



الجامعة الألمانية الأردنية  
German Jordanian University

School of Applied Medical Sciences (SAMS)

# Pharmaceutical Technology – Solid Forms Laboratory Manual (PCE374)

Edition: 2022

## Course Description:

The series of practical classes provides advanced skills in the area of pharmaceutical technology and has particular emphasis on the methods, materials and testing procedures associated with the manufacture of pharmaceutical grade tablets. Experiments illustrate the flow properties of powders, mixing and milling of powders, wet and dry granulation methods, powder particle size analysis, evaluation of granules flow properties, studying the effect of excipients on granules flow properties, quality control tests, tableting technology, and dissolution of dosage forms.

## Course aims and outcomes:

### A- Aims:

1. To be able to conduct pre-formulation studies
2. To recognize various processes and equipment used in the unit operation: particle size analysis, size reduction, mixing and drying.
3. To understand the consolidation process of solid dosage forms and the operation of tablet presses.
4. To recognize various manufacturing methods for solid dosage forms
5. To recognize the ingredients used in the formulation of solid dosage forms
6. To evaluate physical and release properties of solid dosage forms
7. To recognize the problems encountered during the manufacturing of solid dosage forms

### B- Course Intended Learning Outcomes :

Upon successful completion of this course students will be able to ...

#### a. Knowledge and understanding:

1. To be able to describe the commonly used equipment used in the operation unit: particle size analysis, size reduction, mixing and drying.
2. To be able to operate some equipment used in size reduction, mixing and drying.
3. To be able to describe the consolidation process of powders and the operation of equipment used for solid powder consolidation.

4. To recognize various manufacturing process for solid dosage forms with their advantages, utility, and limitations: wet granulation, double compression or slugging and direct compression.
5. To know the categories of inactive ingredient used in the manufacturing of solid dosage forms, the function of each category and examples of each category.
6. To know various problems encountered during the manufacturing of solid dosage forms, such as capping, weight variation, and sticking, and the possible remedies for each problem.
7. To be able to perform quality control tests for the intermediate and final solid dosage forms.  
These tests include compressibility, flow rate, weight variation, friability, hardness, disintegration and dissolution.
8. To be able study and evaluate physical and release properties of solid dosage forms.

**b. Intellectual skills:**

1. To be able to analyze and present the data obtained from the unit operation unit, such as particle size analysis after size reduction.
2. To be able to suggest formulations and manufacturing procedure for solid dosage forms.
3. To be able to suggest remedies for the problems encountered during the manufacturing of solid dosage forms.

**c. Subject-specific skills:**

1. Deductive reasoning
2. Numerical Analysis
3. Written/oral communication
4. Information retrieval and analysis
5. Practical application of theory
6. Report writing

**d. Transferable skills**

1. To gains knowledge and analytical skills to work with people in pharmaceutical firms.

2. To have the ability for quick adaptation to the working environment in pharmaceutical firms
3. To have the ability to deal with and suggest solutions to the problems encountered during the manufacturing process of pharmaceutical dosage forms in pharmaceutical firms.

## TABLE OF CONTENTS

### Contents

Course Description: .....	i
STUDENT GRADING AND EVALUATION .....	v
REPORTS EVALUATION .....	vi
EXPERIMENT 1 .....	1
SOLUBILIZATION OF MEFENAMIC ACID.....	1
Experiment 2 .....	10
POWDER MIXING .....	10
Experiment 3 .....	18
SIZE REDUCTION OF POWDERS.....	18
Experiment 4 .....	26
CHARACTERIZATION OF GRANULES.....	26
EXPIREMENT 5 .....	44
TABLETS PREPARATION AND TESTING .....	44
EXPERIMENT 6 .....	2
QUALITY CONTROL OF TABLETS .....	2
EXPERIMENT 7 .....	12
DISSOLUTION TEST OF TABLETS.....	12
EXPERIMENT 8 .....	20
CONSISTENCY OF FORMULATED PREPARATIONS: CAPSULES COMPOUNDING AND UNIFORMITY OF ITS WEIGHT .....	20
EXPERIMENT 9 .....	23
DISINTEGRATION OF TABLETS AND CAPSULES .....	23

## STUDENT GRADING AND EVALUATION

- **Reports (20%)**

Each week students should provide reports of the previous week's experiments. Reports are graded individually and not as groups (check the next section of the manual on how reports will be graded).

- **Quizzes (30%)**

A maximum of two quizzes will be given this semester.

- **Laboratory Evaluation (10%)**

**No student is allowed in the lab without their lab coat, lab manual, lab notebook, lab goggles and markers.**

Each student is evaluated weekly based on the following points:

A. Attendance punctuality.

B. Behavior in the laboratory and adherence to basic lab requirements.

C. Team work spirit.

D. Mastering the technique.

E. Oral Discussion during the lab: each student will be asked about certain point in the experiment during the practical session.

- **Final Exam (40%)**

The final exam will be a written test, which includes MCQs and essay questions from all of the experiments taken during the semester.

## REPORTS EVALUATION

### Typical Components of a Laboratory Report

#### 1. Title Page

Please include lab number and title, Student name, date submitted, course code.

**2. Results and discussion :** Not more than two pages long (words excluding graphs and or the recorded readings; avoid blank pages)

-The length of your results section will depend on the experiment.

-All of your data and observations go into this section, in table form. Attach any graphs printed out in the lab. This should be the easiest section to write.

-Provide sample calculations for key elements of the lab: dilutions, standard curve use, etc.

-Make sure you:

1. Properly label all graph axes;

2-Always report the units with each measurement;

3-Report your parameters with the appropriate number of significant Digits.

Then discuss your results:

a) Summarize the key scientific idea(s) behind the lab. If there was a key equation , report it here and describe its significance.

b) Did the results confirm or refute the scientific principles involved? Discuss the precision of your data (e.g. how good the  $r^2$  was of a fitted linear regression). Were the results obtained what you expected? Sometimes in the lab you may observe a trend opposite to what you were expecting. It is up to you to either re-evaluate your understanding of the phenomena, or try to identify the sources of error

#### 3. Conclusions

Conclusions are relatively short compared to the discussion. They are typically 1-2 paragraphs, and serve as the bottom line of the lab. In sentence form, report the final estimated values of parameters, and summarize the results/discussions with a closing thought. Recommendations for future work or how the lab could change may also be included here.

#### 7. References

Include literature references you referred to in this section. If you did not refer to the references , you do not need to include them here.

#### 8. Appendices

You may include extra calculations, additional information, and supplementary analyses attached as appendices.

## GENERAL NOTES FOR WRITING THE REPORTS

- Acronyms of any materials, test names, etc. should be mentioned in full form the first time they are used.  
Example: Writing API is not accepted, instead you are expected to write active pharmaceutical ingredient (API) then use the API acronym in the rest of the report.
- Use only scientific language. This/that/here/there/so are not accepted.  
For example: instead of using “So” use therefore, due to or as a result, instead of using “This” or “That” write the previously mentioned material or mention the name of it.
- Copying the exact words from books, articles or even internet pages is not acceptable. Instead copy the needed information then change the sentence using your own words and finally add the reference used to the last page of the report.
- If the report contains more than 15 major spelling errors your score will be affected. (Read the report twice at least before printing it).
- When writing the report use the scientific name of the drugs, trade name shouldn't be used alone.  
Example: Revanin is not acceptable, use [Paracetamol] or [Revanin<sup>®</sup> (Paracetamol)].

## Cheating regulations

- Cheating is defined as conduct (whether successful or not) aimed at deceiving the University into acknowledging a false level of attainment by a student. Cheating including assisting someone else to cheat (including attempting to assist someone else to cheat) may be subject to disciplinary action in accordance with the University's Disciplinary Procedure.
- Any form of cheating is strictly forbidden under this regulation but, in order to assist understanding, a number of specific forms of cheating are described. These include but are not limited to the following examples:
  - Submitting other people's work as your own - either with or without their knowledge. This includes copying reports; using notes or unauthorised materials in examinations; submitting work you have paid for as your own; impersonation - taking an assessment on behalf of or pretending to be another student, or allowing another person to take an assessment on your behalf or pretend to be you.
  - Plagiarism - taking or using another person's thoughts, writings or inventions as your own. To avoid plagiarism you must make sure that quotations from whatever source



are clearly identified and attributed at the point where they occur in the text of your work by using one of the standard conventions for referencing.

- Collusion - except where written instructions specify that work for assessment may be produced jointly and submitted as the work of more than one student, you must not collude with others to produce a piece of work jointly, copy or share another student's work or lend your work to another student when it is likely that some or all of it will be copied.
- Duplication - submitting work for assessment that is the same as, or broadly similar to, work submitted earlier for academic credit, without acknowledgement of the previous submission.
- Falsification - the invention of data, its alteration, its copying from any other source, or otherwise obtaining it by unfair means, or inventing quotations and/or references.
- Custom Writing Services - this includes the use of any service which produces custom materials. The University may consider any request placed with any form of custom writing service to be a form of cheating, whatever use is then made of the material produced, and therefore to be an offence under the University Regulations.
- Assisting Others to Cheat - The University considers assisting others to cheat (including attempting to assist someone else to cheat) as a form of cheating.

<b>Regulations</b>	
<b>Signing the Consent Form</b>	During your first lab session you have to read and sign the consent form given in the next page of this manual and hand it to your TA (or instructor).
<b>Attendance</b>	Lab session attendance is mandatory. The student is allowed maximally 15% absentia of the total module hours. According to the rules you are allowed to be absent maximum for 2 lab session (even with excuses). More than this percentage, a student with an excuse will be drawn from the module. Otherwise, the student will be deprived from the module with zero mark assigned.
<b>Online-sessions</b>	Regarding the online-given lab sessions:  If you don't submit your report on the assigned time, you will be considered ' <u>absent</u> ' on that session.
<b>Reports</b>	You have to depend on yourself to prepare your report. Copying from each other is NOT allowed. <b>Similar copies of reports will be graded ZERO.</b>  You may discuss together, search for the solution or ask your instructor or TA; but at the end you should write the answers in your own language.



