The Hashemite University

The Faculty of Pharmaceutical Science

Jordan - Zarqa

Laboratory Manual

Course code: 131701437

Course Name: Industrial Pharmacy (1) practical

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Preface

There are a lot of rules and guidelines that accompany working in a laboratory, since there are chemicals and equipment that can be dangerous if handled improperly. Rising above the details, there are three basic tenets that will permeate through each laboratory:

1) Be aware of the specific hazards and protect yourself accordingly

2) Think about the exercises as you are doing them, and learn the techniques and principles behind them

3) ***Have fun!*** Lab is a refreshing change from the classroom, where you have an opportunity to observe concepts in action, rather than just being told how they work.

This laboratory has been designed to allow you to examine the basics of the formulation, manufacturing, characterization and evaluation of solid dosage forms

This manual will guide you to learn the fundamental principles of industrial pharmacy. Although a brief introduction is provided for each lab exercise, this manual does not contain all the necessary information for you to completely understand the theory behind each lab.

To make learning easier you should do the following prior to attending the lab:

1) Read the experiment form the manual
2) Watch the recorded Experiment summary on *Moodle*
3) Learn how to perform the necessary calculations.

If you find a specific section, step, or explanation in this manual vague or difficult to follow, ask the instructor for help. ***Please let us know, so we can improve the manual for future editions.***

Introduction

Course Description:

The series of practical classes provides advanced skills in the area of pharmaceutical industry and has particular emphasis on the methods , materials and testing procedures associated with the manufacture of solid dosage forms particularly tablets.

Experiments illustrate the flow properties of powders, mixing and milling of powders, wet and dry granulation methods, powder particle size analysis, tableting technology, Tablets testing and tablets dissolution

Course Objectives

At the end of this course students are expected:

1. To recognize various processes and equipment used to manufacture solid dosage forms: particle size analysis, size reduction, mixing and drying.
2. To understand the manufacturing process of solid dosage forms and the operation of tablet presses.
3. To recognize various manufacturing methods for solid dosage forms
4. To recognize the ingredients used in the formulation of solid dosage forms
5. To recognize and understand the problems encountered during the manufacturing of solid dosage forms.
6. To solve any problem encountered during the manufacturing of solid dosage forms.

To prepare for a lab: read the part of the lab manual pertaining to that lab exercise, understand the rationale of the exercise, watch any associated videos on the laboratory website (Moodle) , perform any calculations that are needed, be aware of any potential hazards. **The laboratories start on time**.

Attendance

Attendance at each lab is mandatory; Attendance will be recorded as you enter the lab. You are expected to be available, and attend your entire lab period on your scheduled dates. In some instances, you will be permitted to leave early provided your work is submitted, your lab area is properly cleaned, and the post-lab talk is finished.

You are required to present your Tag name, be properly dressed (lab coat, safety glasses, face mask and gloves).

Outer coats, laptops and backpacks are not permitted in the laboratory. These should be kept in your locker.

You will not be allowed to enter the lab if you wear: Shorts, short skirts or very long dresses

Assessment:

The module will be assessed by written reports. the practical report will include full details of the experimental procedure and results.

An assessment of individual student's practical skills will be made on each practical day. At the end of each group report, you will be asked as a group to indicate the relative contribution to the practical work. Individual student marks for group work, will reflect the group assessment of individuals contributions. If you do not provide this assessment, then all members of the group will be given the same mark, which will then be moderated according to the results of the assessment of individual student's practical skills.

Learning Outcomes/Skills:

Deductive reasoning

Numerical Analysis

Written/oral communication

Information retrieval and analysis

Practical application of theory

Report writing

Reading list / references:

Reading List	
1	Aulton M., Taylor Kevin (ed.), Aulton's Pharmaceutics The design and Manufacture of Medicine, Elsevier, 4th edition, 2013.
2	Khar RK, Vyas SP, Ahmad FJ, Jain GK (2013). Lachman/liebermans: The Theory and Practice of Industrial Pharmacy. 4th editionCbs Publishers & Distributors.
3	***Remington: The Science and Practice of Pharmacy, LIPPINCOTT WILLIAMS & WILKINS, 21th ed, 2006.***

Course Outline:

Topic	Topic Details	Estimated no. of hours
1	**Introduction, General Instructions and Laboratory Safety Rules**	1
2	**Powder Mixing**	2
3	**Particle size reduction& Particle Size Analysis By Sieving**	2
4	**Granulation Of Powders**	2
5	**Characterization Of Granules and Powder**	2
6	**Effect Of Additives On The Physical Properties Of Granules and powder**	2
7	**Formulation and Characterization of an Effervescent Granules**	2
8	**Tablets**	2
9	**Quality Control Of Tablets / part 1**	2
10	**Quality Control Of Tablets / part 2**	2

Marks:

Assessment Method
Laboratory Quizzes
Laboratory Reports
In lab performance
Theortical Midterm Exam
Theoretical Final exam

EXPERIMENT 1

SIZE REDUCTION OF POWDERS:

INTREODUCTION:

The **Size Reduction** of powders is performed in many different industries, and is often an essential step in the production of pharmaceutical dosage forms, particulate raw materials, including drugs and formulation additives, may be milled to yield a powder with particle size distribution necessary for both satisfactory manufacturing processes and dosage forms with the desired properties.

Why do we perform size reduction?

It is established, for certain drugs, that changes in particle size distribution of specific surface area may affect drug release characteristics and also influence drug absorption. In other cases, changes in the specific surface area of powders, e.g. Kaolin and Magnesium Trisilicate, may influence their adsorptive capacities. The particle size of commonly used formulation additives may influence processes; such as mixing, granulation, compaction, the suspension of particles in liquids and the dispersion of particles in liquids, ointments, pasts, and suppository bases.

Mechanisms of Size Reduction:

1. Attrition
2. Impaction
3. Shearing
4. Compression

The choice of milling equipment will be dependent upon the powder properties, the size distribution of the raw material and the size expected for the product, after milling.

Rotary Ball Mill

- **Milling Chamber** is a cylinder-like housing move in a horizontal rotater.
- The **grinding medium** (large and small spherical charges) causes size reduction by **two mechanisms**:
  1. Attrition: during the balls hitting with each other and balls hitting against the wall of ball mill (mainly due to small spheres).
  2. Impact: upon balls falling especially the large ones they grind the wall.

• **The factors which affect the milling are:**

1. Speed of rotation: should have an optimum speed, why?

   Rate of milling is very important because each ball is exposed to two forces:

   a. Gravitational Force b. Centrifugation Force

   Depending on the rate of milling (velocity), one of the two forces is the predominant, **explain.**

   At **Critical Speed** → Gravitational force <<< Centrifugation force

   Critical Speed = 76.6 / $\sqrt{(\mathrm{d})\ (\mathrm{feet})}$

   (***d***) is the diameter of ball mill milling chamber (feet) = 30 cm

   Optimum Speed = 60 - 85% of Critical Speed (to achieve efficient milling)
2. Filling volume of mill: the balls should only occupy two thirds (2/3) of the chamber.
3. Milling time.

PARTICLE SIZE ANALYSIS BY SIEVING

There are different methods used for particle size analysis such as:

1- Optical microscopy
2- Electron microscopy
3- Sedimentation
4- Electrical stream sensing zone method
5- Laser light diffraction
6- Sieving

Sieving method

Sieving method is a simple and cost-effective method for particle size analysis. It consists of a sieve set "6-8 sieves" arranged in a way that coarser sieve will be on the top of the finer. The sample will be placed on the top of the coarsest sieve, then the set will be shaken so as the particles will be distributed on the sieves according to their sizes.Therefore, this method classifies the particles in the sample into size ranges which can be presented as size distribution histograms from which average size can be determined.

Two terms to express the sieve size are used:

1. ***Based on particle diameter***
   assuming particles are spherical, the sieve pores will be made in a width representing certain diameter "unit mm or µm". For example, sieve of 2mm means particles of diameter less than 2mm will pass through where as those of greater than 2 mm or equal will be retained on the sieve.

2. ***Mesh no. = no of openings / linear inch.***
   as mesh no. increase particles that can pass through will have smaller size.

Mean particle size and particle size distribution

The mean particle size of an analyzed sample can be considered as a rough description for the size of sample. However, it is unusual for particles to be completely monosized. Most powders contain particles with a large number of different equivalent diameters.

The distribution of particles into different size ranges can be plotted in the form of histogram. A histogram presentation allows different particle size distributions to be compared. The value of the peak is the ***mode*** (highest frequency).

Presentation of size distribution

1) Frequency distribution curves

In these curves the number or weight of particles lying within a certain range of mean particle size is plotted against the size range or mean particle size.

2) Cumulative frequency distribution

In these curves, either the cumulative percent over or under a particular size is plotted versus particle size.

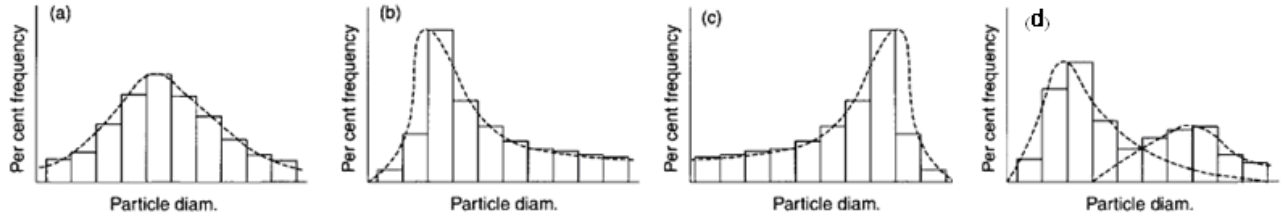
Shapes of size distributions

a) Normal distribution: The mode separates the frequency curve into two symmetrical halves.

b) Positively skewed: A frequency curve with an elongated tail towards the higher size range.

c) Negatively skewed: A frequency curve with an elongated tail towards the lower size range.

d) Bimodal: The frequency curve containing two peaks (two modes)



OBJECTIVES:

1. To study the Efficiency of "Ball Mill" in reducing particle size of Sucrose when operated at 30 rpm.
2. To study the effect of time on Particle Size and PSD of Sucrose while using " Ball Mill" operated at 30 rpm.
3. To estimate the "Optimal Milling Time" for Sucrose size reduction using "Ball Mill" operated at 30 rpm.

EXPERIMENTAL:

a. Materials:

Coarse Sucrose

b. Apparatus:

- Rotary Ball Mills with ceramic spherical charges
- Sieves and Shaker (Jolting Sieving Apparatus)
- Stop Clock

c. Method:

NB: all equipment and tools should be cleaned prior to use.

1. Prepare of the Rotary Ball Mill:
    a. Clean the housing of the mill and the grinding medium (the small and large spherical charges).
    b. Fill the housing with the grinding medium to its half (maximum two thirds of it)

** **The ratio of small spheres to large ones should be 3:1**

2. Weigh 500 gm coarse sucrose and place it in the milling chamber of the Rotary Ball Mill.
3. Secure the gasket and lid of the milling chamber and place on the rollers.
4. Start the milling process (turn the miller on 30 rpm), commence milling and timing simultaneously.
5. 20 gm samples should be taken after predetermined time intervals which are 10, 20, 30 and 40 minutes. When sampling, remove the appropriate mill sample, weighing 20 gm, and continue milling for the other mill for the scheduled time.
6. Analyze the particle size of each sample by Sieve analysis method.
7. Discard the remaining powder and clean the milling chamber and balls.

Particle Size Analysis:

1. Prepare the sieving apparatus by cleaning sieves
2. Weigh the collecting pan and each sieve alone and record the weights as tare weight.
    ➔ Tare weight represents the weight of empty cleaned sieve (or collecting pan)
3. Assemble the sieves provided to you with the coarsest one the top and collecting pan at the base

4. Weigh 20 gm of coarse sucrose (zero-time sample = un-milled sucrose) from the main container.
5. Place the sample on the coarsest sieve, fit the lid and put the receiver at the bottom and clamp the whole set securely in the sieve shaking apparatus.
6. Switch on the shaker and run for 5 min.
7. After the time elapsed, stop the shaker, loose each sieve in turn starting with the coarsest one and record the weight of the sieves and collecting pan with the powder retained on each as gross weight.
   ➔ Gross weight represents the weight of each sieve (or collecting pan) with the powder retained.
8. Repeat the above steps (after cleaning the sieves and collecting pan) for samples taken at 10, 20, 30 & 40 minutes.
9. Tabulate your results according to the following example:

NB:

- The cascading speed of 30 rpm measured by tachometer should be used.
- The sieves used are analytical tools, in order to maintain sieves of good quality, they should be handled with care, and removal of powder from the mesh should be done only by gentle brushing.

Results and Data Analysis

Results

Pore Size mm	***Tare Weight gm***	***Gross Weights, gm***				
		Un-milled Sucrose	***10-minute Sample***	***20-minute Sample***	***30-minute Sample***	***40-minute Sample***
0						

Data Analysis

- ✓ For each samples of the five (un-milled sucrose, 10, 20, 30 & 40 minutes) do thefollowing analysis:

Un-milled Sucrose (Zero-time Sample)

Collecting pan

Pore Size, mm	Tare weight, gm	Gross weight, gm	Net weight, gm
0	T_1	G_1	$N_1 = G_1 - T_1$
0.038	T_2	G_2	$N_2 = G_2 - T_2$
0.125	T_3	G_3	$N_3 = G_3 - T_3$
0.250	T_4	G_4	$N_4 = G_4 - T_4$
0.500	T_5	G_5	$N_5 = G_5 - T_5$
0.710	T_6	G_6	$N_6 = G_6 - T_6$
1.000	T_7	G_7	$N_7 = G_7 - T_7$
1.400	T_8	G_8	$N_8 = G_8 - T_8$
1.700	T_9	G_9	$N_9 = G_9 - T_9$

Pore Size Interval mm	Interval Mid-Point mm	Upper Interval Limits mm	Lower Interval Limits mm	Net Weight grams	% Retained	Cumulative % Over Size	Cumulative % Under Size
0.000 - 0.038	0.019	0.038	0.000	N_1	$=(N_1/50)*100$		
0.038 - 0.125	0.0815	0.125	0.038	N_2	$=(N_2/50)*100$		
0.125 - 0.250		0.250	0.125	N_3	$=(N_3/50)*100$		
0.250 - 0.500		0.500	0.250	N_4	$=(N_4/50)*100$		
0.500 - 0.710		0.710	0.500	N_5	$=(N_5/50)*100$		
0.710 - 1.000		1.000	0.710	N_6	$=(N_6/50)*100$		
1.000 - 1.400		1.400	1.000	N_7	$=(N_7/50)*100$		
1.400 - 1.700		1.700	1.400	N_8	$=(N_8/50)*100$		
1.700 --			1.700	N_9	$=(N_9/50)*100$		
				$= \sum$ Net Weights			

Assume this to be a large pore size e.g. 2 mm, such that all un-milled particles will pass through.

$$\text{Interval Mid-Point} = \frac{\text{Upper Interval Limit} + \text{Lower Interval Limit}}{2}$$

$$\%\ \text{Retained} = \frac{\text{Amount Retained}}{\text{Sample Weight}} * 100\%$$

Cumulative % Over Size is defined as the percentage of particles that have particlesizes lager than the interval lower limit.

Ex.1: Cumulative % Over Size for 1st interval = $\frac{N1+ N2+\cdots + N9}{\sum NetWeights} * 100\% = 100\%$

Ex.2: Cumulative % Over Size for 2nd interval = $\frac{N2+ N3+\cdots + N9}{\sum NetWeights} * 100\%$

Ex.3: Cumulative % Over Size for 3rd interval = $\frac{N3+ N4+\cdots + N9}{\sum NetWeights} * 100\%$

Cumulative % Under Size is defined as the percentage of particles that have particlesize smaller than the interval upper limit.

Ex.1: Cumulative % Under Size for 1st interval = $\frac{N1}{\sum NetWeights} * 100\%$

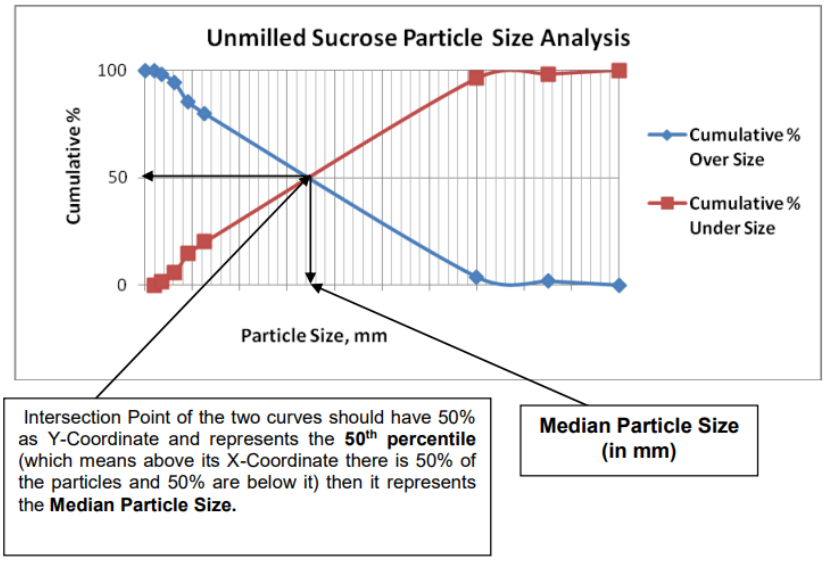
Ex.2: Cumulative % Under Size for 2nd interval = $\frac{N1+ N2}{\sum NetWeights} * 100\%$

Ex.3: Cumulative % Under Size for last interval = $\frac{N1+\cdots + N9}{\sum NetWeights} * 100\% = 100\%$

➔ Plot on the sample sheet:

Cumulative % Over Size vs. Intervals Lower Limits, and

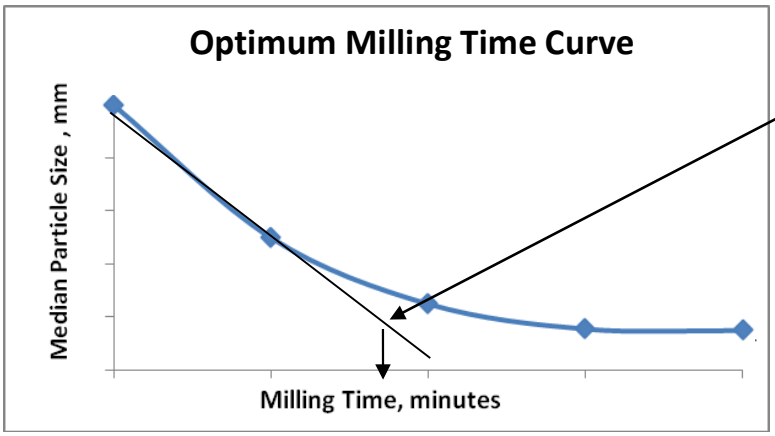
Cumulative % Under Size vs. Intervals Upper Limits



✓ Now repeat the above analysis done for the un-milled sample for all other 4 samples (at 10, 20, 30 & 40 minutes) and find the Median Particle Size at each time

Milling Time minutes	Median Particle Size mm
0	M_1
10	M_2
20	M_3
30	M_4
40	M_5

- Then plot the Optimum Milling Time Curve

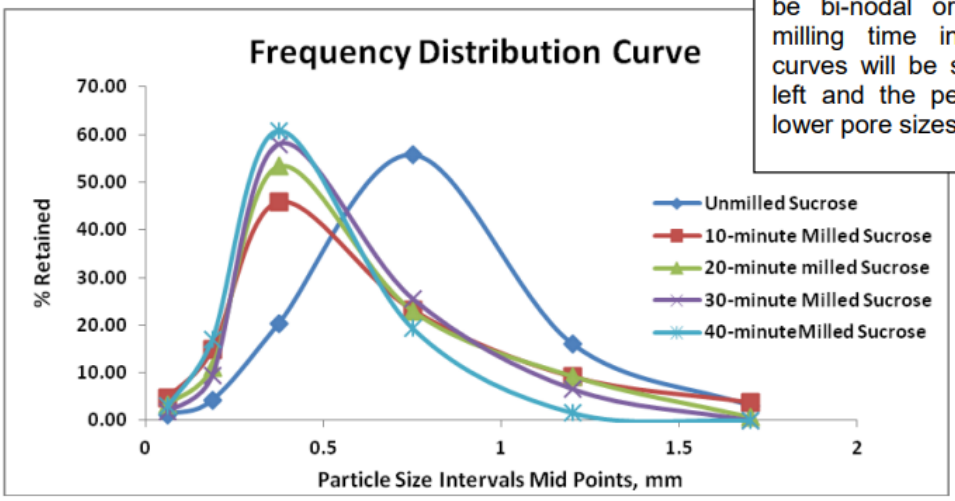


The X-Coordinate of the plateau phase beginning represents the **Optimum Milling Time** sinceany further milling will cause minimal changes in the medianparticle size and will be time consuming.

