolids are stored in an incubator at 50°C for 48 hours and then transferred to a freezer at -5°C for 48 hours.

#### Special evaluation tests

- 1- For ophthalmic ointments: Sterility testing.
- 2- For creams: Determination of the emulsion type.



# **Quality Control Tests of Liquid Dosage Forms**

#### **Objectives**

After reading this chapter, the student will be able to:

- 1. Know the general evaluation tests of liquid dosage form.
- 2. Identify different QC tests for suspension.
- 3. Identify different QC tests for emulsion.

### VII. Liquid Dosage Forms Evaluation

General Evaluation Tests

#### 1. Organoleptic properties

The color, odor, taste, clarity and other physical characters of the product are noted by visual examination.

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#### 2. Specific gravity

It can be determined with a hydrometer.

#### 3. Rheological studies

The viscosity can be determined with a viscometer.

#### 4. pH determination

The pH of the liquid dosage form can be determined with a pH meter.

#### 5. Uniformity of content

Assays of the active ingredients must be carried out to ensure that the dose contains the labeled amount of drug. It is determined by chemical or spectrophotometric analysis.

#### **Special Tests for Suspensions**

#### 1. Sedimentation volume (F)

The sedimentation volume, F, is defined as the ratio of the ultimate volume ( $V_u$ ) of the sediment to the original volume ( $V_0$ ) of the suspension before settling.

 $F = V_u / V_o$ 

The larger this ratio, the better is the redispersibility.

The sedimentation volume, F, of a product may have a value of less than 1, or equal to 1.

When F is less than 1, we have ordinary case in which the sediment settles to some ultimate volume that is less than the original volume of the suspension.

When F= 1, the sediment is equal to the total volume of the suspension. Such a product is quite acceptable from a pharmaceutical standpoint because, on standing, it show no sediment or clear supernatant.

A certain volume of the suspension is poured into a measuring cylinder and its sedimentation volume (F) is measured at different time intervals. The values of F are plotted versus time. The obtained plot will, at zero time, start at 1.0 with the curve then being either horizontal or gradually sloping downward with time. One can compare different formulations and choose the best by observing the lines. The better formulations are those producing more horizontal or less steep lines.

#### 2. Redispersibility

Redispersibility describes the ease of redispersion of the formed sediment by moderate shaking to yield a homogeneous system.

Ease of redispersion of the suspension can be determined either by simple agitation of the suspension in the container or by the use of a mechanical shaking device which simulates human arm motion during the shaking process and can give more reproducible results when used under controlled conditions.

#### 3. Particle size changes

Any change in the particle size of the suspension can give an indication of crystal growth or conversion of the drug from one polymorphic form into another. The freeze-thaw cycling technique is applicable to stress the suspension to promote crystal growth and by using a microscope, Coulter counter device or laser diffraction device, the particle size can be measured. It is noteworthy that the suspension must be first diluted and deflocculated to ensure that each individual particle is measured rather than each floccule.

This method indicates the probable future state of suspensions after long storage at room temperature.

#### Special Tests for Emulsions

#### 1. Dilution test

This test is used to identify the emulsion type.

Take a few drops of the emulsion in a test tube and dilute it with 2 - 3 drops of water. If the water is distributed uniformly in the emulsion, then the emulsion is o/w type, but if the water separates out as a layer, then the emulsion is w/o type.

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#### 2. Creaming, sedimentation and coalescence

In creaming, the dispersed globules move upward and form a thick layer at the surface of the emulsion, whereas in sedimentation, the dispersed globules move downward and form a thick layer over the bottom of the container. Creaming or sedimentation is a temporary phase because it can be re-distributed by mild shaking or stirring to get a homogeneous product.

In coalescence (or cracking), the dispersed globules coalesce together and two separate layers of the dispersed phase and continuous phase are formed which are difficult to redisperse by shaking or stirring to get the original product. Hence, cracking is more serious in comparison to creaming.

#### 3. Stability to freeze-thaw cycling

The emulsion is exposed to freeze-thaw cycling and visually examined for any creaming or coalescence.

In freeze-thaw cycling, the emulsion is stored in an incubator at  $50^{\circ}$ C for 48 hours and then transferred to a freezer at  $-5^{\circ}$ C for 48 hours.

# **Quality Control Tests of Parenteral**

#### Objectives

After reading this chapter, the student will be able to:

- 4. Identify different QC tests for parenteral product.
- 5. Understand the importance of pyrogen test

### VIII. Parenteral Products Evaluation

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#### Evaluation of parenteral products

The tests under the liquid dosage form evaluation are carried out in addition to the following

#### 1. Volume in container

The volume of one container (for > 10 ml injections) or 3 containers (for 3-10 ml injections) or 5 containers (for < 3 ml injections) is carefully transferred to a graduated cylinder to be measured.

For oily injections the containers are warmed to be easily transferred to a graduated cylinder, then cooled before measuring the volume.

The volume should not be less than the labeled volume. A certain volume excess is allowed and it ranges from 2-20% according to the volume of the injection. As volume of the injection increases, volume excess decreases e.g. for 0.5 ml injection, volume excess is 20%, and for 50 ml injection, volume excess is 2%.