الجامعة الألمانية الأردنية  
German Jordanian University

## School of Applied Medical Sciences

### Pharmaceutical Technology – Solid Forms Lab. – (PCE374)

# Consent Form

Student Full Name:

Student ID Number:

Student Emergency Contact Telephone Number:

I hereby acknowledge receipt of safety codes and procedures that are required in the current edition of SAMS/PCE department safety regulations, all of which I have read, instructed, viewed, understood and agree to observe. Moreover, I will be aware of my special risks with the work I am doing and that should use protective equipment without any exemption. My own health and that of safety and that of others depend on this. In addition, it is my responsibility to cooperate with safety measures and seek consultation from lab supervisor about any unclear procedure/statement. I understand that I have registered in this practical course with the number of students decided by the PCE administrative department and I understand that the instructors in this course applied their best to keep people apart to help reduce the spread of coronavirus (COVID-19). On that aspect I will be committed to 1) have face covering to minimize the time of sharing breathing zone; 2) to be apart from my colleagues or staff by 2 meters through following floor tapes or signage to remember this social distancing; 3) to work side by side or facing away rather than face to face; 4) to limit the movement and follow the instructor regulations to rotate between equipment/tools; 5) to limit touching of surfaces or any stuff I will not use and to keep myself belongings without sharing ; 6) to report your concern of developing any of COVID 19 symptoms\*; 7) to safely discard disposable items and clean reusable ones thoroughly; and 8) to ensure washing my hand thoroughly with soap and water (20 seconds) or an alcohol-based hand sanitizer as soon as possible before and after entering the laboratory assigned hall. Otherwise of all the above I understand that my activity will be stopped, and the staff will end my class.

Signed.....

Date.....

**Instructor:**

**TA:**

\*The main symptoms of coronavirus are:

- a high temperature – this means you feel hot to touch on your chest or back (you do not need to measure your temperature)
- a new, continuous cough – this means coughing a lot for more than an hour, or 3 or more coughing episodes in 24 hours (if you usually have a cough, it may be worse than usual)
- a loss or change to your sense of smell or taste – this means you've noticed you cannot smell or taste anything, or things smell or taste different to normal.

Most people with coronavirus have at least one of these symptoms. Once you report any of these symptoms you are recommended to kindly leave the class and visit the **university clinic** and we will give you all the support needed, so please keep us posted so we can assist you and trace your case.

# EXPERIMENT 1

## SOLUBILIZATION OF MEFENAMIC ACID

### OBJECTIVES:

To evaluate various approaches to solubilize a weakly acidic drug (Mefenamic acid):

1. pH solubility profile: the solubility will be checked in different buffer systems.
2. The solubility at constant pH and variable concentration of a co-solvent (ethanol).
3. Salt formation: Sodium salt of the drug will be prepared and checked for solubility improvement.

### INTRODUCTION:

Before a drug becomes available to its receptors, it should be dissolved in the biological fluids surrounding the receptors; therefore, solubility is an important subject in pharmaceutical sciences. There is a solubility problem with nearly 40% of the drug candidates, and any attempt to predict the solubility is quite important in drug discovery investigations.

The oldest rule for solubility prediction is “like dissolves like”. Water is the unique biological solvent and aqueous solubility is one of the most important physicochemical properties (PCPs) of drugs. Aqueous solubility is also a key factor in the design of oral, parenteral, and ophthalmic formulations of poorly water-soluble drugs. **Solubility is defined as the maximum quantity of a drug dissolved in a given volume of a solvent/ solution at specific temperature.**

For ionizable drugs, the solubility could be affected by the pH of the solution, and the intrinsic solubility ( $S_0$ ) is defined as the concentration of a saturated solution of the neutral form of the drug in equilibrium with its solid. The United States Pharmacopeia classified the solubilities of drugs into seven classes, as listed in Table 1.

**TABLE 1. DESCRIPTIVE CLASSIFICATION OF DRUG SOLUBILITY. <sup>(1)</sup>**

<b>Parts of Solvent Required for Dissolving One Part of the Solute</b>	
Very soluble	<1
Freely soluble	1–10
Soluble	10–30
Sparingly soluble	30–100
Slightly soluble	100–1,000
Very slightly soluble	1,000–10,000
Practically insoluble	>10,000

Aqueous solubility has an essential role in the bioavailability of oral drug formulations. There is an established classification, namely, the biopharmaceutical classification system (BCS), which divides drugs into four classes in terms of their solubility and permeability. The BCS classification correlates the in-vitro solubility and permeability to the in-vivo bioavailability.

Soluble and permeable drugs are class I drugs with oral bioavailability being limited by their ability to reach the absorption sites. Class II drugs are poorly soluble but permeable drugs through the gastrointestinal tract (GI), meaning that their oral absorption is limited by the drug's solubility and, as a consequence of the Noyes–Whitney equation, by their dissolution rate. Class III drugs are soluble but poorly permeable and their oral bioavailability is limited by the barrier properties of the GI tract. Drugs of class IV are low soluble and poorly permeable compounds with the limitations of classes II and III.

The drug candidates of class I possess suitable bioavailabilities and show appropriate drugability potentials; the bioavailability of drug candidates of class II can potentially be improved by developing suitable formulation designs, while those that belong to classes III and IV are most likely to return to the lead optimization phase for the improvement of their PCP. Table 2 lists the details of the BCS along with a number of examples for each class.

**TABLE 2. BIOPHARMACEUTICAL CLASSIFICATION SYSTEM<sup>(2)</sup>**

	<b>High Solubility</b>	<b>Low Solubility</b>
High permeability	Class I Acetaminophen Caffeine Prednisolone Phenobarbital Diazepam	Class II Flurbiprofen Warfarin Carbamazepin Grisofulvin Phenytoin
Low permeability	Class III Acyclovir Allopurinol Atenolol Captopril Famotidine	Class IV Acetazolamide Azathioprine Chlorthiazide Furosemide Mebendazole

## SOLUBILIZATION OF DRUGS

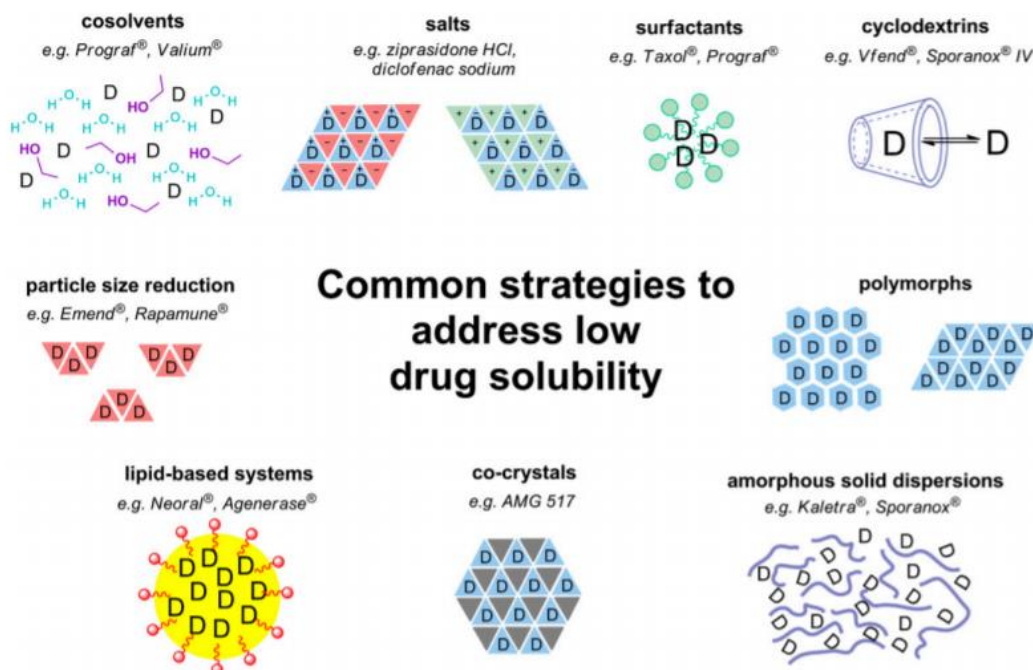
There are several methods to enhance the aqueous solubility of drugs including cosolvency, hydrotropism, complexation, ionization, and the use of surface active agents.

### Cosolvency

In cosolvency mixing a permissible nontoxic organic solvent with water is the most common technique to enhance the aqueous solubility of drugs. The common cosolvents that are used in the pharmaceutical industry are ethanol, propylene glycol, glycerine, glycofural, polyethylene glycols (PEGs) (mainly 200, 300, and 400), N, N-dimethyl acetamide, and room temperature ionic liquids.

### Salt formation

A drug substance often has certain suboptimal physicochemical or biopharmaceutic properties that can be overcome by pairing a basic or acidic drug molecule with a counter ion to create a salt. The process gives an enhanced solubility of drug which causes a remarkable change in the biopharmaceutic characteristics of the poorly soluble and poorly bioavailable drugs. The salt formation method is a simple way to modify the properties of a drug with ionizable functional groups to overcome undesirable features of the parent drug.



**FIGURE 1. COMMON STRATEGIES CURRENTLY USED TO ADDRESS LOW DRUG SOLUBILITY IN DRUG DISCOVERY AND DEVELOPMENT.<sup>(3)</sup>**

### Preparation of Buffers

A compound can buffer the pH of a solution only when its concentration is sufficient and when the pH of the solution is close (within about one pH unit) to its pKa. To make a buffer you must first pick a compound whose **pKa is close to the pH** you want for the solution, and then decide what the buffer concentration should be. Typically, buffer **concentrations** are between 1 mM and 200 mM, depending on the desired ionic strength and the buffering capacity required.