- ✓ Now plot the Frequency Distribution Curve

On the same chart, plot % Retained vs. Particle size intervals mid-points for all sample

The resultant curves could be bi-nodal or normal, as milling time increases the curves will be shifted to the left and the peak will have lower pore sizes.



EXPERIMENT (2)

MIXING OF POWDERS

INTRODUCTION:

Aim of Mixing:

The main aim of powder mixing in pharmaceutical practice is to achieve dose uniformity within the solid dosage form (tablets, capsules & powders), particularly so important in case of very potent drugs like Digoxin.

Factors affecting mixing of solids:

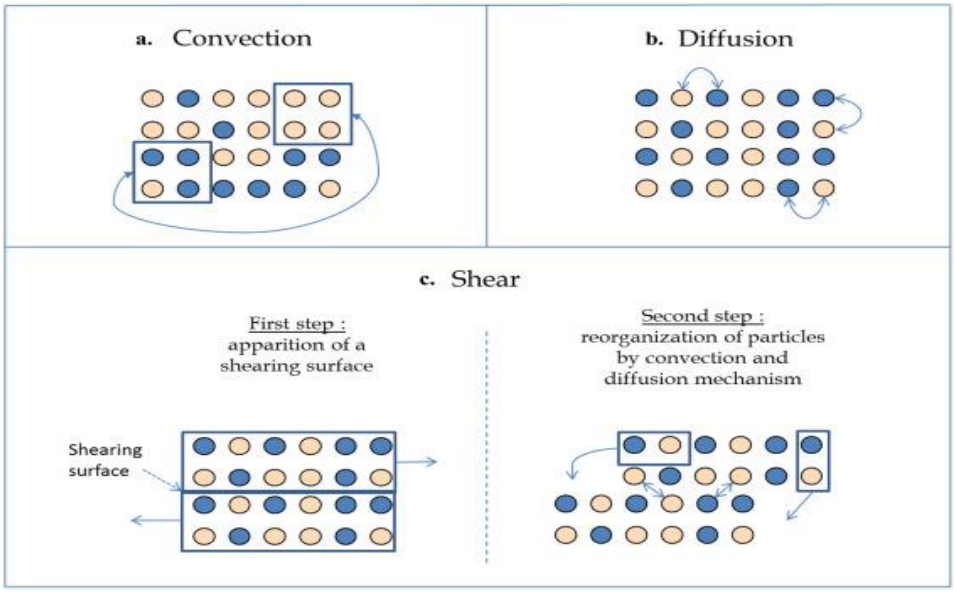
- Parameter related to the particles : like particle size, particle shape, size distribution, particle density, Cohesive forces and Hygroscopic properties
- Mixer type and properties: Movement type of mixer, Presence of Blades The addition of baffles or rotating bars will also cause convective mixing, for example the V-mixer with agitator bar.
- Speed of mixing (Agitation Speed): Too high a rotation speed will cause the material to be held on the mixer walls by centrifugal force, and too low a speed will generate insufficient bed expansion and little shear mixing.
- Filling Volume
- Segregation tendency of individual components (based on density difference).

Mechanisms of Mixing:

1. Diffusion: It is redistribution of particles by random movement of particles relative to each other.

2. Convection: Movement of a group of adjacent particles from one place to another within the mixture.

3. Shear: It is the change in configuration of ingredients through the formation of slip planes in the mixture (Layer of powder flows over another layer) or (Sliding of particles in planes over each other).



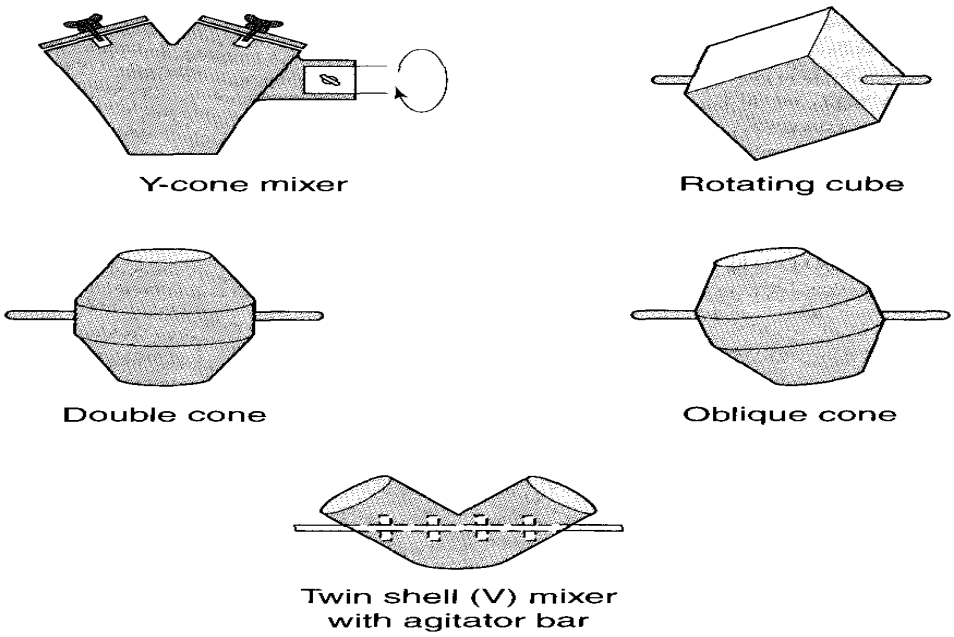


Fig. 13.6 Different designs of tumbling mixers.

Tumbling mixers are rotating vessels of variable shapes. The container is designed in a way to avoid symmetry (symmetry gives poor mixing) ?!

In this Experiment Cube mixer or V-mixer will be used:-

- **Cube mixer**:
  - motor drive mixer
  - The housing in the Cube Mixer is manufactured from glass.
  - Equipped with Baffles but not Blades
  - Tumbling movement, in which ingredients are tilted by the rising side of the drum until they exceed their normal angle of repose, hence they will fall over their selves.
  - Cube mixer provides the three mechanisms of mixing, but in different ratios … shear is the predominant.
  - Cube mixer is problematic due to the presence of corners, why?

- **V- mixer:**
  - motor drive mixer
  - The housing in the V- Mixer is manufactured from stainless steal
  - The function is based on a special 3D blending effect in the pant-leg region, which is generated through a combination of: dividing, cascading and an intermeshing mixing mechanism.
  - During blending, materials tumble periodically towards the apex and the legs, while they move along the horizontal rotation at the same time.

OBJECTIVE:

1. To study the efficiency of "Revolvo-Cube Mixer or V- Mixer" in preparation of 5% wlw mixture of Sodium Salicylate in Lactose (Particle Size < 1mm), when operated at 25 rpm.
2. To study the Effect of time on the homogeneity of 5% wlw mixture of Sodium Salicylate in Lactose (Particle Size < 1mm) prepared using Revolvo-Cube Mixer V- Mixer operated at 25 rpm.
3. To estimate the "Optimal Mixing Time" for 5% wlw mixture of Sodium Salicylate inLactose (Particle Size < 1mm) prepared using Revolvo-Cube Mixer or V- Mixer operated at25 rpm.

EXPERIMENTAL PART :

a. Materials:

Lactose, Sodium Salicylate,

b. Apparatus:

Cube Mixer or V- mixer, UV/VIS Spectrophotometer.

c. Method:

NB: all equipment and tools should be cleaned prior to use.

1. Prepare 500gm of 5% w/w Na-Salicylate in Lactose (25 gm Na-Salicylate(500gm*5 % w/w) with 475 gm Lactose (500gm -25gm)).

N.B.: Pass all powders before weighing using 1mm pore size sieve, why?

2. Place the powders in the mixing chamber of the Revolvo-Cube Mixer (placepowder of the largest quantity (lactose) first then Na-Salicylate)

3. Start mixing (operating speed = 25 rpm), commence mixing and timing simultaneously.
4. Take 5 samples (200 mg = 0.200 gm each) at 5, 10, 20 & 30 minutes, (such that 5 samples at each time).
    a. Samples should be taken randomly from 5 different places of the powdermixture → Random Spot Samples.
    b. The weights of samples should be close to each others (±10% → 0.200±0.02gm) otherwise results will be affected, why? Explain.

5. Determine the content of Na-Salicylate in each sample at each time (all samples will be analyzed at each time interval. Follow the analytical technique described below:
    a. Put each sample in 100 mL Volumetric Flask.
    b. Add 10 - 15 mL of distilled water and mix until all powders are completelydissolved.
    c. Complete the volume by D.Water up to the 100 mL mark then mix well.
    d. Measure the samples absorbance using UV/VIS spectrophotometer:

- Blank should be 0.20% w/v Lactose in D.Water (200 mg Lactose in 100 mL V.Flask, dissolve lactose in 10 - 20 mL of D.Water, then complete up to the100 mL mark using D.Water.

λmax for absorbance measurement is 254 nm

NOTE: ***Absorbance linear range is (0.200 - 1.200), solutions of absorbance out of this range should be diluted.***

NOTE: Sampling is an integral part of mixing because at anytime, spot samples generate the data necessary to evaluate the quality of the mixture. The data for statistics are generated by assaying the active ingredient(s) in a number of random samples taken from the blend at a specified time.

The mean assay value of a group of random samples taken from the mixture is a measure of the central tendency of the batch population (active ingredient content).

In addition of the mean, the spread or dispersion of individual samples about the mean can be calculated by using the Standard Deviation or the Variance.

Standard Deviation can be calculated by using the following equation:

$$S = \sqrt{\sum_1^n \frac{(Y_i - \hat{Y})^2}{n-1}}$$

Variance:

$$V = \sum_1^n \frac{(Y_i - \hat{Y})^2}{n-1} = S^2$$

Coefficient of Variation (C.V.) (Relative Standard Deviation, RSD):

$$C.V. = \frac{Standard\ Deviation}{mean} * 100\%$$

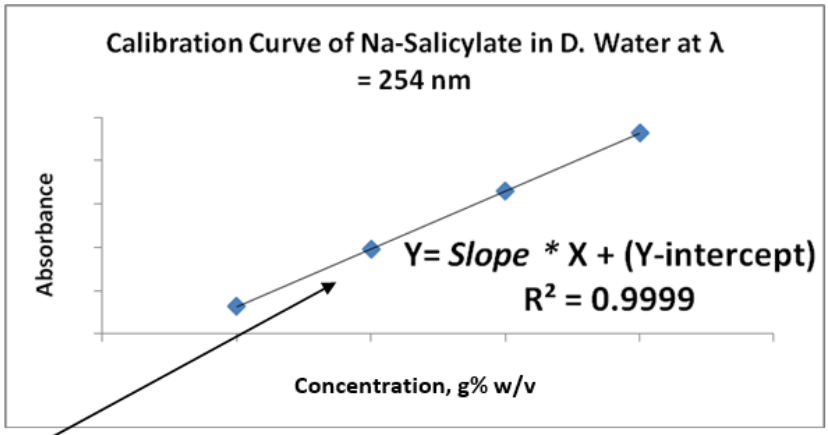
Results and Data Analysis

Results - Mixing Sample

Mixing Time minutes	*Sample Absorbance*				
	1	*2*	*3*	*4*	*5*
5					
10					
20					
30					

Data Analysis

A) Calibration Curve Equation:



Example:

Absorbance read of the first sample at 5 minutes is equal to **0.200**, calculate this solution concentration.

- Using the calibration curve equation:
  $Y = Slope * X + (Y - intercept)$
  Which means:
  $Absorbance = Slope * Concentration\ (gm\%\ w/v) + (Y - intercept)$
- Substitute:
  $0.200 = Slope * Concentration\ (gm\%\ w/v) + (Y - intercept)$
- Now:

$$Concentration\ (gm\%\ w/v) = \frac{0.200 - (Y - intercept)}{Slope}$$

2) Mixing Samples Analysis

1. Use calibration curve equation to calculate the concentration of each sample in mg% w/v
2. Calculate the concentration of each sample in mg% w/w.

   e.g. Sample no. 1 concentration mg% w/w = $\frac{mg\%\ w/v}{200\ mg} * 100\%$

   200 mg is the sample weight
3. Calculate: mean, Standard Deviation (S), Variance (V) (V= S^2), and Coefficient of Variation (C.V.) (Relative Standard Deviation, RSD) of the samples concentrations in mg% w/w at each sampling time.

$$C.V. = \frac{Standard\ Deviation}{mean} * 100\%$$

Always use Excel tables and equations

Mixing Time minutes	Sample Number	Absorbance	Concentration		Mean	Standard Deviation	Variance	Coefficient of Variation, %
			mg% w/v	mg% w/w				
5	1	A_1						
	2	A_2						
	3	A_3						
	4	A_4						
	5	A_5						

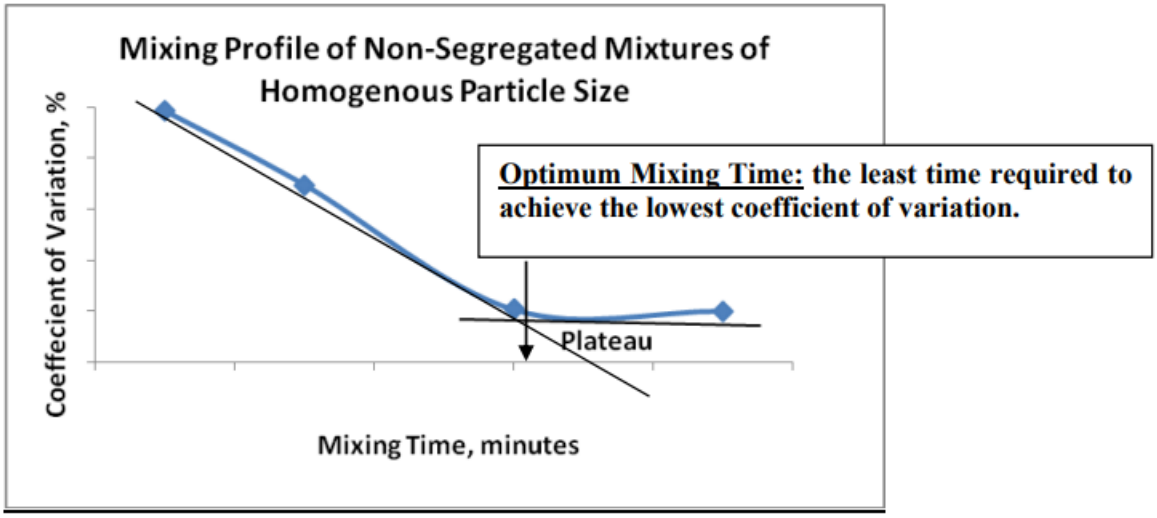
4. Construct the Mixing Profile by plotting Coefficient of Variation vs Mixing Time in minutes.

Mixing Time minutes	Coefficient of Variation CV
5	CV_5
10	CV_{15}
20	CV_{30}
30	CV_{45}

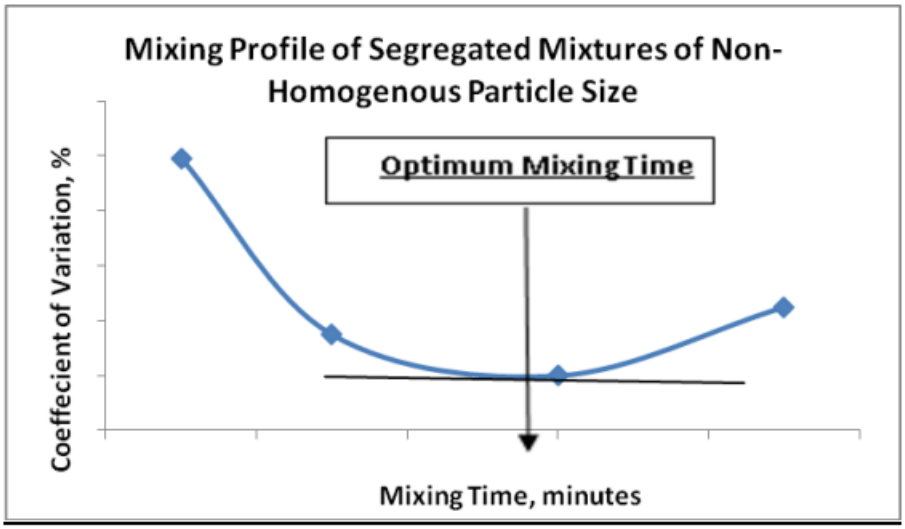
<u>Use Excel sheets, tables, and equations to perform all required data analysis</u>

Examples on Mixing Profiles:

Case 1:



Case 2:



EXPEREMENT 3

GRANULATION OF POWDERS

INTRODUCTION

Granulation, the process for producing large aggregates from smaller particles, is widely used in the pharmaceutical industry, especially in the manufacture of compressed tablets. Granular materials have several advantages when compared with fine powders:

1. Controlled size and shape

2. Improved flow properties

   The flow properties of powders are of critical importance in the production of pharmaceutical dosage forms. Pharmaceutical powders should be of good, rapid and regular flowability, i.e. free flowing, for the following reasons:

   a. Uniform feed from storage containers or machine hoppers into the tablet dies and capsule dosators, allowing uniform particle filling which maintains weight uniformity.
   b. Uneven Powder flow can result in excess entrapped air within powders, which may cause capping or lamination of tablets.
   c. Uneven powder flow can result from excess fines which increase increase dust contamination risks during powder transfer and processing.