#### 2. Sterility testing

All products labeled sterile must pass the sterility test. There are two basic methods for sterility testing. One involves the direct inoculation technique of test samples on culture

media. A specified volume of the tested product is transferred aseptically to culture tubes containing a suitable culture medium. The tubes are plugged with sterilized cotton wool and incubated for 7 days at a temperature of 30 to 35<sup>o</sup>C. The tubes are then examined visually for turbidity which indicates microbial growth. Thus, if the tubes remain clear, this indicates that the product is sterile, but if they become turbid, this indicates that the product is not sterile.

The second method involves filtering the test samples though membrane filters (bacterial filters), washing the filters with fluids to remove inhibitory properties (as preservative) and transferring the membrane aseptically to appropriate culture media.

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#### 3. Pyrogen testing

The injection may cause a rise in body temperature, injection producing this reaction is said to be pyrogenic (meaning produce fever) and injection free from this effect is described as apyrogenic. Pyrogens cause fever may lead to death in large doses. Pyrogens are the metabolic products of microorganisms. They are phospholipids. The most dangerous pyrogens are those produced by Gm - ve bacilli.

#### Pyr<mark>ogens ar</mark>e:

- 1- Thermostable can withstand autoclaving & pass through many filters. They can be destroyed by heating at 175°C for 3 hours, or 200 °C for 1 hours, or 250 °C for half an hour.
- 2- Water soluble, therefore, they are not removed by bacterial filters.
- 3- Unaffected by bactericides.
- 4- Non-volatile, but can be transferred during distillation with the droplets carried by the steam as the pyrogens are soluble in the water droplets. To prevent that the still must be of a design that prevents the carry over of water spray from the boiler.

Pyrogen testing is performed by the rabbit method.

Inject 1 ml of the test solution in the ear vein of the rabbit. The rectal temperature of the rabbit is measured at 1, 2 & 3 hr after injection. If there is any rise in temperature of 0.6°C or more above the normal temperature which has been measured before injection, then the test solution is considered pyrogenic, but if the rabbit does not show

any rise in temperature, this indicates that the solution is apyrogenic. Generally 5 - 8 rabbits are used for this test and the average is calculated.

#### 4. Clarity testing

It is a test for particulate matter. The presence of particulate matter in ophthalmic preparations will be irritant to the eye. On the other hand, the presence of particulate matter in parenteral preparations particularly those which are given intravenously will be dangerous as they may block the blood vessels with serious results. Therefore it is very important to check the final package for clarity.

The solution under test is examined visually in presence of a source of light against black & white backgrounds for the detection of light-coloured and dark-coloured particles respectively. The contents of the container are slowly inverted and rotated and the solution is examined for the presence of turbidity, dust or any other foreign particles. If any particulate matter is visible, the package is rejected.

- \* Particles can be counted using Coulter counter device.
- \* Sources of particulate matter include:

Raw materials, processing equipment, container and environmental contamination.

#### 5. Leakage testing (leaker test)

It is a test for perfect sealing of the ampoules.

The ampoules are immersed in a deeply coloured dye solution containing methylene blue and maintained under negative pressure in a vacuum chamber or under positive pressure in an autoclave. When the pressure is released, the dye solution will enter the ampoules with defective sealing. Thus, the ampoules are washed and examined. Any coloured ampoules indicate imperfect sealing.

Vial and bottles are not subjected to such a leaker test because the rubber closure is not rigid.

# **Quality Control Tests of Aerosols**

#### **Objectives**

After reading this chapter, the student will be able to:

- 1. Identify different QC tests for aerosols, inhalations and spray.
- 2. Evaluate aerosol via physicochemical characteristics.
- 3. Differentiate between physical and chemical evaluation of aerosols.
- 4. Know biological tests for aerosol evaluation.

### IX. Aerosols, Inhalations, and Sprays Evaluation

Pharmaceutical aerosols are pressurized dosage forms containing one or more active ingredients which upon actuation emit a fine dispersion of liquid or solid materials in a gaseous medium. Aerosols are of two types:

a) Inhalations are drugs or solutions of drugs administered by nasal or oral respiratory route for local action on the bronchi or for systemic effects through absorption from the lung.

b) Sprays may be defined as aqueous or oleaginous solutions in the form of coarse droplets or as finely divided solids to be applied topically to the nasal or pharyngeal tract or to the skin.

Pharmaceutical aerosols can be evaluated by a series of physical, chemical, and biological tests including:

#### A- Flammability and combustibility:

- 1. Flame extension (flame projection)
- 2. Flash point
- 3. Closed drum test
- B- Physicochemical characteristics:

#### 1. Vapor pressure

- 2. Density
- 3. Moisture content
- 4. Identification of the propellant
- **C- Performance:**
- 1. Aerosol valve discharge rate
- 2. Spray pattern
- 3. Dosage with metered valves
- 4. Net contents
- 5. Foam stability
- 6. particle size determination

#### **D- Biological:**

- 1. Therapeutic activity
- 2. Toxicity

#### A- Flammability and combustibility

#### 1- Flame extension

This test indicates the effect of an aerosol formulation on the extension of an open flame. The product is sprayed for about 4 seconds into a flame. Depending on the nature of the formulation, the flame will be extended. The exact length of the extended flame is measured by a ruler. & Populati

#### 2- Flash point

is determined by chilling the product to a temp. of -25°F and transfer the product to the test apparatus, then increase the temperature slowly. The temperature at which the vapor ignites is taken as the flash point.