If the pH is expected to decrease during the experiment, choose a buffer with a pKa slightly below the working pH. Conversely, if the pH is expected to increase during the experiment, select a buffer with a pKa slightly above the working pH.

Having decided on the total buffer concentration, **you must adjust the ratio of the protonated and unprotonated forms of the buffer in your solution to give the desired pH.**

Typically, buffers are composed of weak acids and their salts, or weak bases and their salts. If the protonated form is uncharged, it is an acid (like acetic acid), and its unprotonated form is a salt (e.g., sodium acetate). Conversely, if the unprotonated form is uncharged it is a base (like Tris base), and its protonated form is a salt (e.g., TrisHCl).

Two practical ways to make a buffer are described below:

#### 1- The simple but slow method

To avoid adding extra salt to a solution, prepare a buffer composed of an acid and its salt by dissolving the **acid form of the buffer** in about **~60% of the water** required for the final solution volume then adjust the pH using a strong base, such as **NaOH**. When preparing a buffer composed of a base and its salt, **start with the base form** and adjust the pH with strong acid, **such as HCl**.

After the pH is adjusted, dilute to just **under the final solution volume**. Check the pH and correct if necessary, then add water to the final volume.

Main drawbacks: **Slow**, May require **lots of base (or acid)**, If the base (or acid) is concentrated, it is easy to **overshoot the pH**, If the base (or acid) is dilute; it is easy to **overshoot the volume**, Ionic strength will be unknown and Adding a strong acid or base can result in temperature changes which will make pH readings inaccurate (due to its dependence on temperature) unless the solution is brought back to its initial temperature.

## 2- The Mentally Taxing Method

Using the buffer **pKa**, calculate the amounts (in **moles**) of acid/salt or base/salt present in the buffer at the desired pH. If both forms (i.e., the acid and the salt) are available, convert the amount required **from moles to grams**, using the molecular weight of that component, and then weigh out the correct amounts of both forms.

**Decide what the total concentration** of buffer will be in the solution, and convert the concentration to amount (in moles) >>> using the volume of solution, and then >>> to grams, using the molecular weight of the buffer form available.

Then calculate the **amounts (in moles)** of each form that will be present in the final solution, using the **buffer pKa and the desired pH**.

Advantages: Fast, easy to prepare, additional pH adjustment is rarely necessary, and when necessary, the adjustment is small and ionic strength is easily calculated.

Disadvantages: Requires the buffer pKa and solving two equations.

The following is further illustration on how to prepare a buffer according to the mentally taxing Method



## I. Decide on the Buffer Properties

Before making a buffer, you must know what **molarity** you want it to be, what volume to make and what the desired pH is. Most buffers work best at concentrations between **0.1 M and 10 M**.

The pH should be within 1 pH unit of the acid/ conjugate base pKa. For simplicity, this sample calculation will be for 1 L of buffer. The following table (Table 1) shows some of acid-base conjugates and their pKa value.

If you need a buffer of pH 5 you can use acetic acid and sodium acetate or benzoic acid and sodium benzoate.

If you need a pH of 3.5 you can use citric acid and sodium citrate (mono).

If you need a pH of 7.4 you can use  $\text{H}_2\text{PO}_4^-$  (dihydrogen phosphate such as potassium phosphate monobasic)  $\text{HPO}_4^{2-}$  (hydrogen phosphate such as potassium phosphate dibasic).

**Table 1. Weak Acids and their Ka and pKa values.** <sup>(4)</sup>

Weak Acid	Equation	$K_a$	pK <sub>a</sub>
acetic acid	$\text{HC}_2\text{H}_3\text{O}_2 \rightleftharpoons \text{H}^+ + \text{C}_2\text{H}_3\text{O}_2^-$	$1.8 \times 10^{-5}$	4.74
ammonium ion	$\text{NH}_4^+ \rightleftharpoons \text{H}^+ + \text{NH}_3$	$5.6 \times 10^{-10}$	9.25
benzoic acid	$\text{C}_6\text{H}_5\text{CO}_2\text{H} \rightleftharpoons \text{H}^+ + \text{C}_6\text{H}_5\text{CO}_2^-$	$6.4 \times 10^{-5}$	4.19
carbonic acid (1)	$\text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^-$	$4.3 \times 10^{-7}$	6.37
carbonic acid (2)	$\text{HCO}_3^- \rightleftharpoons \text{H}^+ + \text{CO}_3^{2-}$	$5.6 \times 10^{-11}$	10.2
chlorous acid	$\text{HClO}_2 \rightleftharpoons \text{H}^+ + \text{ClO}_2^-$	$1.2 \times 10^{-2}$	1.91
formic acid	$\text{HCHO}_2 \rightleftharpoons \text{H}^+ + \text{CHO}_2^-$	$1.8 \times 10^{-4}$	2.74
hydrocyanic acid	$\text{HCN} \rightleftharpoons \text{H}^+ + \text{CN}^-$	$6.2 \times 10^{-10}$	8.21
hydrofluoric acid	$\text{HF} \rightleftharpoons \text{H}^+ + \text{F}^-$	$7.2 \times 10^{-4}$	2.14
hypobromous acid	$\text{HOBr} \rightleftharpoons \text{H}^+ + \text{OBr}^-$	$2 \times 10^{-9}$	7.7
hypochlorous acid	$\text{HOCl} \rightleftharpoons \text{H}^+ + \text{OCl}^-$	$3.5 \times 10^{-8}$	6.46
hypoiodous acid	$\text{HOI} \rightleftharpoons \text{H}^+ + \text{OI}^-$	$2 \times 10^{-11}$	9.7
lactic acid	$\text{CH}_3\text{CH}(\text{OH})\text{CO}_2\text{H} \rightleftharpoons$	$1.38 \times 10^{-4}$	3.86
	$\text{H}^+ + \text{CH}_3\text{CH}(\text{OH})\text{CO}_2^-$		
nitrous acid	$\text{HNO}_2 \rightleftharpoons \text{H}^+ + \text{NO}_2^-$	$4.0 \times 10^{-4}$	2.4
phenol	$\text{HOC}_6\text{H}_5 \rightleftharpoons \text{H}^+ + \text{OC}_6\text{H}_5^-$	$1.6 \times 10^{-10}$	8.8
phosphoric acid (1)	$\text{H}_3\text{PO}_4 \rightleftharpoons \text{H}^+ + \text{H}_2\text{PO}_4^-$	$7.25 \times 10^{-3}$	2.14
phosphoric acid (2)	$\text{H}_2\text{PO}_4^- \rightleftharpoons \text{H}^+ + \text{HPO}_4^{2-}$	$6.31 \times 10^{-8}$	7.2
phosphoric acid (3)	$\text{HPO}_4^{2-} \rightleftharpoons \text{H}^+ + \text{PO}_4^{3-}$	$3.98 \times 10^{-13}$	12.4

## II. Determine the Ratio of Acid to Base

Use the **Henderson-Hasselbalch equation** to determine what ratio of acid to base is required to make a buffer of the desired pH. Use the pKa value nearest your desired pH and the ratio will refer to the acid-base conjugate pair that corresponds to that pKa.

### Example:

Prepare 500 mL of a 0.1 M buffer solution with a pH of 5.0 using acetic acid and sodium acetate.

**Solution:**

The Mass Method will be used here. The conjugate acid-base pair to be used is acetic acid,  $\text{C}_2\text{H}_5\text{O}^2$  and acetate ion,  $\text{C}_2\text{H}_4\text{O}^{1-}$ , to be represented as HA and  $\text{A}^-$ , respectively. From the Henderson-Hasselbach Equation we have:

$$\text{Log} ([\text{A}^-]/[\text{HA}]) = \text{pH} - \text{pK}_a$$

where  $\text{pK}_a$  is the  $\text{pK}_a$  of the conjugate acid, acetic acid, in this case. Therefore:

$$\text{pK}_a = -\log(1.86 \times 10^{-5}) = 4.74.$$

Substitution into the equation above gives:

$$\text{Log} ([\text{A}^-]/[\text{HA}]) = 5.00 - 4.75 = 0.25$$

And:

$$([\text{A}^-]/[\text{HA}]) = 10^{0.25} = 1.77$$

We must prepare a solution with this ratio of concentrations. **Note, that this is also a mole ratio:**

$$n_{\text{A}^-}/n_{\text{HA}} = 1.77$$

The total concentration of conjugate acid and conjugate base is 0.1 M. Therefore:

$$(n_{\text{A}^-} + n_{\text{HA}}) / 0.500 \text{ L} = 0.10 \text{ M}$$

From the previous equation:

$$n_{\text{A}^-} = 1.77 n_{\text{HA}}$$

And therefore,

$$(1.77 n_{\text{HA}} + n_{\text{HA}}) / 0.500 \text{ L} = 0.10 \text{ M}$$

Solving for  $n_{\text{HA}}$  gives:  $n_{\text{HA}} = 0.018 \text{ mol}$ .

$$n_{\text{A}^-} = 0.0177 \times 1.82 = 0.032 \text{ mol}.$$

In this case,  $n_{\text{HA}}$  and  $n_{\text{A}^-}$  are the moles of acetic acid and acetate ion, respectively, that must be added to 500 mL of solution.

Note that although the conjugate base is acetate ion, **it must be weighed out as Sodium Acetate.**

The molar masses of acetic acid and sodium acetate are 60.05 g/mol and 82.03 g/mol, respectively.