3. Overcome the following Limitation of Direct Compression process:

   a. Poor content uniformity due to the differences in particle sizes and bulk densities between tablet ingredients especially in low dose formulations.
   b. Low compressibility
   c. Large proportions of diluents may be needed to improve the compressibility and this resulted in large tablets.
   d. Interactions between tablet components may be high.
   e. Static charge build up may prevent uniform distribution of the drug

- **Granules are prepared by two methods:**

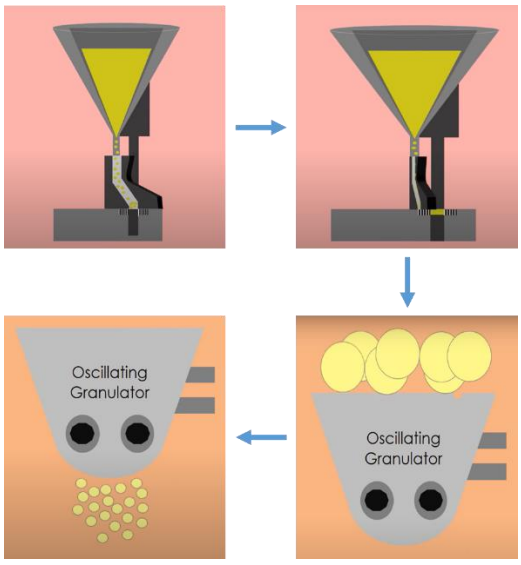
  1) Dry granulation (Compression granulation)

  2) Wet granulation (massing and screening).

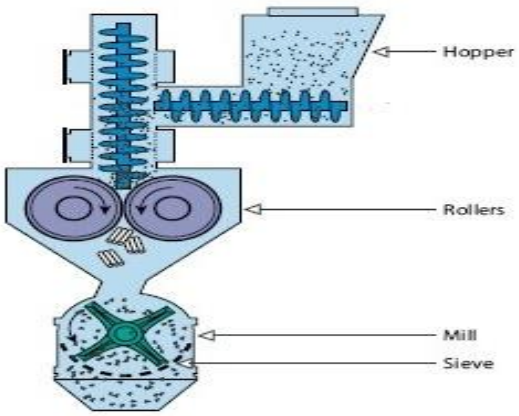
Granulation is also defined as the process of collecting particles together by creating bonds between them. There are several different methods of granulation. The most popular, which is used by over 70% of formulation in tablets manufacture is wet granulation. Dry granulation is another method used to form granules.

➢ **Dry Granulation (Compression Granulation)**

- Dry granulation can be conducted on a press using slugging tooling or on a roller compactor. Dry granulation equipment offers a wide range of pressure and roll types to attain densification.
- **In tablet press**, the powder blend is forced into the dies by a feeding mechanism for granulation. Initial compacts are called **slugs** and **the process is known as slugging**.



- **Roller compactor** can be used to replace slugging. The roller compactor exerts known pressure on powder material that flow between two rolls and a thin ribbon is produced, resembling slugs.



Advantages of dry granulation

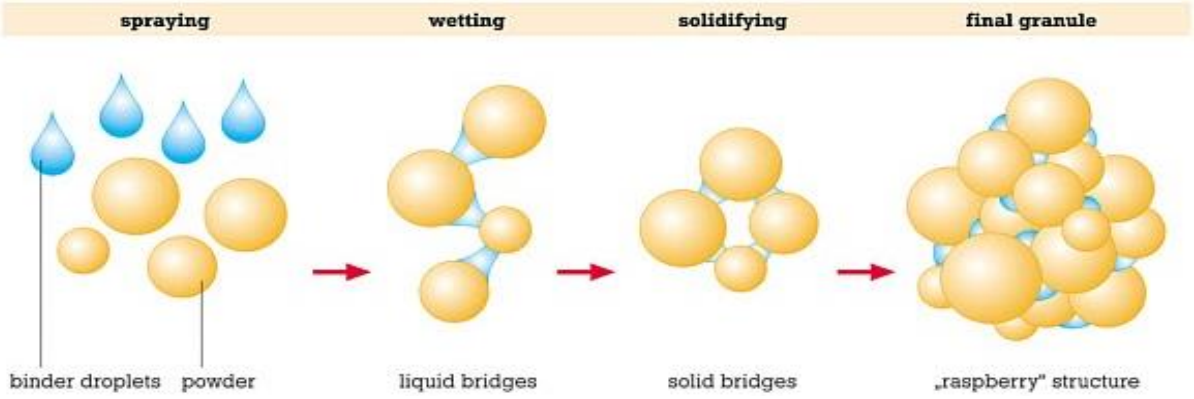
1. Good for moisture sensitive and heat sensitive drugs
2. Process times are often reduced and equipment requirements are streamlined; therefore, the cost is reduced.
3. Less equipment space than wet granulation

Limitations:

1. Dry granulation often produces a higher percentage of fine or non-compacted products, which could compromise the quality or create yield problems for the tablet.
2. It requires drugs or excipients with cohesive properties.
3. It involves the compaction of the components of a tablet formulation by means of a tablet press or specially design machinery followed by milling or sifting prior to the final compression.
4. the process may require repeated compaction steps to attain the proper granule end point.

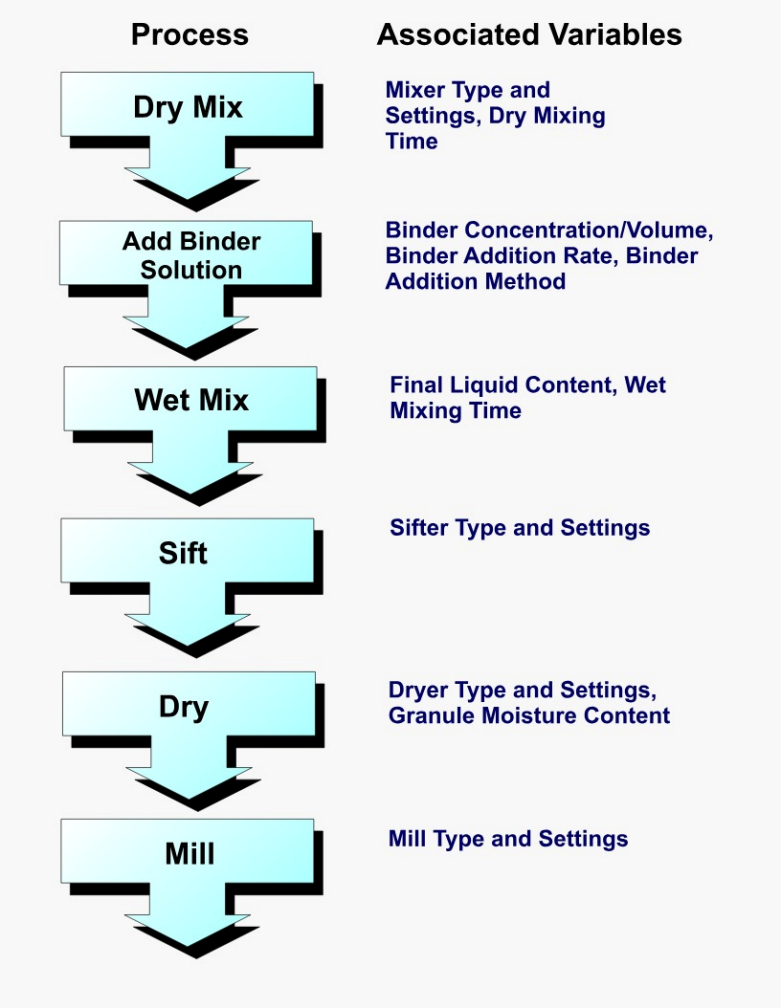
- **Wet Granulation process:**

Wet granulation is a process of using a liquid binder or adhesive to the powder mixture. The amount of liquid can be properly managed, and over wetting will cause the granules to be too hard, and under wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvents.



The materials in granulation process are divided to:

1. Intra-granular materials
2. Extra-granular materials



General procedure:

A. Intra-granular materials (Pre-mix) preparation:

1. Weigh the materials in the formula (active ingredients and excipients)
2. Pass the weighed materials through suitable sieve
3. Mix the materials together.

B. Binding or granulating liquid Preparation:

Binding or granulating solution can be: water, alcohol, hydro-alcoholic solution, acacia, and starch mucilage, solution of gelatin or Povidon (PVP).

C. Granulation step:

1. Wet powder mixing: The granulating liquid is added to the ingredients until a coherent or damp mass is obtained. (When you press a ball from the mass in the palm of the hand the ball crumbles under moderate pressure into clean portions).
2. Wet size reduction: Pass the mass through hammer mill or oscillating granulator equipped with screen of large perforation to produce coarse granules (Wet screening)

D. Granules drying step: using oven or Fluid bed dryer (FBD) at suitable temp.

The problem that might appear during oven drying is when water moves from the interior of the powder bed towards the hotter surface to evaporate; this creates convection currents that, by mass flow, carry soluble drug or soluble dyes to the surface. This leads to the formation of a depleted lower layer and enriched upper layer. If proper mixing is not performed after such drying, dose non-uniformity and/or mottling may result.

E. Re-granulation: Granules sifting and Size reduction (milling)

F. Final blend preparation:

1. Add the extra-granular materials to the resulted granules.
2. Compress the last ingredients into tablets using the suitable tablet machine.

OBJECTIVES

1. To investigate several different factors that may affect the properties of granules when prepared using "wet process" i.e. massing and screening.
2. To evaluate the four tested "binders" based on the following criteria:
   a. Macroscopical properties of prepared granules
   b. % Yield per unit mass of the binder

Note:

- ***Best binder:***
  Macroscopical properties include particle size, particle size distribution (PSD), particles shape, uniformity of particles shape, percentage of fine particles in the final granules, and color changes
  Based on this:
  Granules with the largest particle size, narrow PSD, spherical shape,uniform shape, least percentage of fine particles, and no color changes (unless a coloring agent is used there should be no color changes) are prepared using the "Best binder

- ***Most efficient binder:***
  The highest % Yield per unit mass of the binder indicates the highest efficiency.

EXPEREMENTAL PART

a. Materials:

Lactose, Starch Mucilage 7.5 gm% w/v, Sucrose Solution 50 gm% w/v, PVP solution 10 gm% w/v

b. Apparatus:

-Pharma test Kneader

- Pharma test Oscillating Granulator

-Magnetic Stirrer Hotplate

c. Method:

NB: all equipment and tools should be cleaned prior to use.

1. Prepare the three binders to be evaluated:
   a. **Distilled Water**
   b. **Sucrose Solution 50 gm% w/v:** in a Erlenmeyer flask place 50 gm of coarse sucrose, then add D.Water up to the 75-mL mark with continuous stirring, use hot plate to accelerate the process, when sucrose completely dissolve, complete the volume with D.Water up to the 100-mL mark, mix well then use.
   c. **Starch Mucilage 7.5 gm% w/v** (aqueous paste); disperse 7.5 gm of starch in up to 100 mL of D.Water in E.flask, then put the prepared dispersion on a magnetic hot plate (use a magnetic bar inside the dispersion), continue warming the dispersion with continuous stirring until a translucent paste is formed.
   d. **PVP Solution 10 gm% w/v:** in a Erlenmeyer flask place 10 gm of PVP, then add D.Water up to the 75-mL mark with continuous stirring, use hot plate to accelerate the process, when PVP completely dissolve, complete the volume with D.Water up to the 100-mL mark, mix well then use.
2. Pass enough large quantity of lactose through a 1.4 mm sieve to remove any lumps or aggregates
3. Weigh 400 gm of the sieved lactose and transfer to Kneader.

4. Start paste preparation by adding the binder (start with D.Water) portion-wise,

   i.e. using a 10-mL syring add several additions each of 3 mL of D.Water every 30 second each time to different place, after each addition of the binder cover the chamber and operate the kneader with medium velocity for 30 seconds to 1 minute.

5. After the third addition and massing for 1 minute, turn the kneader off and test the mixture for the end point, How?

   The required end point is just prior to paste formation, which can be measured by taking a mass from the mixture using your hand and squeezing it between the balm and fingers, then hitting it with other hand index finger, if it remained coherent and only broken from the peripheries then the end point is achieved, so return the mass to the kneader and perform massing for extra1 minute to ensure homogeneity and get rid of any large agglomerate that might be formed. If the squeezed mass breaks down completely, continue the addition of the binder and check for end point using the above method after each addition till end point is reached.

6. After achieving the end point, transfer the wet mass to an empty cleaned tray, use spatula to completely remove the mixture from the kneader chamber.

7. Allow the paste to pass through the 1.6 mm sieve fitted to the oscillating granulator, collect the wet granules from the granulator in a pre- weighed clean tray and spread to form a thin bed of granules.

8. Weigh the tray containing the wet granules, and record it as wet weight.

9. Dry the granules in preheated oven at 70 °C for 45 minutes.
10. After 45 minutes, remove the tray containing the dried granules from the oven and record its weight as dry weight.
11. Pass the dry granules through 1.6 mm sieve fitted to the oscillating granulator → Re-granulation.
12. Put the granules in a appropriately labeled plastic bag (Granules A) and reserve them in dry place closed place to be tested in the next experiment.
13. Repeat steps 2 - 12 three times, first using Sucrose Solution 50 gm% w/v, secondly just enough Starch Mucilage 7.5 gm% w/v, and finally using PVP solution 10 gm% w/v (Granules B, Granules C and Granules D), respectively.

Results and Data Analysis

Results

Binder		***End Point***	***Tray Weight***	***Wet Weight***	***Dry Weight***
Type	***Code***	***mL***	***gm***	***gm***	***gm***
Distilled Water	***A***				
Sucrose *	***B***				
Starch **	***C***				
PVP ***	***D***				

*** added as …** . . . . . .

**** added as …** . . . . . .

***** added as …** . . . . . .

Data Analysis

- ✓ Arrange your results and calculated numbers in table similar to the following: next page
- ✓ Evaluate the tested binders according to the following criteria:
    1. % Yield per unit mass of the binder (the highest %Yield / 1 gm of the binder is ***the most efficient binder***, Why?)
    2. Granules Macroscopical Properties (shape, uniformity of shape, size, uniformity of the size and size distribution, color, …) to determine ***the best binder***.
- ✓ Properties of granules due to the used binder.

Binder Type	Granules	End Point ml	Tray Weight gram	Wet Weight gram	Dry Weight gram	Practical Weight gram	Binder Weight gram	Theoretical Weight gram	% Yield	% Yield perunit mass of Binder
Distilled Water	A	X	T_1	W_1	D_1	$P_1 = D_1 - T_1$	=X*1 gm/mL		%1	
Sucrose (added as Sucrose Solution 50g%w/v)	B	Y	T_2	W_2	D_2	$P_2 = D_2 - T_2$	=Y*50 gm/100mL		%2	
Starch (added as Starch Mucilage 7.5g% w/v)	C	Z	T_3	W_3	D_3	$P_3 = D_3 - T_3$	=Z*7.5 gm/100mL		%3	
PVP (added as PVP solution 10 g% w/v)	D	L	T_4	W_4	D_4	$P_4 = D_4 - T_4$	=L*10 gm/100mL		%4	

Theoretical Weight = Un-Granulated Powder Weight + Amount of used Binder

= Lactose (400 gm) + Amount of used Binder

For Granules A: Theoretical Wt = 400 gm + (X*Water Density) = 400 gm + (X*1 gm/mL)

For Granules B: Theoretical Wt = 400 gm + Sucrose Weight = 400 gm + (Y*50 gm/100mL)

For Granules C: Theoretical Wt = 400 gm + Starch Weight = 400 gm + (Z*7.5 gm/100mL)

For Granules D: Theoretical Wt = 400 gm + PVP Weight = 400 gm + (L*10 gm/100mL)

$$\% \text{ Yield} = \frac{\text{Practical Weight}}{\text{Theoretical Weight}} * 100\%$$

% Yield per unit mass of binder =

$$\frac{\%\ Yield}{binder\ weight}$$

Example for *Granules A*:

% Yield per unit mass of D.Water =

$$\frac{\%_1}{X * 1\ gm/mL}$$

EXPEREMENT 4

CHARACTERIZATION OF GRANULES AND POWDER

INTRODUCTION

The preparation of essentially all dosage forms involves the handling of solid materials. Among all finished products, solid dosage forms are the most predominant in terms of volume and value. The importance of solid-handling properties, especially flow properties, cannot be overemphasized. The flow properties of solids have great impact on the tableting and encapsulation processes since these dosage forms manufacturing processes require flow of powder materials from a storage containerto filling station, such as tablets dies or capsule fillers. Weight uniformity of course is dependent on the uniform and rapid flow of powders. The flow properties of solids also have great influence on the mixing and de-mixing of powders that take place before tableting or encapsulation.

There are some simple criteria that are useful to predict flow properties from measurements made on static heap or bed of the powder and there are, listed below, other tests may be included to characterize the granules.

1. Flow test:
    a. Flow Rate
    b. Angle of Repose
    c. Bulk Density and Tapped Density
2. Moisture Content
3. Particle Size Analysis

Forces that can act between solid particles are:

1. Frictional Forces
2. Surface Tension Forces
3. Electrostatic Forces
4. Cohesive Forces
5. Mechanical Forces caused by interlocking of particles of irregular shape.

All of these forces can affect the flow properties of a solid. Surface-tension forces between particles can be significant where capillary condensation can occur, and small liquid bridges

can be formed between particles if moisture content is high. On the other hand, it should be taken into consideration that the usual presence of even minute quantities of water is sufficient to minimize the effect of electrostatic forces.With fine powders, the magnitude of friction and cohesive forces usually predominate. For larger particles, such as granules, frictional forces normally predominate over cohesive forces.

METHODS FOR CHARACTERIZATION OF POWDER FLOW:

(1) Flow Rate:

Flow Rate is defined as the amount of powders (in grams) allowed to flow/pass through the funnel per time (in seconds) required to pass. Flow time is measured using "Free Standing Cone and Fixed Funnel Method".

Types of granules according to their flow properties: freely flow-able granules, granules need tapping to flow, Rat-hole pattern, and granules need tapping with rat- holing pattern.

(2) Angle of Repose:

It gives a measure of the frictional forces which oppose the flow of a loose powder.

Angle of repose is the maximum angle possible between the Surface of the pile (heap) of powder and the horizontal plane.

$$\text{Tan } \theta = \frac{H}{R} = \frac{H}{\frac{1}{2}D} = \frac{2H}{D}$$

Where:

- **θ:** is the angle of repose
- **H:** is the height of a heap of powder
- **D:** is the diameter of heap of powder
- **R:** is the radius of heap of powder

Factors affecting the angle of repose:

1- Particle Size

2- Particle Shape

3- Particle density

4- Presence of moisture

5- Technique of measurement

How the angle of repose changes from powder to another. This depends on the cohesive forces and particle size. When the powder leaves the funnel to the formed pile, the chance that these particles will roll down outside the pile depends on the resultant of the gravity force responsible for downward movement of particles, andthe cohesive and frictional forces responsible for sticking the particles to the top of pile. Thus, when we have smaller granule size and higher cohesive forces, thechance of sticking to the top of pile will be higher leading to higher buildup of the pile in the vertical direction and consequently higher angle of repose. Conversely, with larger size and less cohesive forces, the particle will tend to roll down to the sides leading to spreading of the granules over wide area, which would lead to lower height and wider diameter of the pile.