#### 3- Closed drum test

This test is used to indicate the hazard of spraying aerosol in an enclosed space in presence of a flame.



A 55 gallon drum with a hinged lid is used for this test. A paraffin candle is placed into the drum and ignited. The test aerosol is sprayed into the drum through an opening until an explosion takes place or for a period of 60 seconds, whichever occurs first. The results of this test are used to classify the aerosol product and, according to such classification, certain precautions are written on the label.

#### B- Physicochemical characteristics:

#### 1- Vapour pressure

The pressure can be measured simply with a pressure gauge. Excessive variation in pressure indicates the presence of air in the head space.

#### 2- Density

The density of an aerosol system may be accurately determined by the use of a hydrometer or a pycnometer.

#### 3- Moisture content

Many methods have been found useful for this purpose. The Karl Fishcer method or gas chromatography can be used for this purpose.

#### 4- Identification of the propellant

Gas chromatography or infrared spectroscopy have been used to identify the propellants and also to indicate the propotion of each component in a blend.

#### **C- Performance:**

#### 1- Aerosol valve discharge rate

& Populat This is determined by taking an aerosol product of known weight and discharging the contents for a given period of time using a standard apparatus. By reweighing the container after the time limit has expired, the change in weight per time is the discharge rate, which can then be expressed as (gram/second or gram/minute).

#### 2- Spray pattern

The method is based on spraying the content of the aerosol on a piece of paper that has been treated with a dye-talc mixture. Depending on the nature of the aerosol, an oil soluble dye or water soluble dye is used. The dye goes into solution and is absorbed onto the paper. This will give a record of the spray (finger print) which can be used for comparison purposes.

#### 3- Dosage with metered valve:

This test is used to determine reproducibility of dosage each time and the amount of medication actually received by patient. Reproducibility of dosage can be determined by assay technique where one or two doses are dispensed into a solvent and the solution is assayed to determine the drug content. Another method that can be used involves accurate weighing of filled container followed by dispensing several doses. The container is then reweighed, and the difference in weight is divided by the number of doses dispensed to give the average dose.

#### 4- Net content test

Several methods can be used to determine whether sufficient product has been placed into each container. The tared cans that have been placed onto the filling line are reweighed and the difference in weight is the net content. The other method is a destructive one in which a full container is weighed and then all its contents are dispensed. Reweighing will give the net content.

#### 5- Foam stability testing

Various methods have been suggested for the determination of foam stability. The life of a foam can range from few seconds (for some quick breaking foams0 to one hours or more depending on the formulation. Several methods have been used which include a visual evaluation, measuring the time for a given mass to penetrate the foam, measuring the time for a given rod that is inserted into the foam to fall, and by the use of a rotational viscometer.

#### 6- Particle size determination: can be determined by:

1- Cascade impactor method in which a stream of particles is projected through a series of nozzles onto glass slides at high velocity. The larger particles will become impacted first on the lower velocity stages and the smaller particles pass on and are collected at later stages.

2- Light scattering method in which the aerosol settles under a turbulent condition and the change in light intensity of a Tyndall beam is measured.

#### **D- Biological testing:**

#### 1- Therapeutic activity:

The aerosol is administered whether by inhalation or by topical application to the test area in the usual manner, and the amount of drug absorbed can be determined to indicate the therapeutic activity.

2- Toxicity:

Toxicity testing should include both inhalation and topical effects. Inhalation toxicity can be determined by exposing test animals to the vapour sprayed from an aerosol container. Aerosols applied topically may be irritating to the effected area and/or may cause a chilling effect. The degree of chilling is dependent on the type and amount of the propellant present.

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### **References and Recommended books**

- 1. Ansel, H.C., Popovich, N.G. and Allen, L.V., editors.Pharmaceutical Dosage Forms and Drug Delivery Systems, 10th edition. Philadelphia: Williams & Wilkins. (2014).
- 2. Aulton's Pharmaceutics: The design and manufacture of medicine, Micheal Aulton, 4th Edition, 2013.
- 3. Modern Pharmaceutics, Editors: G. S. Banker and C. T. Rhodes, Marcel Dekker Inc., New York, 1990.
- 4. Clark's Analysis of Drugs and Poisons, 3rd edition. London: The Pharmaceutical Press. (2004).
- 5. PHARMACEUTICAL MANUFACTURING HANDBOOK, Regulations and Quality, SHAYNE COX GAD, PH.D., D.A.B.T. Copyright © 2008 by John Wiley & Sons, Inc. All rights reserved
- 6. Book Coordinator ; Mostafa Fathallah

nistry of t

7. General Directorate of Technical Education for Health