The masses of acetic acid and sodium acetate that must be dissolved in 500 mL of solution are:

$$\text{Mass of acetic acid} = 0.018 \text{ mol} \times 60.05 \text{ g/mol} = 1.08 \text{ g}$$

$$\text{Mass of sodium acetate} = 0.032 \text{ mol} \times 82.03 \text{ g/mol} = 2.62 \text{ g}$$

The procedure for preparing this buffer solution is to add the above masses of acetic acid and sodium acetate to a 500 mL volumetric flask, and diluting to the mark with distilled water.

**EXPERIMENTAL PART:****Materials:**

Mefenamic acid, 0.1 M NaOH, NaOH solid pellets, potassium dihydrogen orthophosphate,  $\text{KH}_2\text{PO}_4$ , disodium hydrogen phosphate.  $\text{Na}_2\text{HPO}_4$ .

**Equipment and glassware:**

Conical flasks 250 ml, pipette 10 ml, Volumetric Flasks 100 ml and 50 ml, graduated cylinder 10 ml and 50 ml, mortar, beaker 100 and 20 ml, Thermostatic-Shaker, UV spectrophotometer.

**Procedure:**

Make your calculations to make **100 ml (0.1 M)** of the following buffers (Justify the type of buffers used and determine the type of HA and A- to be used).

pH	Buffer type	HA (g)	A- (g)
3.0	Acetate		
4.0	Acetate		
5.0	Acetate		
6.0	Phosphate		
7.4	Phosphate		
8.2	Phosphate		

**a. pH solubility profile**

- 1- Prepare 100 ml of acetate buffer with pH of 3.0, 4.0 and 5.0 and phosphate buffer with pH of 6.0 and 8.2 and 500 ml of phosphate buffer with pH 7.4.
- 2- Into a conical flask, add 50 ml of each buffer
- 3- Add an amount of Mefenamic acid to each flask.
- Put the flask on a shaker for 15 minutes, observe the bottles for excess drug and if needed add more solid drug.
- 4- Filter the mixtures then dilute with 0.1 M NaOH if needed and measure the UV absorbance at 287 nm.
- 5- Construct a calibration curve of the drug in 0.1 M NaOH.
- 6- Convert the absorbance value to concentration and then calculate the solubility.
- 7- Plot the solubility versus buffer pH.

**b. Effect of co-solvent on drug solubility**

- 1- In conical flasks, prepare the following binary mixture (total 50 ml):

Phosphate buffer (ml)	50	45	40	35	30	25
Ethanol (ml)	0	5	10	15	20	25
Total volume (mL)	50	50	50	50	50	50

2- Perform solubility study in the binary mixtures as previously stated in part a.

3- Plot solubility versus ethanol concentration (V/V).

## REFERENCES:

- <sup>(1)</sup> Heikkilä, Tiina. (2010). *Miniaturization of Drug Solubility and Dissolution Testings*. 1st ed. [pdf]. Helsinki. Faculty of Pharmacy of the University of Helsinki, Available at: [https://pdfs.semanticscholar.org/1bc7/17ec8b3d66017e6c9e1c0d6270009de4092b.pdf?\\_ga=2.3904560.1891278837.1582720558-1440014261.1557314079](https://pdfs.semanticscholar.org/1bc7/17ec8b3d66017e6c9e1c0d6270009de4092b.pdf?_ga=2.3904560.1891278837.1582720558-1440014261.1557314079). [Accessed 26 Feb. 2020].
- <sup>(2)</sup> R. P. Kabra, S. S. Kadam, A. S. Kulkarni, C. G. Mamde.(2014). Role of Solid Lipid Nanoparticles in Oral Drug Delivery. *International Journal of Current Pharmaceutical Sciences*, [online] Volume(1) p. 47-62. Available at: [www.corepublications.in](http://www.corepublications.in). [Accessed 26 Feb. 2020].
- <sup>(3)</sup> Hywel D. Williams, Natalie L. Trevaskis, Susan A. Charman, Ravi M. Shanker, William N. Charman, Colin W. Pouton, and Christopher J. H. Porter.(2013). [Accessed 26 Feb. 2020].
- <sup>(4)</sup> Oneill, Thaddeus. (2018). *Water: the medium of life*. [image] Available at: <https://www.slideserve.com/thaddeus-oneill/water-is-polar-and-forms-h-bonds-with-itself-responsible-for-high-boiling-point-of-water>. [Accessed 26 Feb. 2020].

## Experiment 2

### POWDER MIXING

#### OBJECTIVES:

To study the process of mixing and calculating the optimum mixing time.

#### INTRODUCTION:

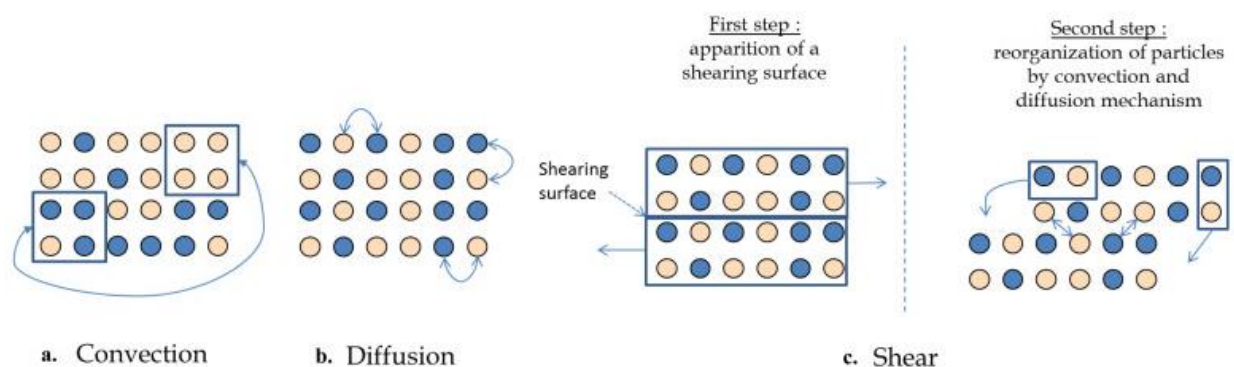
The main aim of powder mixing in pharmaceutical practice is to achieve dose uniformity in solid dosage form (tablets, capsules, and powders), particularly so important in case of very potent drugs like Digoxin, Ethinyl estradiol.

#### Parameters that affect the mixing process:

- Particle Parameter: like particle size, particle shape, size distribution, particle density, cohesive forces, hygroscopic properties, and hardness.
- Type of mixer: speed, batch volume and movement.
- Segregation tendency of individual components based on density difference.

Efficiency of Powder Mixing using different mixers is affected by: Presence of Blades, Filling Volume and Agitation Speed

**Figure 1:** Mechanisms of Mixing: Diffusion, Convection, and Shearing. <sup>(1)</sup>



**Revolvo-Cube Mixer:**

Motor drive mixer where the housing in the Cube Mixer is manufactured from stainless steel. It is equipped with Baffles but not Blades. It uses the tumbling movement. However, the cube mixer is problematic due to the presence of corners.



**FIGURE 2. REVOLVO-CUBE MIXER**



**FIGURE 3. DOUBLE CONE MIXER <sup>(3)</sup>**

**EXPERIMENTAL PART:****a. Materials:**

Lactose, Sodium Salicylate, Distilled water

**b. Apparatus:**

Double cone mixer, UV/VIS Spectrophotometer.

**c. Method:**

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

1. Prepare 250g of 5% w/w Sodium Salicylate in Lactose (pass all powders before weighing in 1mm sieve)
  2. Place the powders in the mixing chamber, starting with the material with the bigger quantity first.
  3. Start the mixing process at 25rpm, take 5 random samples at each of the following time intervals: 2mins, 5mins, 10mins, 15mins, 30mins, each sample should weight 200mg (samples should be close to each other  $0.2g \pm 0.02g$ ).
  4. Determine the content of Na-Salicylate in each sample at each time. Put each sample in 100 mL Volumetric Flask, then add around 10 - 15 mL of distilled water and mix until all powders are completely dissolved. Complete the volume by Distilled Water up to the 100 mL mark then mix well.
  5. Measure the samples absorbance using UV/VIS spectrophotometer:
    - Blank should be 0.20% w/v Lactose in Distilled Water (200 mg Lactose in 100 mL Volumetric Flask, dissolve lactose in 10 - 20 mL of Distilled Water, then complete up to the 100 mL mark using Distilled Water.
    - max for absorbance measurement is  $\lambda = 254 \text{ nm}$
- **Calibration Curve:**
- Prepare 0.10gm% w/v of Na-Salicylate in D.water (place 100 mg NaSalicylate in 100 mL V.Flask, dissolve then complete volume up to the 100 mL mark with D.Water then mix well  
→ **Standard Stock Solution**
  - Withdraw 10, 20, 25 & 35 mL using volumetric pipettes from the Standard Stock Solution and place each in a different 100 mL V.Flask and complete the volume up to 100 mL mark with D.Water then mix well → **Standard Solutions**
  - Measure the standard solutions absorbances using D.Water as a blank, and at  $\lambda_{\text{max}} = 254 \text{ nm}$ .