Accordingly, the angle of repose will decrease. Values for angle of repose $\leq 30°$ generally indicate a free-flowing material and angles $\geq 40°$ suggest a poorly flowing material.

The angle of repose given in Table following may be used as a guide to flow.

Table: Angle of repose as an indication of powder flow properties	
Angle of Repose (degrees)	Type of Flow
< 20	Excellent
20 - 30	Good
30 - 34	Passable [a]
> 40	Very Poor
[a] May be improved by Glidant, e.g. 0.2% Aerosil.	

(3) Compressibility Index (Carr's Index, CI):

Bulk and Tapped Density: The bulk and tapped density of pharmaceutical powders are often measured for process ability. The tapped density is measured for two primary purposes: (i) the tapped value is more reproducibly measured than the bulk value, and (ii) the "flow-ability" of a powder is inferred from the ratio of these two measured densities. The "tapped" density of pharmaceutical powder is determined using a tapped density tester, which is set to tap the powder at a fixed impact force and frequency. The methods for measurement in the U.S. pharmaceutical industryare specified in the U.S. Pharmacopeia (USP). Tapped density by the USP method isdetermined by a linear progression of the number of taps.

This is done by measuring the initial volume (Bulk Volume) of the sample andrecording its weight. From this data we can calculate the bulk density by:

$$\text{Bulk Density} = {}^{Weight}/_{Volume} = \text{grams per ml}$$

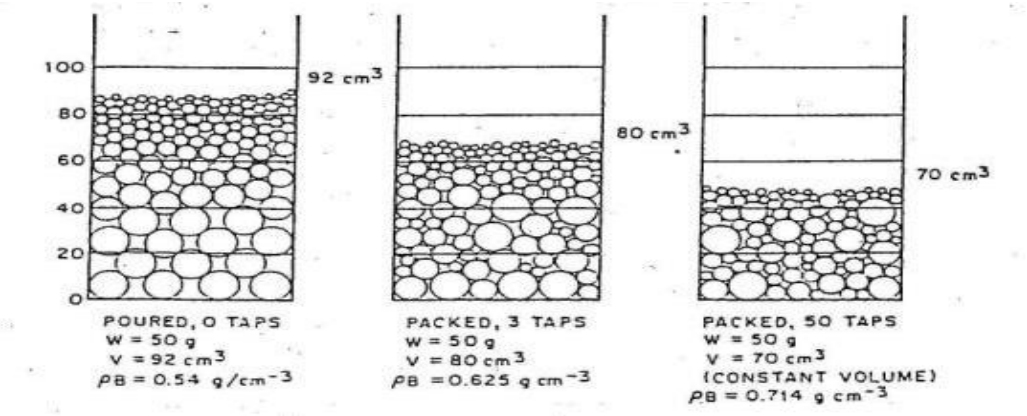
and by measuring the volume after the system is allowed to tap until reaching a constant volume (Tapped Volume) of the sample and by using these data we calculate the tapped density by:

$$\text{Tapped Density} = {}^{Weight}/_{Tapped\ Volume} = \text{grams per ml}$$

Pouring to the cylinder must not be directly into the cylinder. It has to be poured through a funnel, which would allow for free flowing of individual particles, rather than packed powder due to previous handling. After pouring, you may not have even surface, which will make reading the volume difficult. For this, it is allowed or you to make two taps by hand to make the surface even. Tapping should not produce particle, or changes in particle size distribution of the tested material.

How the Bulk Density and Tapped Density change?

The most important factor that changes these densities is particle size distribution. Suppose that we have two granules A and B. A has narrow particle size distribution and B has wide particle size distribution. When A is poured and because of the uniform particle size, the granules will arrange with same spaces that cannot be filled with small particles, obviously because there are no fines to fill these spaces. Accordingly, when this powder is tapped, small change in volume is expected, again because there are no fine particles to move into the formed spaces upon pouring. On the contrary, B upon pouring will have interspaces among the large particles than between the small particles. The large spaces between the large particles will befilled with the small particles upon tapping and consequently large reduction in the volume is expected. The following figure illustrates this.



In Summary;

- If our granules have large uniform particle size distribution, then initially they will have optimum arrangement, thus tapped volume will not markedly change.
- On the other hand, if our formula possesses lots of fines, the material can be compressed to less volume by tapping.

Importance of Bulk Density and Tapped Density:

Bulk and tapped densities can be used to calculate an index called theCompressibility Index as the following:

$$Compressibility\ Index = \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density} * 100\%$$

Now, for the previous two granulations, which one would have higher compressibility index. Of course, B will have ..... (Why?). Now the name of this index indicates thatit is important for compression i.e., the higher the compressibility index the higher the packing and compression. However, this usually not the case, because upon compression fragmentation of granules happen which create new surface area for cohesion. So even if the granulation has narrow large particle size distribution and poor packing, fragmentation will compensate for this. The real importance of the compressibility index is, the larger the granules size and the narrower the size distribution, and consequently, the more flow-able the granules. Values of the compressibility index up to 15% indicate good to excellent flow-ability, and values above 25% indicate poor flow-ability.

This is a simple index that can be determined on small quantities of powder and may be interpreted as in the following Table.

Table: Carr's Index as an indication of powder flow

Carr's Index (%)	Type of Flow
5 - 15	Excellent
12 - 16	Good
18 - 21	Fair to passable[a]
23 - 35	Poor [a]
33 - 38	Very Poor
> 40	Extremely Poor

[a] May be improved by Glidant, e.g. 0.2% Aerosil.

A simple relationship between angle of repose, Carr's index and the expected powder flow is shown in the following Figure.

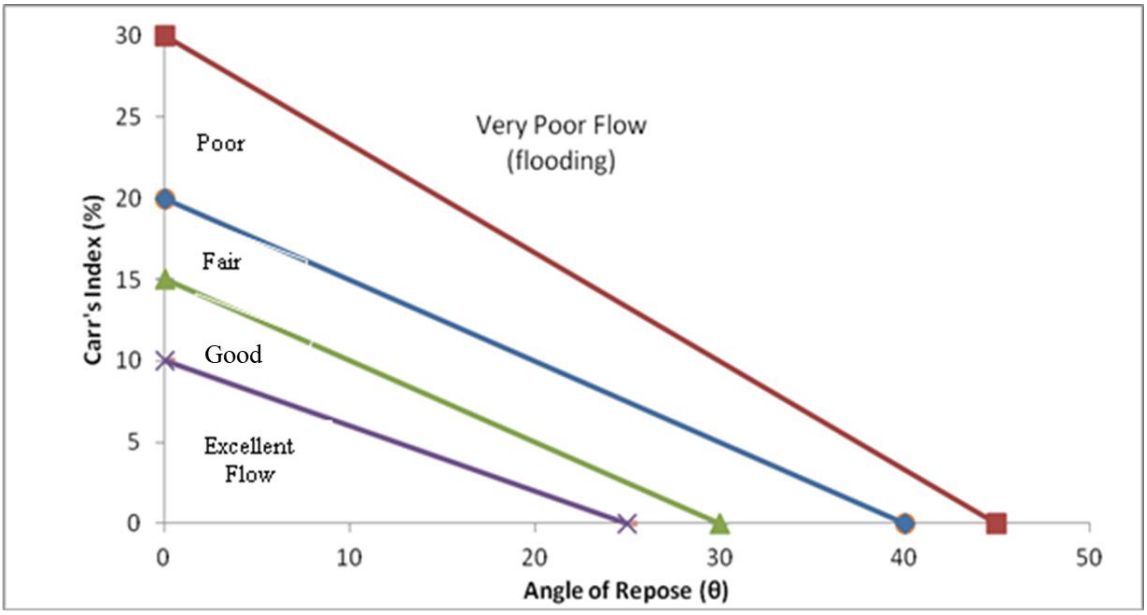


Figure: Relationship between Angle of Repose, Carr's Index of a powder and its flow characteristics

(4) Moisture Content:

Water content or moisture content is the quantity of water contained in a material, such as soil (called soil moisture), rock, ceramic, or wood on a volumetric or gravimetric basis. The property is used in a wide range of scientific and technical areas, and is expressed as a ratio:

A. Moisture Content is calculated as follows:

$$\% \text{ MC} = \frac{Weight\ of\ water\ in\ sample}{Total\ Weight\ of\ Dry\ Sample} * 100\%$$

A weighed sample is placed on the balance and allowed to dry until it is at constant weight.

B. Loss On Drying (LOD) is calculated as follows:

$$\% \text{ LOD} = \frac{Weight\ of\ water\ in\ sample}{Total\ Weight\ of\ Wet\ Sample} * 100\%$$

Example: If exactly 5 gm of moist solid is brought to a constant dry weight of 3 gm:

$$MC = \frac{5-3}{3} * 100\% = 66.7\%$$

Whereas:

$$LOD = \frac{5-3}{5} * 100\% = 40\%$$

Moisture Content is important due to its effects on:

(I) **Flow Properties:** Moisture has two opposite effects on granules flow:

a. It retards the flow due to increase in cohesive forces as a result of surfacetension and capillary attraction.

b. Enhancement of flow as a result of dissipation of surface electrostatic charge. Accordingly, an optimum moisture level should be determined for the drying process of wet granules in order to have balanced effect of the above two factors and consequently optimum flow.

(II) Effect of moisture on cohesiveness upon compression or tableting:

Too low moisture in the dried granulation can lead to poor cohesiveness. On the other hand, too high moisture level can lead to sticking upon compression andcapping if too dry. Accordingly, an optimum moisture level should be determined for the drying process of wet granules in order to have good cohesiveness upon tableting and no sticking.

Important note:

From the angle of repose and compressibility values, a reasonable indication of a material's inherent flow properties should be possible. The important point is that one can be misled if a judgment on flow-ability is based entirely on angle-of-repose measurements. The angle of repose normally increases as particle size is reduced. The angle of repose is inversely proportional to the size of the fine particles but is directly proportional to their weight fraction.

When materials that take up moisture from the atmosphere are exposed to high humidities, that material generally becomes more cohesive, and exhibit very poor flow characteristics. As the storage humidity is increased, angle of repose increase. Itis noted that if particles become more irregular in shape, as a result the angle of repose will be increased.

EXPERIMENTAL

a. Materials:

Granules A, B, C & D from Experimental Granulation (Experiment 3).

b. Apparatus:

Flow Rate Apparatus, Bulk Density Apparatus, Sieve shaker Apparatus,Moisture Content Determination Apparatus.

c. Method:

NB: all equipment and tools should be cleaned prior to use.

For the four batches of granules determine the following:

1. Flow rate:

Fixed base Method:

The simplest way is to allow the material to flow through a funnel orifice onto a horizontal surface beneath as follow:

- Assemble the *apparatus* as shown in the following diagram
- Weigh 30 gm of the granules and determine the time to flow through funnelusing stop watch.
- Repeat three times and determine the average flow time.
- Calculate the Flow Rate:

  Flow Rate = $Weight / Flow\ Time$ = gram per 1 second

2. Angle of Repose:

- Assemble the same apparatus above.
- Put 30 g of your granules in the funnel part
- By moving the lever of the apparatus allow the granules to flow on a base of fixed diameter
- Measure the height of the heap (H) using the caliber then calculate the angle of repose
- Repeat three times and determine the average.

3. Measurement of bulk and tapped density:

- Weigh 50 gm of dried granules, transfer to the measuring cylinder attached to the Bulk Density Apparatus with the minimum disturbance of the bed and measure its volume (Bulk Volume).

$$\text{Bulk Density} = {}^{Weight}/_{Bulk\ Volume} = \text{grams per 1 ml}$$

- Allow the system to tap until a constant volume is reached (600 taps). Record the volume of the tapped granules (Tapped Volume).

$$\text{Tapped Density} = {}^{Weight}/_{Tapped\ Volume} = \text{grams per 1 ml}$$

4. Moisture Content:

- Place about 1.0 gm of the dried granules (*Wet Weight*) on the Moisture Content Determination Apparatus, turn on the heating system, leave until a constant weight is reached and read out the read (*Dry Weight*), then calculate the following:

Moisture Content (MC%)

$$= {}^{(\text{Granules Wet Weight} - Granules\ Dry\ Weight)}/_{Granules\ Dry\ Weight} * 100\%$$

Loss On Drying (LOD%)

$$= {}^{(\text{Granules Wet Weight} - Granules\ Dry\ Weight)}/_{\text{Granules Wet Weight}} * 100\%$$

5. Particle Size Analysis:

- Arrange the sieves on the Sieve Shaker on order of aperture size, with the largest pore size in the top and the receiver at the bottom after recording theirtare weights.
- Sieves to be used are 0.71, 0.500, 0.250, 0.125, 0.09 & 0.064 mm with collecting pan.
- Transfer 20 gm of the granules on top of the upper sieve; allow for 5 minutes' agitation and then stop sieving.
- Weigh the size fractions including any fine powder collected in the receiver (gross weights).

Results and Data Analysis

Results

Flow Rate & Angle Of Repose:

*Amount tested (grams):*_____

Granules Type	Trial Number	Flow Time Second	Angle of Repose Height, cm	Angle of Repose Diameter, cm
A	1			
	2			
	3			
B	1			
	2			
	3			
C	1			
	2			
	3			
D	1			
	2			
	3			
Lactose	1			
	2			
	3			

Bulk & Tapped Densities

*Amount tested (grams):*_____

Granules Type	Bulk Volume, ml	Tapped Volume, ml
A		
B		
C		
D		
Lactose		

Moisture Content

Granules Type	Wet Weight, grams	Dry Weight, grams
A		
B		
C		
D		
Lactose		

Particle Size Analysis

Pore Size mm	*Tare Wt grams*	*Gross Wt, grams*				
		Granules A	*Granules B*	*Granules C*	*Granules D*	*Lactose*
0.000						*Cancelled*

Data Analysis

Flow Rate Analysis:

Granules		Amount Tested	Flow Time, Seconds				Flow Rate
Code	Binder	gm	Trial 1	Trial 2	Trial 3	Average	gm/second
A	Distilled Water		a_1	a_2	a_3	a\	
B	Sucrose		b_1	b_2	b_3	b\	
C	Starch		c_1	c_2	c_3	c\	
D	PVP		d1	d2	d3	d\	
Lactose							

Sample Weight which is equal to 30 grams

Flow Rate = $\frac{Amout}{Flow\ Time}$ **gm/second**

Here;

Flow Rate = $\frac{30}{Avarage\ flow\ time}$ **gm/second**

Example;

Granules A Flow Rate = $\frac{30}{a\backslash}$ **gm/second**

Angle of Repose Analysis:

Granules			Diameter, cm	Radius cm	Height, cm		Angle of Repose	
Code	Binder	Trial			H	Average	Tan θ	θ
A	D.Water	1						
		2						
		3						
B	Sucrose	1						
		2						
		3						
C	Starch	1						
		2						
		3						
D	PVP	1						
		2						
		3						
Lactose		1						
		2						
		3						

Radius = Diameter /2

Average height = $\frac{Trial\ 1+Trial\ 2+Trial\ 3}{3}$

$$Tan\ \theta = \frac{Average\ height}{Radius}$$

$$\theta = \tan^{-1}\theta$$

Bulk and Tapped Densities Analysis

Granules		Amount Tested	Volume, mL		Density, gm/mL		Compressibility
Code	Binder	gm	Bulk	Tapped	Bulk	Tapped	Index, %
A	Distilled Water	50	X	Y	B	T	
B	Sucrose						
C	Starch						
D	PVP						
Lactose							

Bulk Density= $\frac{Amount\ Tested}{Bulk\ Volume}$ **= gm/mL**

Here,

Bulk Density= $\frac{50\ g}{X\ ml}$ **= B gm/mL**

Tapped Density= $\frac{Amount\ Tested}{Tapped\ Volume}$ **= gm/mL**

Here,

Bulk Density= $\frac{50\ g}{Y\ ml}$ **= T gm/mL**

Compressibility Index= $\frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density}$ ***100%**

Here,

CI %= $\frac{T-B}{T}$ ***100%**

Moisture content analysis:

Granules		Wet Weight, gm	Dry Weight, gm	MC %	LOD %
Code	Binder				
A	Distilled Water				
B	Sucrose				
C	Starch				
D	PVP				
Lactose					

MC% $= \frac{Sample\ Wet\ Weight - Sample\ Dry\ Weight}{Sample\ Dry\ Weight} * 100\%$

LOD% $= \frac{Sample\ Wet\ Weight - Sample\ Dry\ Weight}{Sample\ Wet\ Weight} * 100\%$

Particle Size Analysis:

- Apply particle size analysis method used in (Experiment 1) to find the median particle size for each of the prepared granules.

DISCUSSION

Record your results and compare the findings between the four granules, justifyingthe differences.

EXPEREMENT 5

Effect of Additives on the Physical Properties of Granules

INTRODUCTION

There are many formulation additives and process variables involved in the granulation step; and all of these can affect the characteristics of the granulation produced. Therefore, methods to measure certain granulation characteristics have been developed to monitor granulation suitability for tableting.

1. Effect of Glidant:

A **glidant (**also known as ***Flow Promoter)*** is a substance that is added to a powder to improve its flowability. A glidant will only work at a certain range of concentrations. Above a certain concentration, the glidant will in fact function to inhibit flowability (Which means that there's a critical concentration to be used if increasing powder's flowability is intended with respect to the glidant and the powder properties). In tablet manufacture, glidants are usually added just prior to compression.

Examples of glidants include magnesium stearate, Aerosil (colloidal silicon dioxide), starch and talc.

Mechanism of Action: A Glidant's effect is due to a counter-action to factors resulting in poor flowability of powders. For instance, correcting surface irregularity, reducing interparticular friction and decreasing surface charge. The result is a decrease in the angle of repose which is an indication of an enhanced powder's flowability.

Examples of glidants that are used in pharmaceutical industry:

Glidant	**Concentration (%)**
Colloidal silicon dioxide (also Known as : Aerosil and colloidal silica)	0.1-1.0
Talc	1 –10.0
Starch	5 – 10

2. Effect of Lubricant:

A **lubricant** is a substance introduced to reduce friction between moving surfaces.

In pharmaceutical industry lubricants are used to reduce powder-metal friction during compression (to prevent sticking of granules with die and punches upon tableting process) which means decrease adherence of particles to machines. In tablet manufacture, lubricants are usually added just prior to compression (the lowest effective concentration and minimal mixing time) and if not the following effects will result:

a. Reducing the hardness of tablets by decreasing the bonding between granules, resulting in brittle tablets.
b. Reducing dissolution rate: coating of granules especially with hydrophobic lubricants. ?!

For example, Mg-Stearate acts as lubricant only up to 1%, if added in more than 1%
→ hydrophobic layers will be formed at surfaces → retardation of disintegration and dissolution.

Examples of Lubricant that are used in pharmaceutical industry:

Lubrican	**Concentration (%)**
Stearic acid	1.0-3.0
Magnesium stearate	0.25-5.0

Experiment Objectives:

1. To evaluate the effect of Glidants using Talc as an example on granules flow properties
2. To evaluate the effect of Lubricants using Magnesium Stearate as an example on granules flow properties
3. To understand and determine Talc critical concentration with regard to flow properties improvement.

EXPERIMENTAL

a. Materials:

Granules B Experimental Granulation (Experiment 3).

b. Apparatus:

Flow Rate Apparatus, Bulk Density Apparatus

c. Method:

NB: all equipment and tools should be cleaned prior to use.

i. Effect of Glidant:

- Weight **30 g** of granules B and test for
  a. Flow Rate
  b. Angle of Repose
  c. Bulk and Tapped Density

  NB: Use the same procedure used in experiment 4.

- Prepare the following mixtures of Talc in Granules B (total mixture weight is 50 grams)

  Mixture (1): **1 % w/w** Talc in Granules B:

  1. In a plastic bag put **49.5** grams of Granules B and **0.5** gram Talc
  2. Then mix well
  3. Take **30 g** from the resulted mixture and test for:
     a. Flow Rate
     b. Angle of Repose
     c. Bulk and Tapped Density

  NB: All powders should be reserved and collected carefully to be used in mixture (2) preparation

Mixture (2): **3 % w/w** Talc in Granules B:

1. In a plastic bag put **mixture (1)** and **1** gram Talc
2. Then mix well
3. Take **30 g** from the resulted mixture and test for:
    a. Flow Rate
    b. Angle of Repose
    c. Bulk and Tapped Density

NB: All powders should be reserved and collected carefully to be used in mixture (3) preparation

Mixture (3): **6 % w/w** Talc in Granules B:

1. In a plastic bag put **mixture (2)** and **1.5** gram Talc
2. Then mix well
3. Take **30 g** from the resulted mixture and test for:
    a. Flow Rate
    b. Angle of Repose
    c. Bulk and Tapped Density

NB: All powders should be reserved and collected carefully to be used in mixture (3) preparation

ii. Effect of Lubricant:

- Weight **30 g** of granules B and test for

    a. Flow Rate

    b. Angle of Repose

    c. Bulk and Tapped Density

    NB: Use the same procedure used in experiment 4.

- Prepare the following mixtures of Mg-Stearate in Granules B (total mixture weight is 50 grams)

Mixture (1): **0.25 % w/w** Mg-Stearate in Granules B:

1. In a plastic bag put **49.875** grams of Granules B and **0.125** gram Mg-Stearate
2. Then mix well
3. Take **30 g** from the resulted mixture and test for:
    a. Flow Rate
    b. Angle of Repose
    c. Bulk and Tapped Density

NB: All powders should be reserved and collected carefully to be used in mixture (2) preparation

Mixture (2): **0.5 % w/w** Mg-Stearate in Granules B:

1. In a plastic bag put **mixture (1)** and **0.125** gram Mg-Stearate
2. Then mix well
3. Take **30 g** from the resulted mixture and test for:
    a. Flow Rate
    b. Angle of Repose
    c. Bulk and Tapped Density

NB: All powders should be reserved and collected carefully to be used in mixture (3) preparation

Mixture (3): **1 % w/w** Mg-Stearate in Granules B:

1. In a plastic bag put **mixture (2)** and **0.25** gram Mg-Stearate
2. Then mix well
3. Take **30 g** from the resulted mixture and test for:
    a. Flow Rate
    b. Angle of Repose
    c. Bulk and Tapped Density

Results and Data Analysis

Use the same equations and method used in experiment 4 to find out the flow properties measured.

i. Effect of Glidant:

1. Talc Effect on Flow Rate:

Talc % w/w	Amount Tested gm	Flow Time, Seconds				Flow Rate gm/second
		Trial 1	Trial 2	Trial 3	Average	
0.00						
1.00						
3.00						
6.00						

2. Talc Effect on Flow Rate:

Talc %	Trial	Diameter, mm	Radius mm	Height, mm		Angle of Repose	
				H	Average	Tan θ	θ
0.00	1						
	2						
	3						
1.00	1						
	2						
	3						
3.00	1						
	2						
	3						
6.00	1						
	2						
	3						

3. Talc Effect on Bulk and Tapped Densities:

Talc % w/w	Amount Tested gm	Volume, mL		Density, gm/mL		Compressibility Index, %
		Bulk	Tapped	Bulk	Tapped	
0.00						
1.00						
3.00						
6.00						

ii. Effect of Lubricant:

1. Mg-Stearate Effect on Flow Rate:

Mg-Stearate %	Amount Tested gm	Flow Time, Seconds				Flow Rate gm/second
		Trial 1	Trial 2	Trial 3	Average	
0.00						
0.25						
0.50						
1.00						

2. Mg-Stearate Effect on Angle of Repose:

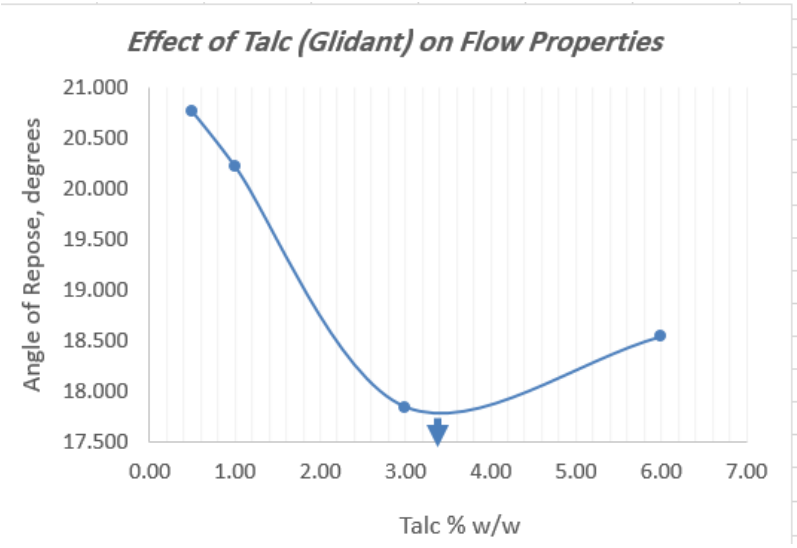
Mg-Stearate %	Trial	Diameter, mm	Radius mm	Height, mm		Angle of Repose	
				H	Average	Tan θ	θ
0.00	1						
	2						
	3						
0.25	1						
	2						
	3						
0.5	1						
	2						
	3						
1.00	1						
	2						
	3						

3. Mg-Stearate Effect on Bulk and Tapped Densities:

Mg- Stearate%	Amount Tested gm	Volume, mL		Density, gm/mL		Compressibility Index, %
		Bulk	Tapped	Bulk	Tapped	
0.00						
1.00						
3.00						
6.00						

DISCUSSION

1. Record your results and compare the findings between the different additive concentrations.
2. Plot a chart that represents the effect of glidant on flow indicators (for example Angle of Repose) to be able to determine Talc critical concentration with regard to flow properties improvement



3. Discuss your findings and propose a formula of good granules for tableting.

Experiment No. 6

Effervescent Granules

Objectives:

1. To prepare effervescent Granules using wet method.
2. To evaluate the prepared effervescent granules.

The effervescent forms are defined within Pharmacopeias as "those granules or tablets to be dissolved in water before administration to patients." They are used to administer water-soluble active ingredients, especially when the large dosage is required.

Effervescent granules are dosage form composed of dry aggregates powder particle; containing a medicinal agent in a dry mixture usually composed of sodium bicarbonate, citric acid, and tartaric acid when added to water, the acids and the base react to liberate carbon dioxide, resulting in effervescence. The resulting carbonated solution masks undesirable taste of any medicinal agent.

Effervescent dosage forms also enhance patient compliance. They are easier to administer, particularly helpful to patients, like children, who are not able to swallow capsules or tablets. A pleasant taste, because of carbonation, helps to mask the bad taste of certain drugs. This could also help to avoid the gastric side effect of certain drugs .They are easy to use and appeal to consumers for color and fizzy appearance more than traditional dosage forms.

Effervescent granules are having: high solubility, high stability, fast dissolving property and are also convenient dosage forms. Just before administration these granules are to be mixed in a glass of water and this solution or dispersion should be immediately drunk. The granules are quickly dispersed by the evolution of Carbon dioxide in water due to interaction between acid and base in the presence of water. Due to the liberation of Carbon dioxide gas, we observe the

dissolution of the active pharmaceutical ingredients in water as well as taste masking effect is also enhanced.

ADVANTAGES

1. Easy to administer
2. Easily portable and Marketing aspects.
3. Onset of action is faster
4. Gentle on the digestive tract
5. It masks unpleasant taste also.
6. More stable than liquid dosage form

Limitations of effervescent formulations

1. It cannot be given to the children because of possibility of gas (CO2) toxicity.
2. If packaging is not done properly then there are chances of degradation by environmental moisture.
3. It has shorter shelf life as compared to other solid dosage forms.
4. It requires special machinery requirements for manufacturing. 5. This dosage form is costly then tablets.

Preparation of Effervescent Granulation

It has been found that citric acid monohydrate and tartaric acid used in the ratio of 1:2, respectively, produces a powder with good effervescent properties. The amount of sodium bicarbonate to be used may be calculated from the reaction which occur when the granules come in contact with water.

MECHANISM OF EFFERVESCENCE

As we already know that Effervescent granules contain acid (citric acid) and base (Sodium bicarbonate) it rapidly reacts in water by releasing CO_2. Due to liberation in CO_2 gas, the active pharmaceutical ingredient (API) is dissolved in water as well as taste masking effect is enhanced. The reaction between the citric acid and Sodium bicarbonate it results in liberation of CO_2 shown as follows

$$C_6H_8O_7.H_2O + 3NaHCO_{3\,(aq)} \rightarrow Na_3C_6H_5O_7 + 4H_2O + 3CO_{2\,(aq)}$$

(Citric acid) (Sodium bicarbonate) (Sodium citrate) (Water) (Carbon dioxide)

$$C_4H_6O_6 + 2NaHCO_3 \rightarrow Na_2C_4H_4O_6 + 2H_2O + 2CO_{2\,(g)}$$

(Tartaric acid) (Sodium bicarbonate) (Sodium carbonate) (water) (Carbon dioxide)

Method of preparation

Dry or Fusion Method

It is the most important method for the preparation of effervescent granules.

In this method the powders are heated using an oven or source of heat. Fusion method uses the water of crystallization present in the citric acids which acts as binding agent. The powdered mixture is stirred well to obtain a uniform mass and is passed through a sieve to obtain granules and is finally dried in an oven

Wet Method

The wet granulation method is the most widely used method. This method firstly involves weighing, sifting of the ingredients using sieve , transferring the sifted material to Rapid Mixer, mixing it for five minutes at a slow speed and adding binder solution to it. Following this, the mass is passed through a sieve and dried at 50°C using tray dryer.

All ingredients are mixed thoroughly for uniform distribution

↓

Pass the powder through sieve to obtain uniform particle size

↓

Add suitable amount of binding agent

↓

Wet mass is passed through the sieve to obtain desired size granules

↓

These granules are dried in hot air oven.

EVALUATION OF EFFERVESCENT GRANULES

1. Angle of repose

Using fixed funnel method, the angle of repose can be determined by passing the prepared granules in funnel. The measurement of height(h) and radius(r) of granule pile gives angle of repose which indicates the flow property of granules.

$\tan \theta = h/r$

$\Theta = \tan^{-1} (h/r)$

Where, h = Height of pile , r = Radius of pile

2. Flow rate

Flow rate of granule has been defined as the rate at which the particular mass emerges through the orifice in funnel of suitable diameter. It can be determined by pouring the weighed quantity of granules in funnel with an orifice of 8mm diameter.

The time required for complete granule mass to emerge out of the orifice was recorded using a stopwatch. The flow rate was calculated from following formula,

$$\text{Flow rate} = \frac{\text{Weight of granules}}{\text{Time in seconds.}}$$

3.Bulk density

In a measuring cylinder, a certain quantity of prepared granules were taken without compacting. The volume occupied by the granule is noted as V1 (bulk volume). Bulk density can be calculated by using the following formula,

$$\text{Bulk density} = \frac{\text{Weight of granules}}{\text{Bulk volume of granules}}$$

4. Tapped density

The volume occupied by the granule is noted as V2 (tapped volume). In a measuring cylinder, a certain quantity of prepared granules were taken and tappedfor 100 timesTapped density can be calculated by using the following formula,

$$\text{Tapped density} = \frac{\text{Weight of granules}}{\text{Tapped volume of granules.}}$$

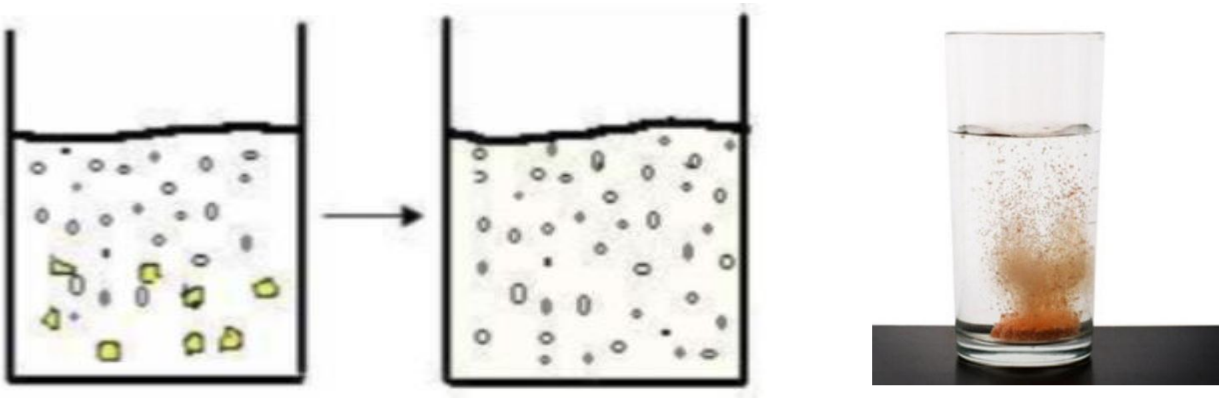
5.Carr's index

The percentage compressibility index of a granule was a direct measure of the potential strength and stability of granule. The Carr"s consolidation index can be calculated by using the following formula,

$$\text{Carr's index} = \frac{\text{(Tapped density – Bulk density)}}{\text{(Tapped density)}} \times 100.$$

6. Effervescence time

In vitro effervescence time was measured by dissolving some quantity of granules in a beaker containing 50 ml of water. Granules were randomly selected from the batch. In vitro effervescence time was measured.



7. Effervescence volume

In vitro effervescence time was measured by dissolving some quantity of granules in a graduated cylinder containing 50 ml of water. Granules were randomly selected from the batch. In vitro effervescence volume was measured.

8. Disintegration test

One dose of effervescent granules is poured in the beaker containing water at 15- 25˚, numerous bubbles of gas is liberated. When the liberation of gas around the granules stop, granules get disintegrated, being either dissolved or dispersed in water. Repeat the operation on 5 other doses. If each of 6 doses disintegrate within 5 minutes, then the preparation complies with this test.

9. Particle size by image analysis

Image analysis is a powerful analytical technique that provides particle shape information in addition to a sample's standard particle size distribution. This technique captures digital images of dispersed particles utilizing an appropriate objective/magnification and CCD camera.

Instrument software assigns a grey scale value to the pixels within the digital images and the operator evaluates the images to differentiate between particles and background. This process is known as "threshold" and based on the value set by the operator, the pixel is turned on or off. Each digital image is then processed by the software, and, once complete, results are available on a variety of size and shape parameters. Image analysis provides a very useful method for the measurement of the size distribution of granular materials. The method is very useful when the grains to be measured are very small ($1 - 25\ \mu m$) .

Experimental Part

Part ❶ : Preparation of effervescent granules

Materials and instrument:

Master Formula:

(to prepare 20.0 g granules)

Material	**Weight (g)**
Magnesium sulfate	2.0 g
Citric acid monohydrate	2.8 g
Tartaric acid	5.6 g
Sodium bicarbonate	9.6 g

-Binder : Ethanol 96%

-Top loading balance

-Stainless steel Tray

-Sieve 1.4mm , 2.0 mm

-Drying oven

Preparation method:

1. Weigh the different ingredients based on the computed amount.
2. Using a mortar and pestle ; triturate the ingredients to ensure uniform and appropriate size for powder.
3. Transfer the powder
4. to a small tray.
5. Add a sufficient amount of ethanol 96% to make it wet.
6. Pass the mixture through sieve 1.4 mm or 2.0 mm.
7. Collect the wet granules in a suitable stainless steel tray.
8. Put in oven at 50 ℃ for 15 minutes.
9. After drying , collect the dry granules and pass through sieve used in step 5.
10. Evaluate the resulted granules as described in part 2.

Part ❷ : Evaluation of effervescent granules

1. Effervescent volume:
   a. Put 50 ml of water in 100 ml graduated cylinder
   b. Weigh2.0 g of granules
   c. Add granules in cylinder containing water
   d. Measure the effervescent volume

2. Effervescent time and Disintegration time
   a. Put 50 ml of water in 100 ml beaker
   b. Weigh 2.0 g of granules
   c. Add granules in beaker containing water
   d. Measure the effervescent time
   e. After 5 minutes, the granules dissolve completely no any residue remaining in the beaker

3. Particle size analysis

   Refer to video to measure particle size of your granules

EXPEREMENT 7

TABLETS PREPARATION

INTRODUCTION

After you have been exposed to various pharmaceutical operations (mixing, granulation, size reduction and particle size analysis), you will apply the knowledge you gained from the previous experiment in suggesting tablets formulation and preparation method.

Tablets are solid dosage forms containing a single dose of one or more active ingredients and usually prepared by compressing uniform volumes of particles (powders or granules) into a definite shape.

➢ Formulation additives:

Drugs are rarely administered as pure chemical substances alone and are almost always given as formulated preparations or medicines. The excipients provide varied and specialized pharmaceutical functions.

a. Diluents (filler):

They are used for bulking small dosage drugs to find a suitable tablet size.

e.g., lactose

b. Binding agents:

Binders (also sometimes called adhesive) hold the ingredients in a tablet together and is added to a drug-filler mixture to ensure that granules and tablets can be formed with the required mechanical strength. These are necessary to form the structure. Which will be maintained after compression. Binders can be added to a powder as a solution or a dry binder.

e.g. sugar, acacia and starch.

c. Disintegrants :

Disintegrants are substances or mixture of substances added to the drug formulations, which facilitate dispersion or breakup of tablets into smaller particles when it comes in contact with gastrointestinal fluids.

e.g.,Starch, Polyvinyl pyrrolidone , carboxymethyl cellulose, sodium starch glycolate etc

d. Compression aids:

production problems can be minimized by using certain materials including:

1. **Lubricants**

   reduce friction between moving surfaces (tablet surface to the die walls and the punches) and as a consequence counter the picking or sticking of tablet.

   e.g., Magnesium stearate

2. **Glidants**

   Glidants enhances the flow of powder or granular mixture by reducing inter-particle friction

   e.g. Colloidal silica and talc.