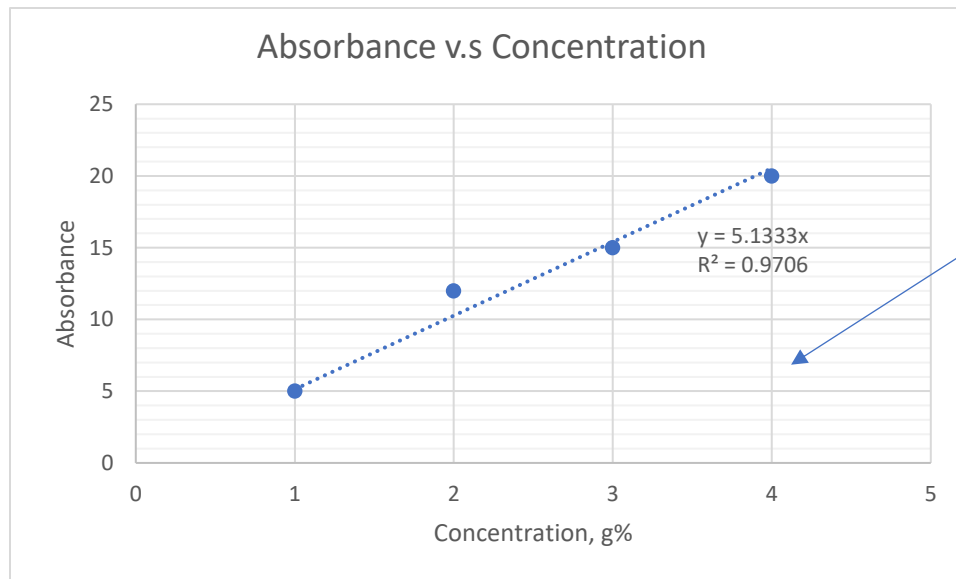
• **Calibration Curve Construction:**

- Plot standard solutions absorbances vs their concentrations in gm%.

e.g. standard solution no. 1 concentration = 0.1 gm% / D.F = 0.01 gm%

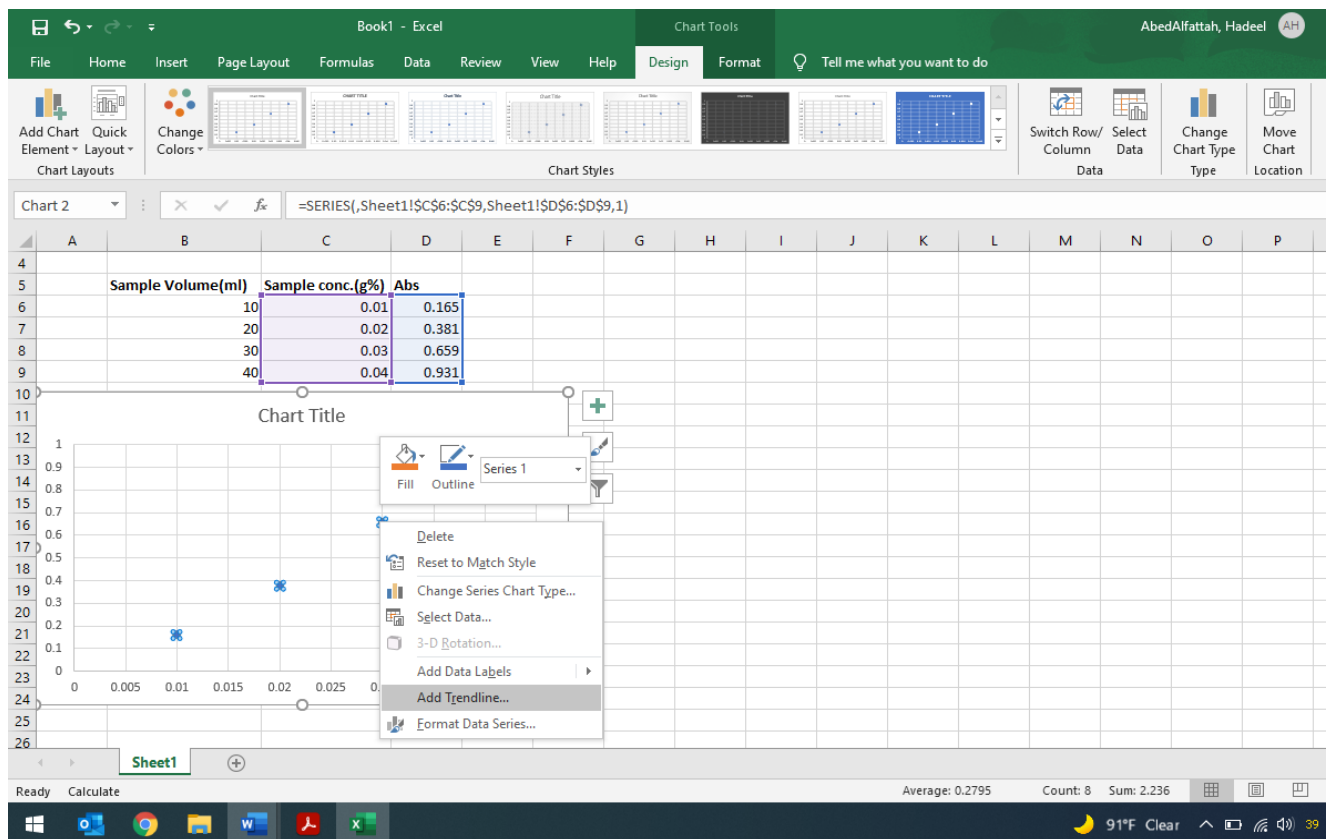
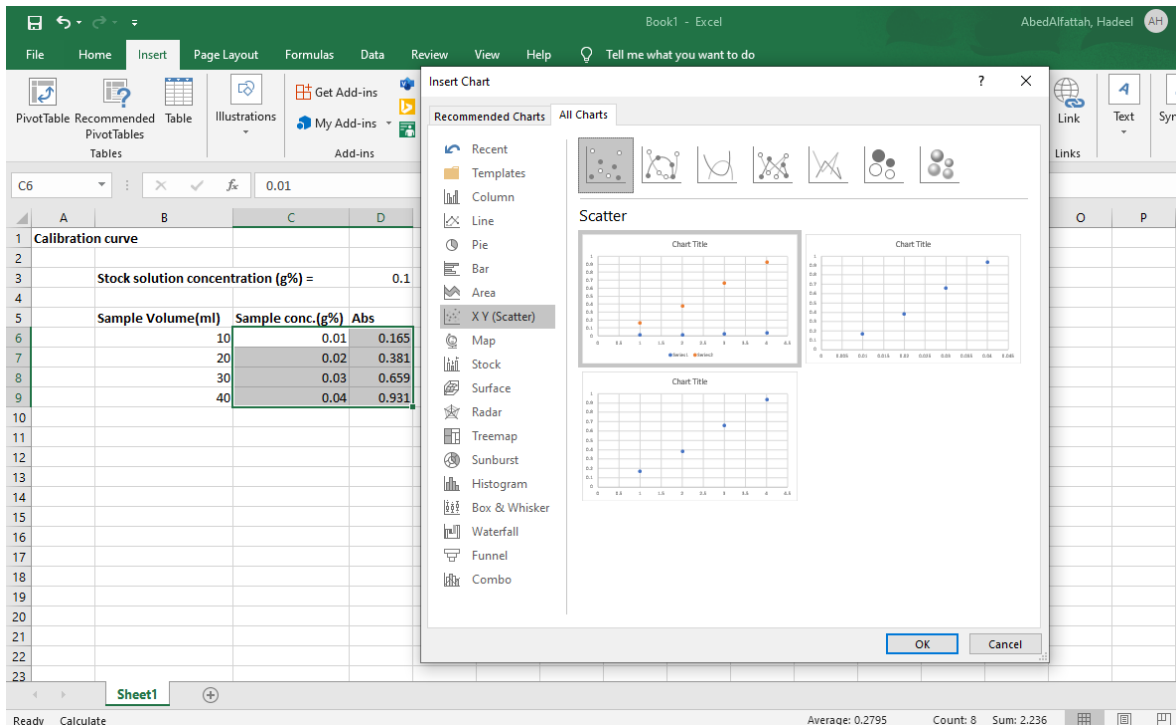
$$\text{D.F (Dilution Factor)} = \frac{\text{Final Volume}}{\text{Initial Volume}}$$

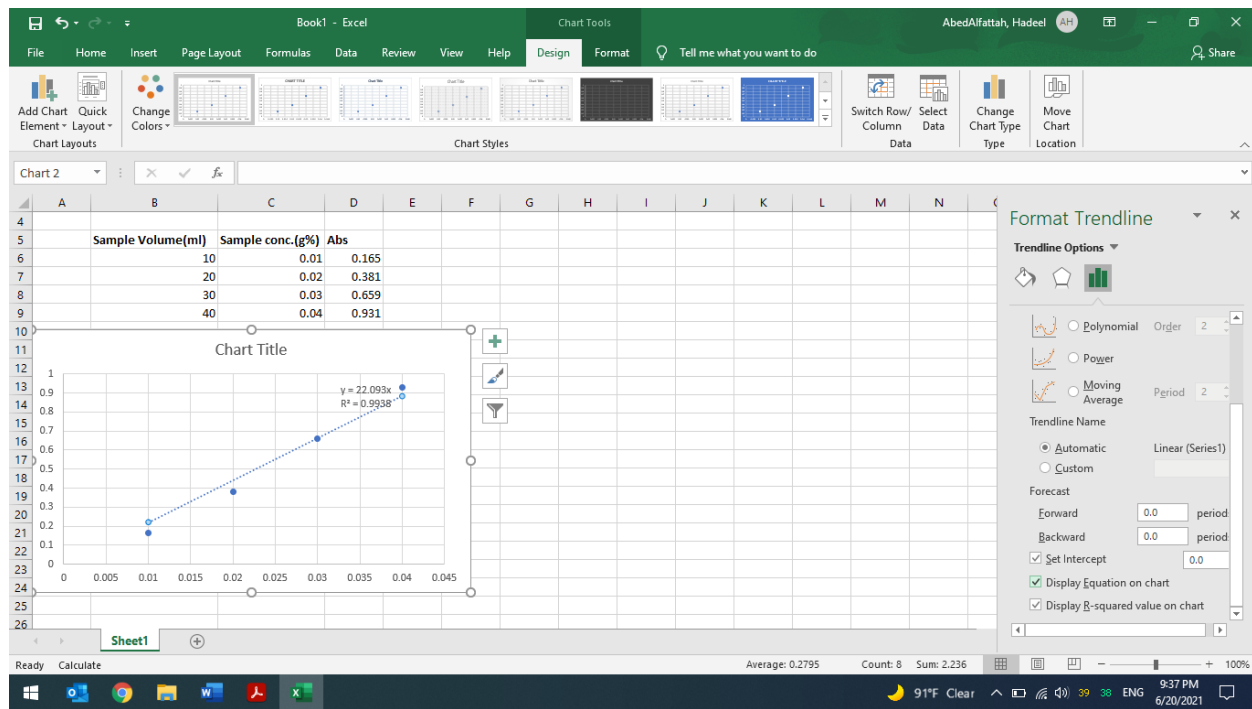
- Apply Beers Law to the calibration curve straight line equation as following:  
 $A = a \cdot b \cdot C$ , where A is the Absorbance, **a is absorptivity (slope of the straight line equation)**, b is cell bath (= 1 cm), and C is the concentration of the substance of interest.



Slope = absorptivity , here absorptivity is  $E\%$  since the concentration unit is g%, the  $E\%$  unit is  $(g\%^{-1} \cdot cm^{-1})$







- Results and data analysis:**

### Mixing Samples Analysis

- Use  $E\%$  (absorptivity,  $\text{gm}\%^{-1}.\text{cm}^{-1}$ ) value from calibration curve to calculate concentrations in  $\text{mg}\%$  w/v of the mixing samples.

e.g. sample no. 1 concentration  $\text{mg}\%$  w/v =  $\frac{\text{Sample Absorbance}}{E\%} \text{ gm}\% * 1000\text{mg/gm}$

- Calculate the concentration of each sample in  $\text{mg}\%$  w/w.

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

200mg is the sample weight

- Calculate : mean, Standard Deviation (S), Variance (V) ( $V=S^2$ ), and Coefficient of Variation (C.V.) (Relative Standard Deviation, RSD) of the five samples.

**Concentration in  $\text{mg}\%$  w/w at each sampling time.**

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

Always use Excel tables and equations

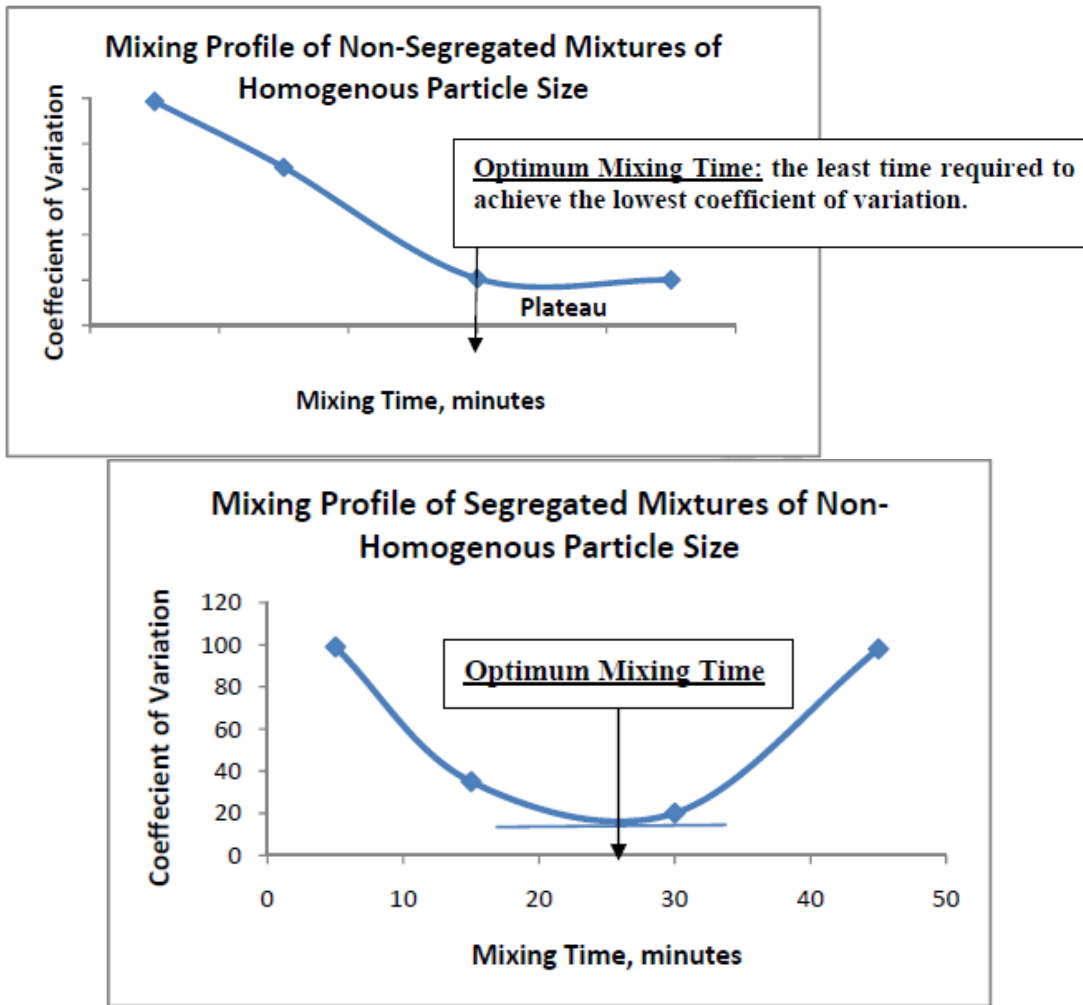
Mixing Time, Minutes	Concentration	Sample Number					Mean	Standard Deviation	Variance	Coefficient of Variation
		1	2	3	4	5				
5	Absorbance	A <sub>1</sub>	A <sub>2</sub>	A <sub>3</sub>	A <sub>4</sub>	A <sub>5</sub>				
	mg% w/v									
	mg% w/w									

- Construct the **Mixing Profile** by plotting **Coefficient of variation v.s Mixing Time** in minutes

Mixing time (min)	Coefficient of variation CV
5	CV <sub>5</sub>
15	CV <sub>15</sub>
30	CV <sub>30</sub>
45	CV <sub>45</sub>

- Use Excel sheets, tables, and equations to perform all required data analysis

### Examples on Mixing Profiles:



- Compare and discuss your results.

### References:

- (1) C.Mayer-Laigle, C.Gatumel, H.Berthiaux. (2014). Mixing dynamics for easy flowing powders in a lab scale Turbula® mixer. *Chemical Engineering Research and Design*, [online] Volume(95), p. 248–261. Available at: <https://www.sciencedirect.com/science/article/pii/S0263876214004808> [Accessed 02 Mar. 2020].
- (2) PROCESS TECHNOLOGY EVOLUTION. (2006). *PMS CUBIC MIXER®*. [online] Available at: [http://www.pms-group.net/product\\_pt\\_cube.html](http://www.pms-group.net/product_pt_cube.html) [Accessed 02 Mar. 2020].
- (3) ERWEKA® (2015), *Double Cone Mixer DKM*. . [image] Available at: <https://totallaboratoryservices.co.uk/products/double-cone-mixer-dkm/> [Accessed 02 Mar. 2020].

## Experiment 3

### SIZE REDUCTION OF POWDERS

#### OBJECTIVES:

This laboratory examines the particle size reduction of sucrose powder and calculating the optimum milling time.

#### INTRODUCTION:

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.

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, pastes, and suppository bases.

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.

#### Aim of size reduction

1. To enhance the dissolution, hence bioavailability of drugs by increasing surface area.
2. To improve the adsorptive capacities.
3. To improve manufacturing processes such as mixing, granulation, etc., usually by changing the surface area of certain additives.

#### Mechanisms of Size Reduction:

Size reduction is accomplished by attrition, impaction, shearing or compression. A Rotary Ball Mill Consists of a Milling Chamber, which is a cylinder-like housing move in a horizontal rotator and a grinding medium (large and small spherical charges) which causes size reduction by two mechanisms: attrition: during the balls hitting with each other and balls hitting against the wall of ball mill (mainly due to small spheres), and impact: upon balls falling especially the large ones they grind the wall.

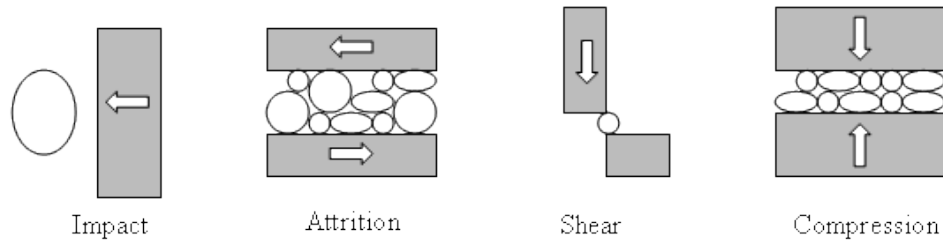


FIGURE 1. SIZE REDUCTION MECHANISMS.<sup>(1)</sup>



FIGURE 2. ROTARY BALL MILL.<sup>(2)</sup>

### Factors that affect milling

**1. Speed of rotation:** should have an optimum speed. Rate of milling is very important because each ball is exposed to two forces; gravitational force and centrifugation force. Depending on the rate of milling (velocity), one of the two forces is the predominant.

At Critical Speed → Gravitational force <<< Centrifugation force

$$\text{critical speed} = 76.6/\sqrt{(\text{diameter (feet)})}$$

(*d*) is the diameter of ball mill milling chamber feet.

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.**

**EXPERIMENTAL PART:****a. Materials:**

Coarse Sucrose.

**b. Apparatus:**

Rotary Ball Mills with spherical charges, Sieves and Shaker.