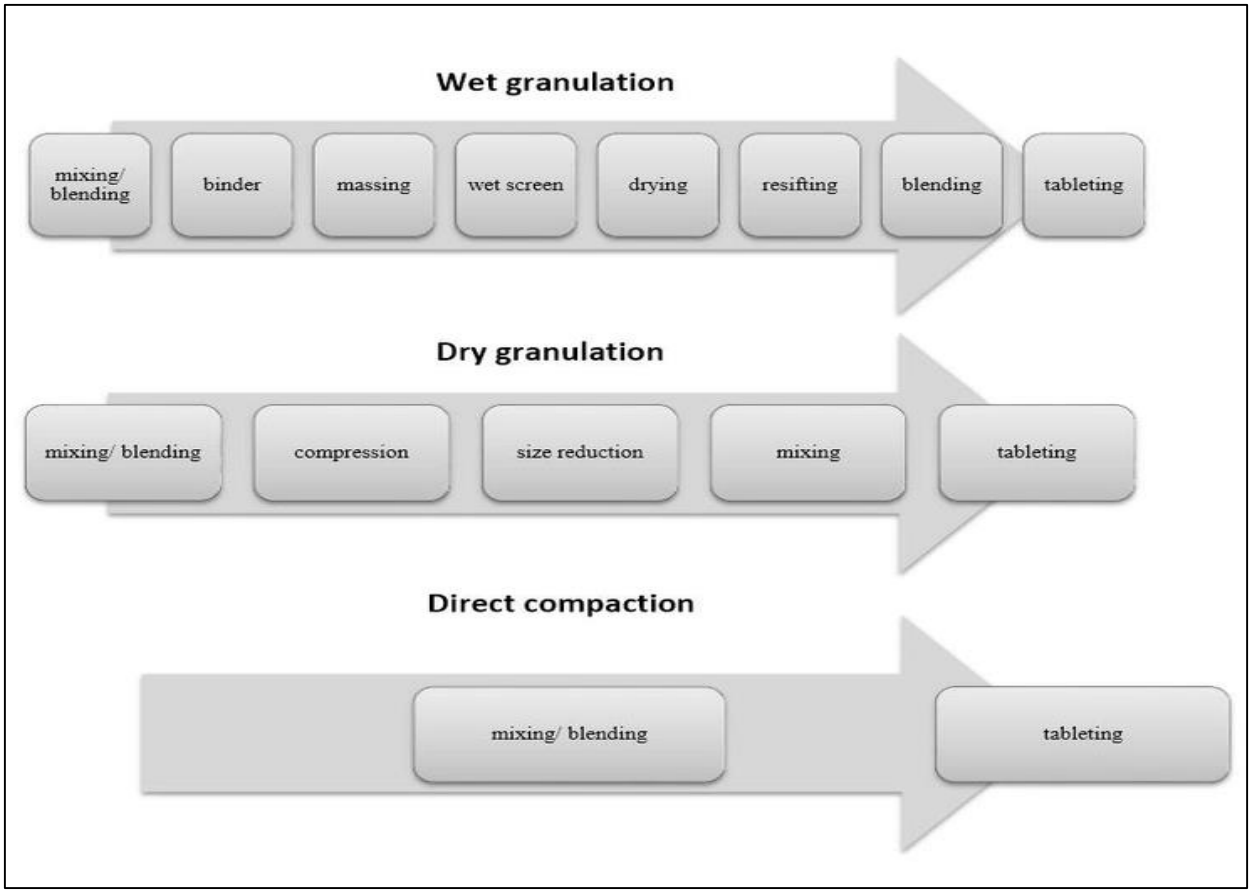
➢ Tablets preparation Methods:

I. Direct compression process

II. Granulation:

   a. wet granulation process

   b. Dry granulation (Compression granulation)



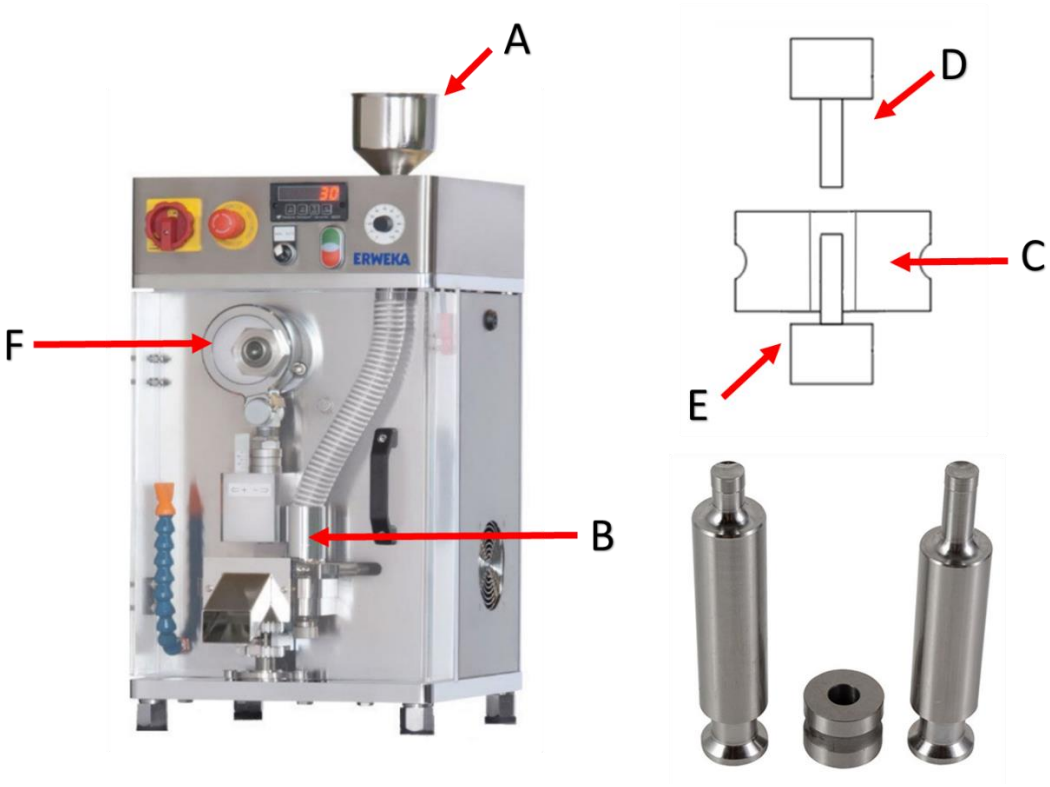
➢ Direct compression:

General procedure:

a. Weigh the suitable amounts of excipients and the drug.
b. Pass the weighed material through suitable sieve.
c. Mix the active ingredient or ingredients with the excipients
d. Add the lubricant to the formula and mix.
e. Compress the formula.

➢ Compression machine (tablet press):

1. Single punch machine



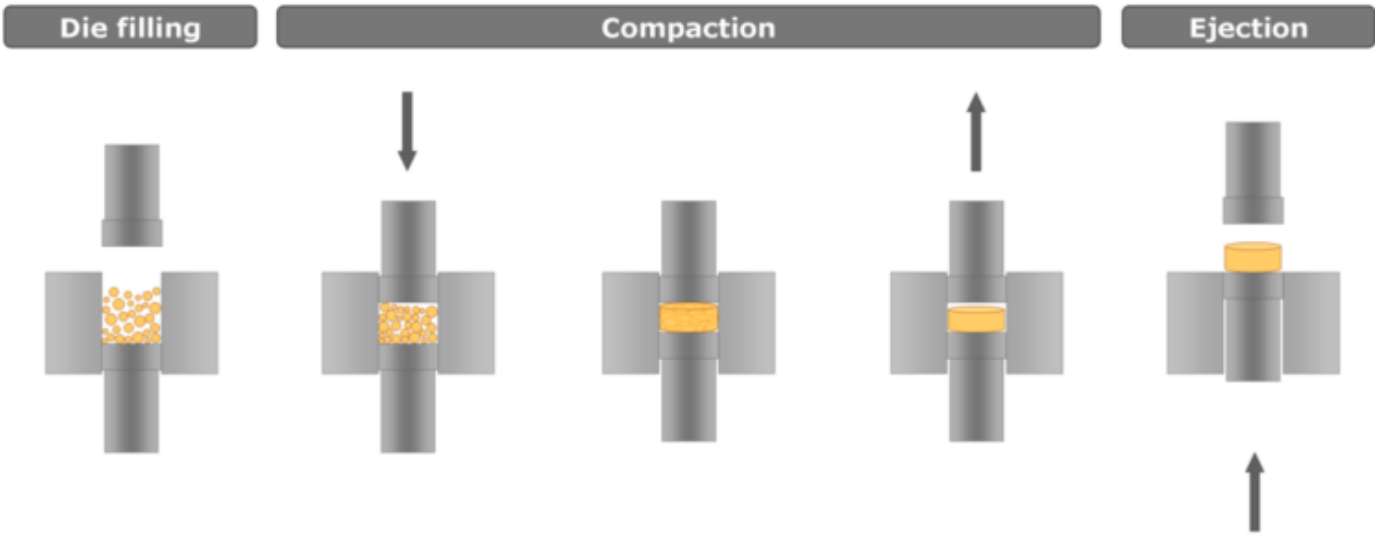
Which consists of the following parts:

a. Hopper for holding & feeding granules.
b. A shoe for uniform feeding of the granules to the die from the hopper.
c. A die to control the shape & size of the tablet.
d. The upper punch for applying pressure on the granules in the die.
e. The lower punch
f. Track for guiding the movement of the punch.

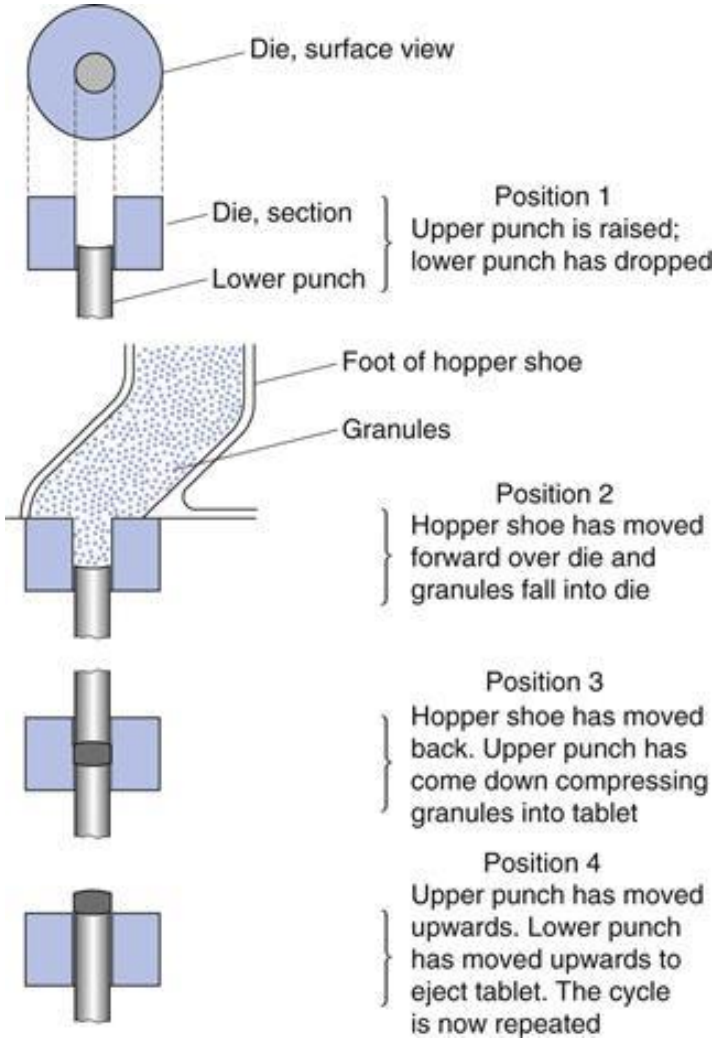
2. Rotary tablet press

➢ Compression cycle:

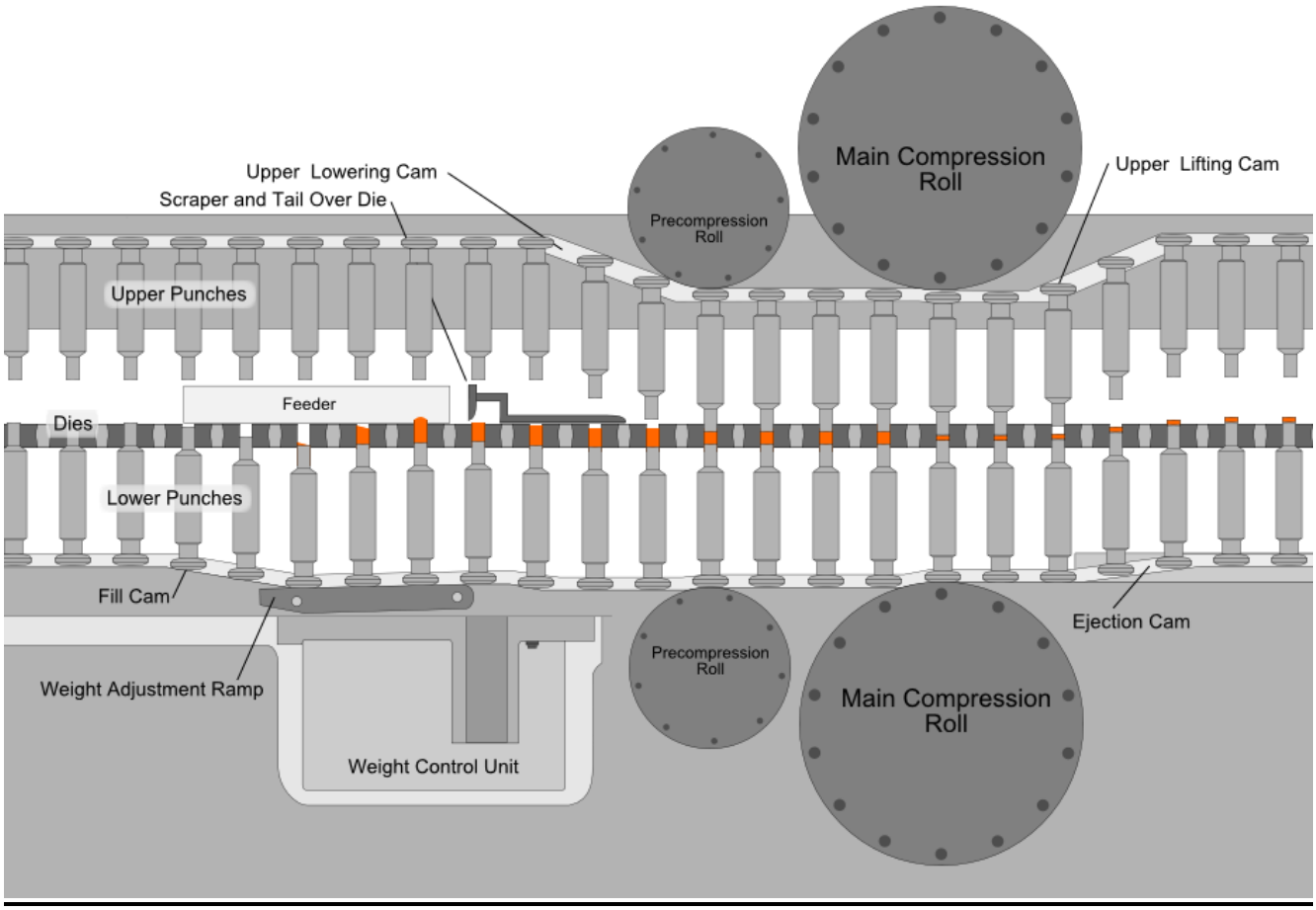
1. **Filling stage:** The blend is emptied from the hopper into the feed shoe which spread the granules over a wide area to provide the die a uniform filling.
2. **Compression stage:** the upper punch will move downward resulting in compression.
3. **Ejection stage:** The lower punch goes upward over the track & the upper punch goes upward resulting in tablet ejection.



The compression cycle of a single-punch tablet press



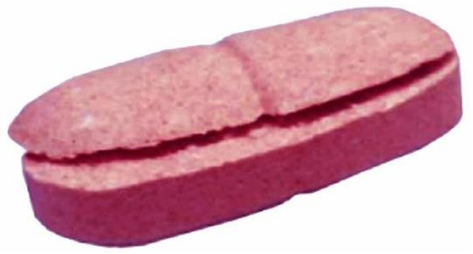
The compression cycle of a rotary tablet press



➢ Problems that may happen during tablet compression:

A. Capping & Lamination:

Capping: Partial or complete separation of the top or bottom crowns of the tablet from the body.



Lamination: Separation of the tablet into two or more distinct layers.

Causes of capping & lamination:

Mainly due to entrapped air during compression stage leading to sudden escape of it after compression.

1. Insufficient compression force results in weak bonding between the granules.
2. Tablet formulations lack good binding properties.
3. Poor granule flow leads to uneven distribution of the material.
4. Over-drying of granules.

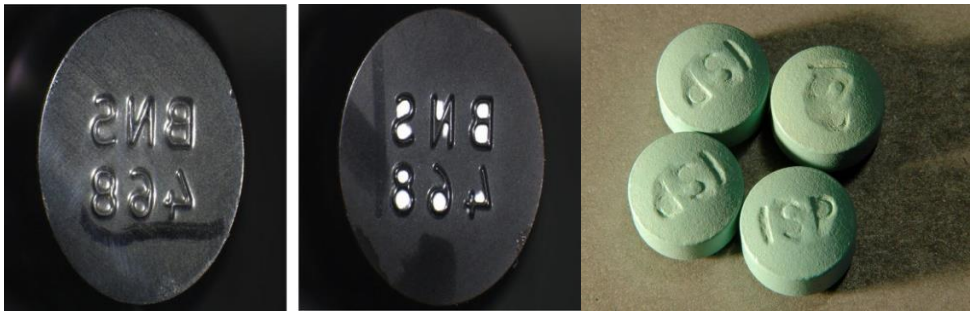
Solving of capping & lamination:

1. Adjust the compression force to improve the bonding between the granules.
2. Incorporate suitable binders or modify the excipient composition to enhance the binding properties of the formulation.
3. Optimize granulation parameters to improve the flowability of the granule.

B. Sticking and Picking

Sticking: The adhesion of tablet material to the punches and dies instead of being ejected smoothly. This can cause challenges in tablet ejection, damage to the tablets, and inconsistencies in overall tablet quality.

Picking: is a specific type of sticking. The removal of the surface material of tablet by sticking to punches. Picking is of particular concern in case of engraved punches, especially with letters of small enclosed areas like "B" and "A", which are difficult to manufacture cleanly.



Causes of sticking and picking:

1. The tablet material and the compression tooling are not properly lubricated.
2. Certain formulations contain hygroscopic or sticky ingredients.
3. The punches and dies have rough surface finishes.
4. Low melting point materials (such as stearic acid and PEG) which may soften from the heat of compression.