**PROCEDURE:****PART 1) Milling of sucrose powder**

1. Preparation of the Rotary Ball Mill: Clean the housing of the mill and the grinding medium (the small spherical charges), then fill the housing with the grinding medium to its half (maximum two thirds).
2. Weigh out 10 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 (calculate the optimum speed).
5. Take 2 gm sample after the predetermined time intervals, which are 3, 4, 5 and 6 minutes. When sampling, remove the appropriate mill sample, weighing 2gm, and continue milling for the other mill for the scheduled time.
6. Discard the remaining powder and clean the milling chamber and balls.

**PART 2) Particle Size Analysis**

1. Prepare the sieving apparatus by cleaning sieves of the following pore sizes: 2.8mm, 0.710mm, 1.4mm, 0.500mm, 0.355mm, 0.250mm, 0.180mm, 0.125mm, 0.090mm, 0.063mm, 0.045mm & the collecting pan (0 mm).
2. Arrange the sieves in a descending order of aperture size (with the largest pore size at the top, and collecting pan at the base).
3. Weigh the collecting pan and each sieve alone and record the weights as tare weight.  
\*Tare weight represents the weight of empty cleaned sieves.
4. Weigh out 2 gm of coarse sucrose (zero time sample = un-milled sucrose) from the main container.

5. Place this sample at the top sieve of those arranged according to their pore sizes, and with the lid in position clamp the sieves to the sieves-shaker and agitate for 10 minutes.

6. After the time elapsed, stop the shaker 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 the each sieve (or collecting pan) with the powder retained.

7. Repeat the above steps (after cleaning the sieves and collecting pan) for samples taken at 3, 4, 5 & 6 minutes.

**NB: 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:

1- For each samples of the five (un-milled sucrose ,3 , 4, 5 & 6 minutes) do the following analysis (Table 1 and 2).

**TABLE 1. PORE SIZES AND DIFFERENT WEIGHTS OF SIEVES AND SUCROSE POWDER.**

Pore Size (mm)*	Tare weight (g)	Gross weight (g)	Net weight (g)
0.000-0.450	T1	G1	$N1 = G1 - T1$
0.045-0.063	T2	G2	$N2 = G2 - T2$
0.063-0.090	T3	G3	$N3 = G3 - T3$
0.090-0.125	T4	G4	$N4 = G4 - T4$
0.125-0.180	T5	G5	$N5 = G5 - T5$
0.180-0.250	T6	G6	$N6 = G6 - T6$
0.250-0.355	T7	G7	$N7 = G7 - T7$
0.355-0.500	T8	G8	$N8 = G8 - T8$
0.500-0.710	T9	G9	$N9 = G9 - T9$
0.710-1.400	T10	G10	$N10 = G10 - T10$
1.400-2.800	T11	G11	$N11 = G11 - T11$
2.800	T12	G12	$N12 = G12 - T12$

\* should be changed according the sieves used in the lab.



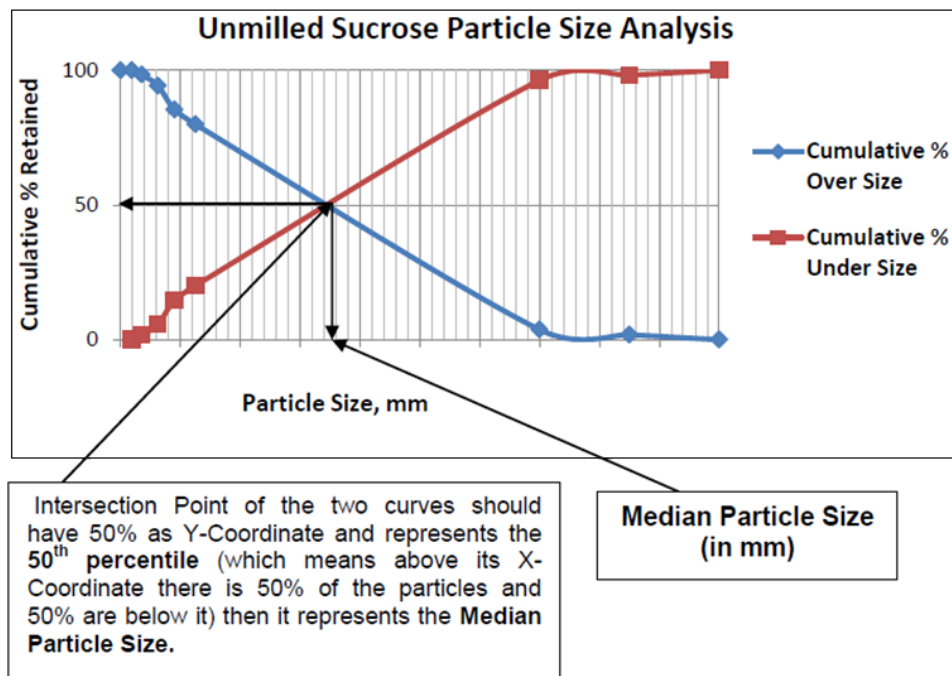
**TABLE 2. SIZE REDUCTION EXPERIMENT DATA FOR SAMPLES AT DIFFERENT TIME INTERVALS**

<b>Pore Size Interval (mm)*</b>	<b>Interval Mid-Point (mm) *</b>	<b>Upper Interval Limits (mm) *</b>	<b>Lower Interval Limits (mm) *</b>	<b>Net Weight (g)**</b>	<b>% Retained</b>	<b>Cumulative %OverSize</b>	<b>Cumulative % UnderSize</b>
0.000-0.045	0.0225	0.045	0.000	N1	$=(N1/2)^*100\%$		
0.045-0.063	0.054	0.063	0.045	N2	$=(N2/2)^*100\%$		
0.063-0.090	0.0765	0.090	0.063	N3	$=(N3/2)^*100\%$		
0.090-0.125	0.1075	0.125	0.090	N4	$=(N4/2)^*100\%$		
0.125-0.180	0.1525	0.180	0.125	N5	$=(N5/2)^*100\%$		
0.180-0.250	0.215	0.250	0.180	N6	$=(N6/2)^*100\%$		
0.250-0.355	0.3025	0.355	0.250	N7	$=(N7/2)^*100\%$		
0.355-0.500	0.4275	0.500	0.355	N8	$=(N8/2)^*100\%$		
0.500-0.710	0.605	0.710	0.500	N9	$=(N9/2)^*100\%$		
0.710-1.400	1.055	1.400	0.710	N10	$=(N10/2)^*100\%$		
1.400-2.800	2.1	2.800	1.400	N11	$=(N11/2)^*100\%$		
>2.8	2.8		2.800	N12	$=(N12/2)^*100\%$		
				= $\Sigma$ Net Weight			

\* should be changed according the sieves used in the lab; \*\* values should be taken from table 1

- **Interval midpoint = (upper limit + lower limit) /2**
- **% retained = (amount retained/ sample weight) \*100%**

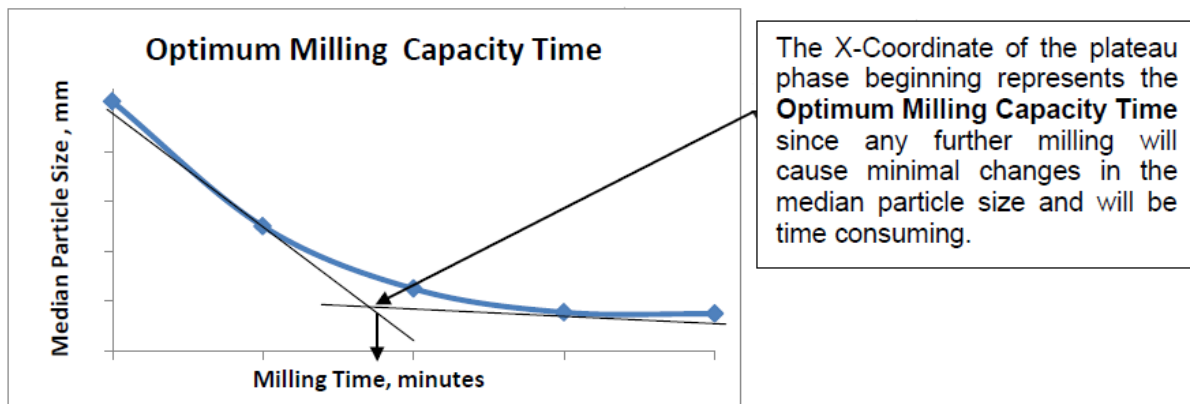
- Cumulative % Over Size** is defined as the percentage of particles that have particle sizes larger than the interval lower limit.  
 Ex.1: Cumulative % Over-Size for 1<sup>st</sup> interval =  $(N_1 + N_2 + \dots + N_9) / \Sigma \text{ Net Weight} * 100\%$   
 $= 100\%$   
 Ex.2: Cumulative % Over-Size for 2<sup>nd</sup> interval =  $(N_2 + N_3 + \dots + N_9) / \Sigma \text{ Net Weight} * 100\%$   
 Ex.3: Cumulative % Over-Size for 3<sup>rd</sup> interval =  $(N_3 + N_4 + \dots + N_9) / \Sigma \text{ Net Weight} * 100\%$
  - Cumulative % Under-Size** is defined as the percentage of particles that have particle size smaller than the interval upper limit.  
 Ex.1: Cumulative % Under-Size for 1<sup>st</sup> interval =  $N_1 / \Sigma \text{ Net Weight} * 100\%$   
 Ex.2: Cumulative % Under-Size for 2<sup>nd</sup> interval =  $(N_1 + N_2) / \Sigma \text{ Net Weight} * 100\%$   
 Ex.3: Cumulative % Under-Size for last interval =  $(N_1 + N_2 + \dots + N_9) / \Sigma \text{ Net Weight} * 100\%$   
 $= 100\%$
- 2- Plot the: (**Cumulative % Over Size vs. Intervals Lower Limits**) and (**Cumulative % Under Size vs. Intervals Upper Limits**) on the same figure.