Solving of picking and sticking:

1. Addition of lubricants and anti-adherents.
2. Modify the formulation by adding appropriate excipients. For example:
    a. the Addition of binder or changing the binder type may result in more cohesive granules so less adhesive to the punches and die.
    b. Replace low melting point material with high melting point material
3. Engraved letters should be designed as large as possible
4. Further drying of granules

Objective:

To prepare Paracetamol 250 mg tablet using single-punch tablet press

EXPERIMENTAL PART

a. Materials:

Paracetamol, microcrystalline cellulose, croscarmellose sodium, Magnesium stearate.

b. Apparatus:

single-punch tablet press

c. Method:

Formula			
Material Name	mg/tablet	gm/batch	role of action
Paracetamol	250		
Microcrystalline Cellulose (MCC)	227		
Croscarmellose sodium	18		
Magnesium stearate	5		
Total	500.0		

Manufacturing Procedure
1.Weigh the materials in the previous table separately
2. Pass the following materials through 1 mm sieve and mix for 5 minutes manually using double PE. Bags. Paracetamol Microcrystalline Cellulose (MCC) Croscarmellose sodium
3.Add Magnesium stearate to the mixture resulted from step 2 and mix for 1 minutes
4. Compress the resulted mixture using single punch compression machine in the lab.

EXPEREMENT 8

QUALITY CONTROL (QC) OF TABLETS / PART 1

What is quality control?

- Quality control is a small part of QA and it is concerned with sampling,testing and documentation during manufacturing and also after completion of manufacturing.
- It is the monitoring process through which manufacturer measures actual quality performance, compares it with standards and find out the causes of deviation from standard to ensure quality product not once but every time.
- In general terms, quality control refers to a procedure or a setof steps taken during the manufacturing of a product to ensure that it meets requirements and that the product is reproducible.

Why there is a need to perform quality control tests for tablets?

- To ensure safety,potency,efficacy,stability,patient acceptabilityand patient compliance of tablet.
- To check whether a pharmaceutical tablet satisfy certainstandards to claim it to be a quality drug or not
- To check that the quality parameters are within the acceptance limits or not.

These tests categorized as following:

A. Official Pharmacopial Tests:

1. Uniformity of Weight.
2. Uniformity of Drug Content.
3. Disintegration Test.
4. Dissolution Test.
5. Hardness.
6. Friability.

B. Non-Official (Non-Pharmacopial) Tests (in House):

1. Uniformity of Thickness.
2. Uniformity of diameter.

1. Uniformity of weight (mass) (European Pharmacopoia (EP))

In the case of pharmaceutical dosage forms, the weight variation test (also referred to as uniformity of dosage units) is a non-destructive test that compares the individual weights of a sample of tablets with the average weight of the selected sample.

The following tests provide limits for the permissible variations in the weights of individual tablets or capsules, expressed in terms of the allowable deviation from the average weight of a sample.

Test Procedure:

1. Weigh 20 tablets individually (i.e. determine the weight of each tablet alone; X1, X2, X3… X20)
2. Calculate the average weight of tablets = (Total weight of tablets / Number of tablets)

   Average weight of tablets (X) = (X1+X2 +X3+…+ X20)/20

3. %deviation = X1-Average Weight / Average Weight*100%

Acceptance criteria:

Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in table I and no tablet deviates by more than twice that percentage.

Table 8.1: Allowed weight percentage deviations according to EP

Average weight of tablets	Allowed Percentage deviation %
80 mg or less	± 10
More than 80mg and less than 250 mg	± 7.5
250 mg or more	± 5

2. Friability of uncoated tablets (EP)

"This test is intended to determine, under defined conditions, the friability of uncoated tablets, the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition.

Apparatus

Use a drum with an internal diameter between (283 – 291) mm and a depth between (36 – 40) mm, made of a transparent synthetic polymer with polished internal surfaces and not subject to static build-up (see Figure 1). One side of the drum is removable. The tablets are tumbled at each turn of the drum by a curved projection with an inside radius between (75.5 mm - 85.5 mm) that extends from the middle of the drum to the outer wall. The drum is attached to the horizontal axis of a device that rotates at (25 ± 1) r.p.m. Thus, at each turn the tablets roll or slide and fall onto the drum wall or onto each other.

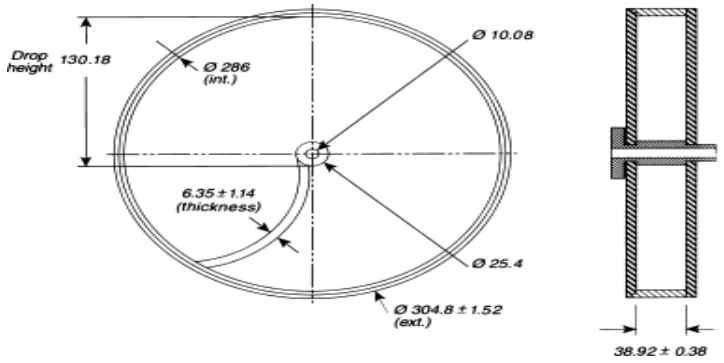
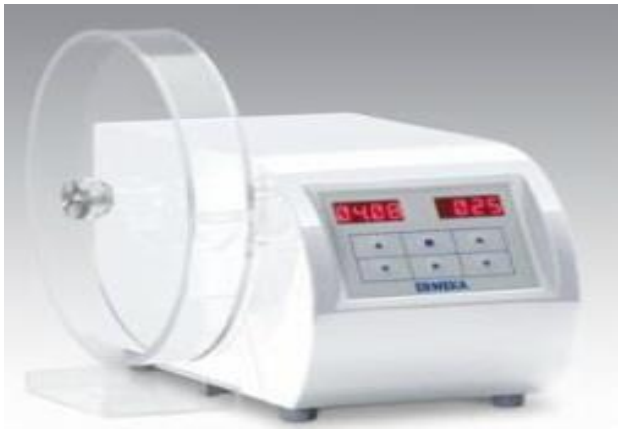


Figure (1): Tablet friability apparatus (*Dimensions are in mm)*



Test Procedure:

1. For tablets with a unit weight equal to or less than 650 mg, take a sample of whole tablets corresponding as near as possible to 6.5 g.
2. For tablets with a unit weight of more than 650 mg, take a sample of 10 whole tablets.

The tablets should be carefully de-dusted prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times (4 minutes if the speed of rotation is 25 r.p.m) , and remove the tablets. Remove any loose dust from the tablets as before, and accurately weigh.

Generally, the test is run once.

The friability test result is expressed as the % mass loss and it is calculated as a following:

$$\% \text{ Weight loss} = \frac{\text{Initial weight} - \text{weight after test}}{\text{Initial weight}} * 100\%$$

Acceptance criteria:

1. If obviously cracked, cleaved, or broken tablets are present in the tablet sample after tumbling, **the sample fails the test.**
2. % Weight loss must not be more than 1%
3. If the results are difficult to interpret or if the weight loss is greater than the targeted value, the test should be repeated **twice** and the **mean of the three tests** determined. A maximum mean weight loss from the three samples of not more than 1.0% is considered acceptable for most products.

NOTE: If tablet size or shape causes irregular tumbling, adjust the drum base so that the base forms an angle of about 10° with the horizontal and the tablets no longer bind together when lying next to each other, which prevents them from falling freely.

3. Hardness Test (EP)

This test is intended to determine, under defined condition, the resistance to crushing of tablets, measured by the force needed to disrupt them by crushing.

This test has been introduced for controlling the mechanical strength of tablets, because it has been difficult to obtain agreement on a standard technique of testing.

Nevertheless, Hardness is an important feature of quality since serious losses can be occurred if tablets are not strong enough to withstand vibration in counting and packing machines since tablets are subjected to packaging, abuse handling by consumers, and coating.

Hardness test is the amount of force needed to crush a tablet. So as pressure compression increases crushing strength increases too.

Apparatus

To perform this test, a tablet is placed between two anvils. Pressure is applied to the anvils, and the crushing strength that just causes the tablet to break is recorded.

Test Procedure:

1. Determine the hardness value for 10 tablets using the specified hardness tester.
2. Calculate the mean of hardness of the10 tablets.
3. units of measurement of tablet hardness mostly follows standards used in materials testing – the International System of Units. Kilogram (kg) , Newton (N)

Acceptance criteria:

There is no pharmacopeial general specification for this test, and the specification differ from product to product and from manufacturer to manufacturer (the results are governed by the house specification**)**

4. THICKNESS

The thickness of a tablet is critical to its therapeutic efficacy since thickness impacts on disintegration and dissolution behavior. In addition, thickness can be a useful indicator of the consistency, or otherwise, of tablet weight which is controlled to ensure dose uniformity. The weight of a compressed tablet is dependent on three factors: **Density**, **Diameter**, **Thickness**.

Though a modern tablet press should provide a good level of uniformity, there are several potential sources of variation, the most important of which is powder flow which can affect the uniformity with which the die is filled before compaction. Mechanical wear and imperfections in the pressing or tooling may also introduce variability, as can the build-up of material on the punch face or die wall during a run. Any of these factors may impact tablet weight and the physical consistency of manufactured tablets.

Monitoring tablet thickness at regular intervals allows potential problems relating to tablet weight and hence content uniformity to be detected and efficiently diagnosed at an early stage. Although thickness of tablets is not included in the pharmacopoeia standards, but it is important to be evaluated as it is one of the methods to control the quality for tablet packaging.

In general, we do not have any tablet thickness limit provided in pharmacobeia, tablet thickness is controlled by the in-house specification. Usually tablets thickness should be controlled with 5% or less of a standard value.

Instrument used to perform test:

Caliper or some Hardness tester measure thickness of tablet.

5. DIAMETER

Tablets are compressed in the pharmaceutical industries using different types of tools including punches & dies on compression machines.Tooling shape and dimensions play an important role to compress the same size & shaped tablets during compression of each batch to maintain batch to batch consistency in terms of shape & diameter/dimensions.

Tablet diameter is dependent on the dimensions of the punch tip or punch face. The tablet diameter or dimensions are mentioned on the first page of the Batch Manufacturing Record (BMR) to ensure that the same-size tablets are compressed all the time during compression of a specific batch using specified tooling.

The tablet diameter testing is a non-official test so most of the person in the pharmaceutical industry do not give much importance to it, but it is most critical check because if our tablet diameter or dimensions are not according to specifications it will create problems not only during tablet blistering but will also lead to deviation and batch reprocessing.

Like the tablet thickness test, the diameter of tablets is also measured using calipers.

The uniformity in diameter of tablets is very important to increase the patient compliance and avoid them from being confuse with different size of the tablets. Different size of the tablets may cause the patient to think that the drugs or tablets have different amount of active ingredient. In general, we do not have any tablet diameter limit provided in pharmacobeia, tablet diameter is controlled by the in-house specification The deviation of individual unit from the mean diameter should not exceed ± 5% for tablets with diameter of less than 12.5mm and ± 3% for diameter of 12.5 mm or more

Objective:

To perform the following QC Tests for Paracetamol 500 mg tablets:

1. Uniformity of weight
2. Friability Test
3. Hardness Test
4. Thickness test
5. Diameter test

EXPERIMENTAL

a. Materials:

Paracetamol 500 mg tablets

b. Apparatus:

Analytical balance, Hardness Tester, Friability tester

c. Method:

NB: all equipment and tools should be cleaned prior to use.

1. **Uniformity of weight Test:**
   a. Measure the weight of 20 tablets individually .
   b. Calculate the Average weight of 20 Tablets.
   c. For each tablet of the 20 tested tablets calculate the Percentage deviation

$$\%\ DEVIATION = \frac{Tablet\ weight - Average\ tablet\ weight}{Average\ tablet\ weight} \times 100$$

   d. Interpretation of the results should be done according to table under UNIFORMITY OF WEIGHT section above.

2. Friability Test:

a. Weight one tablet
    1. if weight of tablet ≤ 650 mg take a sample of whole tablets corresponding as near as possible to 6.5 g.
    2. if weight of tablet > 650 mg , take a sample of 10 whole tablets.

b. Place weighed tablet (record this weight as tablets initial weight) in the drum of the friability tester and close it.

c. Operate the instrument for 4 minutes using 25rpm as rotational speed.

d. After the time elapsed remove the tablets and dust them using a brush.

e. Examine the tablets for any sign of cleaved, cracked or breakage

f. Weigh the tablet and record the weight as tablets final weight.

g. Calculate the Percentage Weight Loss using the following equation

$$Percentage\ Weight\ Loss = \frac{Tablets\ Initial\ Weight - Tablets\ Final\ Weight}{Tablets\ Initial\ Weight} * 100\%$$

3. Thickness, Hardness and Diameter Test:

a. Using the Hardness Tester, measure the thickness, hardness and diameter for 10 tablets.

b. Calculate the mean of the tested values.

Arrange your results in the following tables and calculate the required values using equations mentioned in the procedure section.

A. Uniformity of weight test:

Tablet No.	Tablet weight (g)	Tablet No.	Tablet weight (g)	Tablet No.	Tablet weight (g)	Tablet No.	Tablet weight (g)
1		6		11		16	
2		7		12		17	
3		8		13		18	
4		9		14		19	
5		10		15		20	

Weight of 20 tablets (g): ……

B. Friability test:

Initial Weight (grams)	Final Weight (grams)	Observation (Yes or No)		
		Cleaved	cracked	Breakage

C. Thickness, Hardness and Diameter test:

Tablet No.	Tablet thickness (mm)	Tablet Hardness (N)	Tablet Diameter (mm)
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

Appendix 1
EUROPEAN PHARMACOPOEIA
Uniformity of Weight

the membrane in contact with this surface. Two systems for adhesion to the *cylinder* may be used:

- apply a suitable adhesive to the exposed membrane borders and, if necessary, to the back of the patch,
- apply a double-sided adhesive tape to the external wall of the *cylinder*.

Using gentle pressure, carefully apply the non-adhesive side of the patch to the *cylinder*, so that the release surface is in contact with the dissolution medium and the long axis of the patch fits around the circumference of the *cylinder*.

The system for adhesion used is previously tested for absence of interference with the assay and of adsorption of the active ingredient(s).

Place the *cylinder* in the apparatus, and immediately rotate the *cylinder* at 100 r/min, for example. At determined intervals, withdraw a sample of dissolution medium from a zone midway between the surface of the dissolution medium and the top of the rotating *cylinder*, and not less than 1 cm from the vessel wall.

Perform the assay on each sample as directed in the individual monograph, correcting for any volume withdrawn, as necessary. Repeat the test with additional patches.

Interpretation. The requirements are met if the quantity of active ingredient(s) released from the patch, expressed as the amount per surface area per time unit, is within the prescribed limits at the defined sampling times.

2.9.5. UNIFORMITY OF MASS OF SINGLE-DOSE PREPARATIONS

Weigh individually 20 units taken at random or, for single-dose preparations presented in individual containers, the contents of 20 units, and determine the average mass. Not more than 2 of the individual masses deviate from the average mass by more than the percentage deviation shown in Table 2.9.5.-1 and none deviates by more than twice that percentage.

For capsules and powders for parenteral administration, proceed as described below.

CAPSULES

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 to stand until the odour of the solvent is no longer perceptible. Weigh the shell. The mass of the contents is the difference between the weighings. Repeat the procedure with another 19 capsules.

Table 2.9.5.-1

Pharmaceutical Form	Average Mass	Percentage deviation
Tablets (uncoated and film-coated)	80 mg or less	10
	More than 80 mg and less than 250 mg	7.5
	250 mg or more	5
Capsules, granules (uncoated, single-dose) and powders (single-dose)	Less than 300 mg	10
	300 mg or more	7.5
Powders for parenteral administration* (single-dose)	More than 40 mg	10
Suppositories and pessaries	All masses	5
Powders for eye-drops and powders for eye lotions (single-dose)	Less than 300 mg	10
	300 mg or more	7.5

* When the average mass is equal to or below 40 mg, the preparation is not submitted to the test for uniformity of mass but to the test for uniformity of content of single-dose preparations (2.9.6).

POWDERS FOR PARENTERAL ADMINISTRATION

Remove any paper labels from a container and wash and dry the outside. Open the container and without delay weigh the container and its contents. Empty the container as completely as possible by gentle tapping, rinse it if necessary with *water R* and then with *alcohol R* and dry at 100-105 °C for 1 h, or, if the nature of the container precludes heating at this temperature, dry at a lower temperature to constant mass. Allow to cool in a desiccator and weigh. The mass of the contents is the difference between the weighings. Repeat the procedure with another 19 containers.

30 units is outside 85 per cent to 115 per cent of the average content and none is outside the limits of 75 per cent to 125 per cent of the average content.

TEST B

The preparation complies with the test if not more than one individual content is outside the limits of 85 per cent to 115 per cent of the average content and none is outside the limits of 75 per cent to 125 per cent of the average content. The preparation fails to comply with the test if more than 3 individual contents are outside the limits of 85 per cent to 115 per cent of the average content or if one or more individual contents are outside the limits of 75 per cent to 125 per cent of the average content.

If 2 or 3 individual contents are outside the limits of 85 per cent to 115 per cent but within the limits of 75 per cent to 125 per cent, determine the individual contents of another 20 dosage units taken at random. The preparation complies with the test if not more than 3 individual contents of the 30 units are outside the limits of 85 per cent to 115 per cent of the average content and none is outside the limits of 75 per cent to 125 per cent of the average content.

TEST C

The preparation complies with the test if the average content of the 10 dosage units is between 90 per cent and 110 per cent of the content stated on the label and if the individual content of each dosage unit is between 75 per cent and 125 per cent of the average content.

Appendix 2
EUROPEAN PHARMACOPOEIA
Friability Test

01/2017:20906

2.9.6. UNIFORMITY OF CONTENT OF SINGLE-DOSE PREPARATIONS

The test for uniformity of content of single-dose preparations is based on the assay of the individual contents of active substance(s) of a number of single-dose units to determine whether the individual contents are within limits set with reference to the average content of the sample.

The test is not required for multivitamin and trace-element preparations and in other justified and authorised circumstances.

Method. Using a suitable analytical method, determine the individual contents of active substance(s) of 10 dosage units taken at random.

Apply the criteria of test A, test B or test C as specified in the monograph for the dosage form in question.

TEST A

The preparation complies with the test if each individual content is between 85 per cent and 115 per cent of the average content. The preparation fails to comply with the test if more than one individual content is outside these limits or if one individual content is outside the limits of 75 per cent to 125 per cent of the average content.

If one individual content is outside the limits of 85 per cent to 115 per cent but within the limits of 75 per cent to 125 per cent, determine the individual contents of another 20 dosage units taken at random. The preparation complies with the test if not more than one of the individual contents of the

2.9.7. FRIABILITY OF UNCOATED TABLETS(7)

This chapter provides guidelines for the friability determination of compressed, uncoated tablets. The test procedure presented in this chapter is generally applicable to most compressed tablets. Measurement of tablet friability supplements other physical strength measurements, such as tablet breaking force.

Use a drum, with an internal diameter between 283-291 mm and a depth between 36-40 mm, of transparent synthetic polymer with polished internal surfaces, and subject to minimum static build-up (see Figure 2.9.7.-1.). One side of the drum is removable. The tablets are tumbled at each turn of the drum by a curved projection with an inside radius between 75.5-85.5 mm that extends from the middle of the drum to the outer wall. The outer diameter of the central ring is between 24.5-25.5 mm. The drum is attached to the horizontal axis of a device that rotates at 25 ± 1 r/min. Thus, at each turn the tablets roll or slide and fall onto the drum wall or onto each other.

For tablets with a unit mass equal to or less than 650 mg, take a sample of whole tablets corresponding as near as possible to 6.5 g. For tablets with a unit mass of more than 650 mg, take a sample of 10 whole tablets. The tablets are carefully dedusted prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before, and accurately weigh.

Generally, the test is run once. If obviously cracked, cleaved, or broken tablets are present in the tablet sample after tumbling, the sample fails the test. If the results are difficult to interpret or if the weight loss is greater than the targeted value, the test is repeated twice and the mean of the 3 tests determined. A

(7) This chapter has undergone pharmacopoeial harmonisation. See chapter *5.8. Pharmacopoeial harmonisation.*

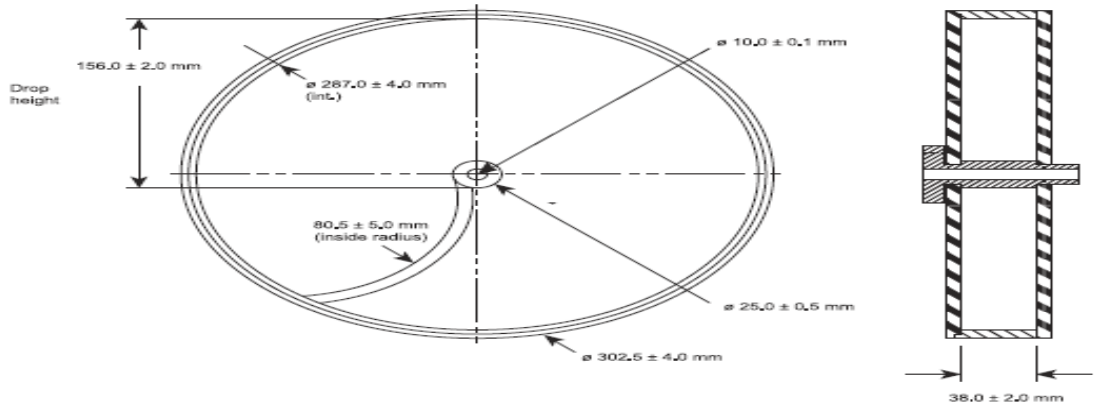


Figure 2.9.7.-1. – *Tablet friability apparatus*

maximum loss of mass (obtained from a single test or from the mean of 3 tests) not greater than 1.0 per cent is considered acceptable for most products.

If tablet size or shape causes irregular tumbling, adjust the drum base so that the base forms an angle of about 10° with the horizontal and the tablets no longer bind together when lying next to each other, which prevents them from falling freely.

Effervescent tablets and chewable tablets may have different specifications as far as friability is concerned. In the case of hygroscopic tablets, a humidity-controlled environment is required for testing.

A drum with dual scooping projections, or apparatus with more than one drum, for the running of multiple samples at one time, are also permitted.

OPERATING PROCEDURE

Place the tablet between the jaws, taking into account, where applicable, the shape, the break-mark and the inscription; for each measurement orient the tablet in the same way with respect to the direction of application of the force. Carry out the measurement on 10 tablets, taking care that all fragments of tablets have been removed before each determination.

This procedure does not apply when fully automated equipment is used.

EXPRESSION OF RESULTS

Express the results as the mean, minimum and maximum values of the forces measured, all expressed in newtons.

Indicate the type of apparatus and, where applicable, the orientation of the tablets.

Appendix 3
EUROPEAN PHARMACOPOEIA
HARDNESS TEST

01/2008:20908

2.9.8. RESISTANCE TO CRUSHING OF TABLETS

This test is intended to determine, under defined conditions, the resistance to crushing of tablets, measured by the force needed to disrupt them by crushing.

APPARATUS

The apparatus consists of 2 jaws facing each other, one of which moves towards the other. The flat surfaces of the jaws are perpendicular to the direction of movement. The crushing surfaces of the jaws are flat and larger than the zone of contact with the tablet. The apparatus is calibrated using a system with a precision of 1 newton.

OPERATING PROCEDURE

Place the tablet between the jaws, taking into account, where applicable, the shape, the break-mark and the inscription; for each measurement orient the tablet in the same way with respect to the direction of application of the force. Carry out the measurement on 10 tablets, taking care that all fragments of tablets have been removed before each determination.

This procedure does not apply when fully automated equipment is used.

EXPRESSION OF RESULTS

Express the results as the mean, minimum and maximum values of the forces measured, all expressed in newtons.

Indicate the type of apparatus and, where applicable, the orientation of the tablets.

EXPEREMENT 9
QUALITY CONTROL (QC) OF TABLETS / PART 2

1. Disintegration Test for Tablets (USP and EP harmonization 2020)

This test is provided to determine whether tablets, capsules, or granules disintegrate within the prescribed time when placed in a liquid medium at the experimental conditions presented below. Compliance with the limits on *Disintegration* stated in the individual monographs is required. Determine the type of units under test from the labeling and from observation, and apply the appropriate procedure to 6 or more dosage units.

For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the disk, if used, is a soft mass
having no palpably firm core.

APPARATUS

The apparatus consists of a basket-rack assembly, a 1000-mL low-form beaker 138–160 mm in height and having an inside diameter of 97–115 mm for the immersion fluid, a thermostatic arrangement for heating the fluid 35°–39°, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate 29–32 cycles/min through a distance of NLT 53 mm and NMT 57 mm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke, the wire mesh remains at least 15 mm below the surface of the fluid and descends to NLT 25 mm from the bottom of the vessel on the downward stroke. At no time should the top of the basket-rack assembly become submerged. The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

Basket-Rack Assembly

The basket-rack assembly consists of 6 open-ended transparent tubes, each 75.0–80.0 mm long and having an inside diameter of 20.7–23 mm and a wall 1.0–2.8 mm thick; the tubes are held in a vertical position by two plates, each 88–92 mm in diameter and 5–8.5 mm in thickness, with 6 holes, each 22–26 mm in diameter, equidistant from the center of the plate and equally spaced from one another. Attached to the under surface of the lower plate is a woven stainless steel wire cloth, which has a plain square weave with 1.8–2.2-mm apertures and with a wire diameter of 0.57–0.66 mm. The parts of the apparatus are assembled and rigidly held by means of 3 bolts passing through the 2 plates. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis. The design of the basket-rack assembly may be varied somewhat, provided the specifications for the glass tubes and the screen mesh size are maintained. The basket-rack assembly conforms to the dimensions found in *Figure 1*.

Disks

The use of disks is permitted only where specified or allowed in the monograph. If specified in the individual monograph, each tube is provided with a cylindrical disk 9.35–9.65 mm thick and 20.55–20.85mm in diameter. The disk is made of a suitable transparent plastic material having a specific gravity of 1.18–1.20. Five parallel 1.9–2.1 mm holes extend between the ends of the cylinder. One of the holes is centered on the cylindrical axis. The other holes are parallel to the cylindrical axis and5.8– 6.2 mm from the axis on imaginary lines perpendicular to the axis and to each other. Four identical trapezoidal-shaped planes are cut into the wall of the cylinder, nearly perpendicular to the ends of the cylinder. The trapezoidal shape is symmetrical; its parallel sides coincide with the ends of the cylinder and are parallel to an imaginary line connecting the centers of two adjacent holes 6 mm from the cylindrical axis. The parallel side of the trapezoid on the bottom of the cylinder has a length of 1.5–1.7 mm, and its bottom edges lie at a depth of 1.5–1.8 mm from the cylinder's circumference. The parallel side of the trapezoid on the top of the cylinder has a length 9.2–9.6 mm, and its center lies at a depth 2.5–2.7 mm from the cylinder's circumference. All surfaces of the disk are

smooth. If the use of disks is specified in the individual monograph, add a disk to each tube, and operate the apparatus as directed under *Procedure*. The disks conform to dimensions found in *Figure 1*.

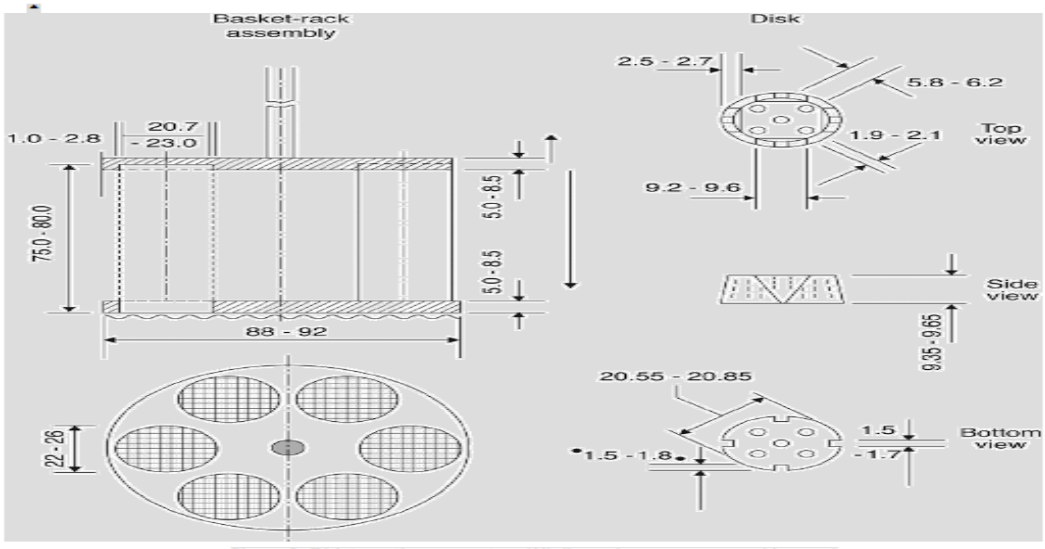
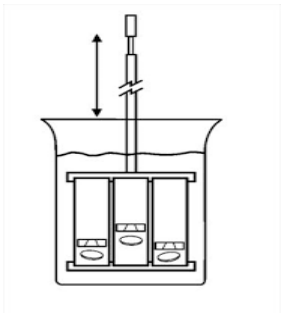


Figure 1. Disintegration apparatus. (All dimensions are expressed in mm.)



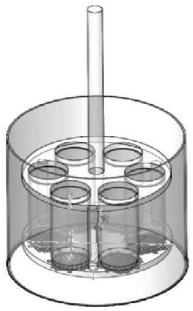


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Figure 2. Disintegration apparatus

PROCEDURE AND CRITERIA

PROCEDURE FOR UNCOATED OR PLAIN-COATED TABLETS:

1. Place 1 dosage unit in each of the 6 tubes of the basket rack assembly and, if prescribed, add a disk.
2. Operate the apparatus, using water or the specified medium as the immersion fluid, maintained at 37 ± 2°. At the end of the time limit specified in the monograph, lift the basket rack assembly from the fluid, and observe the tablets. All of the tablets should have disintegrated completely.

CRITERIA FOR UNCOATED OR PLAIN-COATED TABLETS:

1. If 6 tablets are tested, all 6 of the tablets are disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets.
2. If 18 tablets are tested, the requirement is met if not fewer than 16 of the total of 18 tablets are disintegrated.

Uniformity of drug Content (USP AND EP Harmonization 2011)

To ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of drug substance in each unit. The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance Among dosage units. Therefore, the requirements of this chapter apply to each drug substance being comprised in dosage units containing one or more drug substances, unless otherwise specified elsewhere in this Pharmacopeia. The uniformity of dosage units can be demonstrated by either of two methods, *Content Uniformity* or *Weight Variation* . The test for *Content Uniformity* of preparations presented in dosage units is based on the assay of the individual content of drug substance(s) in a number of dosage units to determine whether the individual content is within the limits set. The *Content Uniformity* method may be applied in all cases.

The test for Weight *Variation* is applicable for uncoated tablets, or film-coated tablets, containing 25 mg or more of a drug substance comprising 25% or more, by weight, of the dosage unit except that uniformity of other drug substances present in lesser proportions is demonstrated by meeting the requirements for Content Uniformity.

To ensure constant dose distribution of drug between tablets, dose variation between tablets is tested in two separate tests;

1- Weight uniformity
2- Content uniformity

A) (Weight uniformity test) is enough If the drug forms greater part of the tablet (more than ≥25 mg and ≥ 25%), any variation in the tablet weight obviously indicates a variation in the active ingredient.

B) (Content uniformity) must be performed If the drug is potent (USP specifies less than < 25 mg of the active ingredient, or comprising < 25% by weight of unit), the excipients form the greater part of the tablet weight and the correlation between the tablet weight and amount of the active ingredient can be poor.

PROCEDURE AND CRITERIA

IF (Content uniformity) is required to test the uniformity of the drug content use a suitable analytical method and apply the criteria of test A, test B or test C as specified in the monograph for the dosage form in question.

Test Procedure:

1. For a sample of 10 randomly selected tablets, Determine the amount of drug in each tablet
2. Calculate the average drug content and the % of the labeled drug content of each tablet as follow:

$$\%content = Actual\ content/Claimed\ or\ Labeled\ content * 100\%$$

Acceptance criteria:

1. The preparation complies with the test if each individual content is between 85 per cent and 115 per cent of the labeled content.
2. The preparation fails to comply with the test if more than one individual content is outside these limits or if one individual content is outside the limits of 75 per cent to 125 per cent of the labeled content.
3. If one individual content is outside the limits of 85 percent to 115 per cent but within the limits of 75 per cent to 125 per cent, determine the individual contents of another 20 dosage units taken at random. The preparation complies with the test if not more than one of the individual contents of the 30 units is outside 85 per cent to 115 per cent of the labeled content and none is outside the limits of 75 per cent to 125 per cent of the labeled content.

Objective:

To perform the following QC Tests for Famotidine 20mg Tablet

1) Disintigration test
2) Content uniformity test

Experimental Part

Part 1 : Disintegration Test

a. Material and Instrument needed:

I. Famotidine 20 mg Tablet

II. Disintegration Tester

III. Water

1. Select 6 tablet of product you want to test
2. Prepare disintegration medium and wait till temperature reached 35-39C
3. Put one tablet in each tube of basket assembly
4. Start the test
5. Record time needed for 6 tablet to disintegrate completely

Part 2: Content Uniformity test

a. **Material and Instrument needed:**
    I. **Famotidine 20 mg Tablet**
    II. **UV spectrophotometer**
    III. **Sonicator**
    IV. **Centrifuge**
    V. **Volumetric flask 50ml , 100 ml**
    VI. **Graduated pippite**
    VII. **Phosphate buffer pH 4.5 (** Phosphate buffer (0.1 M) pH 4.5 ; Prepared by dissolving 13.6 mg of potassium dihydrogen phosphate in one litter water)

Sample preparation:

1. Transfer one tablet to 50 ml volumetric flask.
2. Add 30 ml of phosphate buffer pH 4.5
3. Sonicate for 15 minutes.
4. Complete the volume to 50 ml with solvent and shake.
5. Filter the sample using centrifuge (take 10 ml and transfer to plastic centrifuge tubes)
6. Dilute 2.0 ml of filtrate, and transfer to 100 ml volumetric flask and complete volume with phosphate buffer pH 4.5.
7. Repeat the procedure for another 9 tablets
8. Measure the absorbance of each sample (use buffer as blank) at Wave length: 228 nm
9. Calculate the % content (assay) of Famotidine in each tablet according to the following table.

Tablet no.	absorbance	Diluted Concentration mg/ml	Dilution factor	Concentration mg/ml	Actual Famotidine content mg	% of the labeled drug content
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						

Using calibration curve equation:

Y = slope * x + y-intercept

Concentration (mg/ml) = (absorbance – y intercept) / slope

Concentration (mg/ml) =

diluted concentration * dilution factor

$$\boldsymbol{dillution\ factor} = \frac{\boldsymbol{final\ volume}}{\boldsymbol{intital\ volume}}$$

Example:

$$\boldsymbol{dillution\ factor} = \frac{\mathbf{100}}{\mathbf{2}} = \mathbf{50}$$

Actual Famotidine content mg =

Concentration (mg/ml) * volume (ml)

Example:

$$\textbf{Famotidine content mg} = \boldsymbol{contentration} \times \mathbf{50\ ml}$$

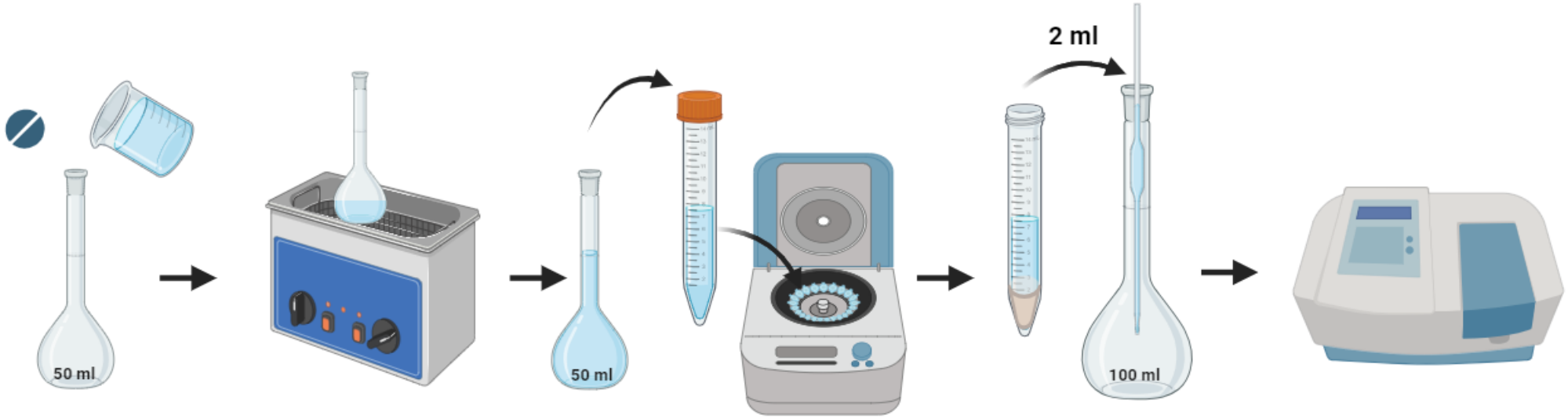
% of the labeled drug content =

$$\frac{actual\ famotidine\ content\ (mg)}{labelet\ famotidine\ content\ (mg)} \times 100$$

Example:

$$\frac{actual\ famotidine\ content\ (mg)}{20} \times 100$$

Famotidine tablets – drug content test



Transfer one tablet to 50 ml volumetric flask.

Add about 30 ml of solvent.

Sonicate for 15 minutes.

Complete the volume to 50 ml

Transfer the sample to a centrifuge tube and centrifuge the sample at 4000 rpm for 5 minutes

From the supernatant, take 2 ml and complete the volume up to 100 with solvent.

Measure the absorbance of the sample.

Note: Repeat the procedure for 10 tablets