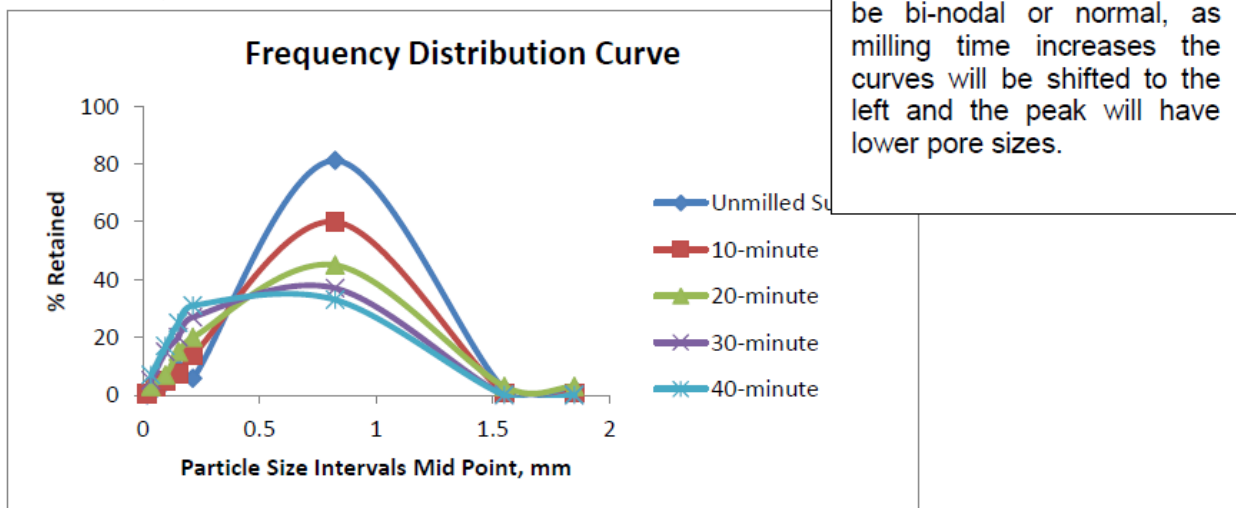
- 3- Now repeat the above analysis done for the un-milled sample for all other 4 samples (at 3,4,5 & 6 minutes) and find the **Median Particle Size** at each time as shown in table 3. Then, plot the Optimum Milling Time Curve

**TABLE 3. MILLING TIME AND MEDIAN PARTICLE SIZE**

Milling Time (min)	Median Particle Size (mm)
0	M1
3	M2
4	M3
5	M4
6	M5



- 4- Finally, plot the **Frequency Distribution Curve**: % Retained vs. Particle size intervals mid-points for all samples.



**REFERENCES:**

- <sup>(1)</sup> Sushant. S, and Archana K, Methods Of Size Reduction And Factors Affecting Size Reduction In Pharmaceuticals, Sud Sushant et al. Int. Res. J. Pharm. 2013, 4 (8). 57-62. [Accessed 02 Mar. 2020].
- <sup>(2)</sup> Retsch GmbH. (2008). *Planetary Ball Mills*. 1st ed. [pdf] Haan: Retsch GmbH. Available at: <https://www.retsch.com/> [Accessed 02 Mar. 2020].

## Experiment 4

# CHARACTERIZATION OF GRANULES

### OBJECTIVES:

To practice the tests needed to characterize granules including flowability, angle of repose, particle size analysis and moisture content.

### 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 container to 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 Rate.
2. Angle of Repose.
3. Bulk Density and Tapped Density.
4. Moisture Content.
5. 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 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.

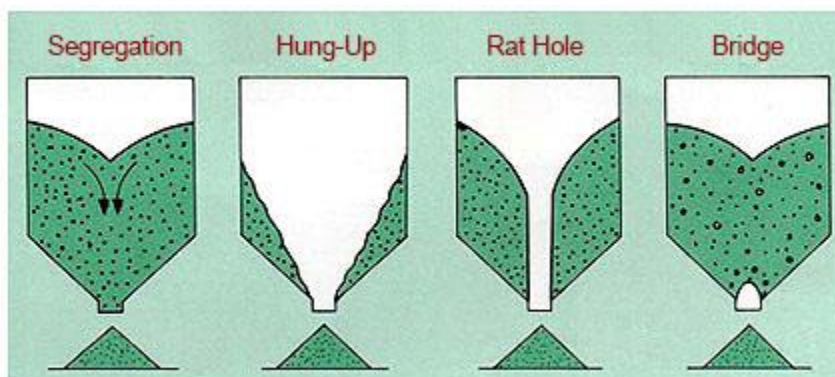
With fine powders, the magnitude of friction and cohesive forces usually predominate. For larger particles, such as granules, frictional forces normally predominate over cohesive forces.

### **Powder Flow Properties:**

#### **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 flowable granules, granules need tapping to flow, rat-hole pattern, and granules need tapping with rat-holing pattern.



**FIGURE 1. PROBLEM IN GRANULES FLOWING.** <sup>(1)</sup>

### **Powder Flowability through a Hole in a Plate**

Many powders are marketed with “viscosity” of the powder specified. This does not refer to the viscosity of the material when dissolved into a liquid, but rather the flowability of the powder itself. The viscosity of a powder may be estimated by observing its ability to fall freely through a hole of known dimensions in a plate. The powder is tested with different hole sizes, ranging from small (e.g. 5 mm) to large (eg 22 mm). The diameter of the smallest hole through which the powder passes three times out of three is taken as the flowability index. The diameter may be used as an empirical measure, or converted into viscosity, which is a comprehensive industry standard.

Mathematically, a “core” cylinder of powder will flow through a hole if the weight of the powder above the hole is greater than the friction of the side surface of the powder:

$$(1) \pi r^2 h d g \geq 2 \pi r h K$$

Where:

h = height of core cylinder of powder

r = radius of hole

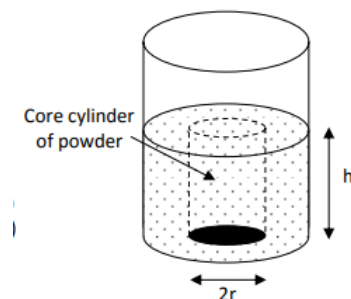
( $\pi r^2 h$  = volume of core cylinder)

g = acceleration due to gravity (981 cm/s<sup>2</sup>)

d = non-tapped bulk density of powder

( $2 \pi r h$  = surface area of core cylinder of powder)

K = coefficient of friction/cm<sup>2</sup> (powder viscosity)



The above equation can be simplified to:

$$(2) r \geq \frac{K \left( \frac{g}{cm} \cdot s^2 \right)}{490 \left( \frac{cm}{s^2} \right) \cdot d \left( \frac{g}{cm^3} \right)}$$

Solving for K (powder viscosity):

$$(3) K(Poise) \leq 490.5 \left( \frac{cm}{s^2} \right) \times r(cm) \times d (g/cm^3)$$

The answer in Poise (P) can be multiplied by 100 to obtain the measurement in centipoise (cP), a more typical viscosity unit. Thus the viscosity of the powder can be estimated by finding the minimum hole diameter the powder will freely flow through.

## 2- Angle of Repose:

A static heap of powder, with only gravity acting upon it, will tend to form a conical mound. One limitation exists: the angle to the horizontal cannot exceed a certain value, and this is known as the Angle of Repose ( $\theta$ ).

One of the methods used to measure the angle of repose is the fixed-base cone method, where funnel is secured with its tip a given height **H** above graph paper placed on a flat horizontal surface. Granulation is carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel.

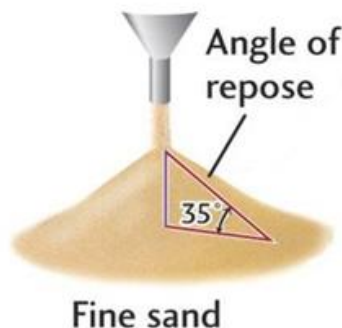


FIGURE 2. ANGLE OF REPOSE,  $\tan \theta = H/R$  <sup>(2)</sup>

Where  $\theta$  is the angle of repose,  $H$  is the height of the cone;  $R$  is the radius of the cone.

In our laboratory, we could not perform the experiment this way, because we were limited with the available amount.

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, and the 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**, the chance 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  $\leq 30^\circ$  generally indicate a free-flowing material and angles  $\geq 40^\circ$  suggest a poorly flowing material.



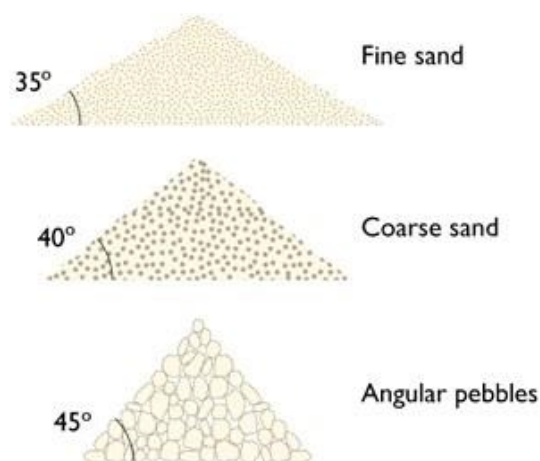


FIGURE 3. DIFFERENT ANGLES OF REPOSE.<sup>(3)</sup>

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. If a **glidant** is used, the angle of repose goes through a minimum and then increases as glidant concentration increases. When materials that take up **moisture** from the atmosphere are exposed to high humidity, that material generally becomes more cohesive, and exhibit very poor flow characteristics. As the storage humidity is increased, angle of repose increase. It is noted that if particles become more **irregular in shape**, as a result the angle of repose will be increased.

TABLE 2. 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*
> 40	Very Poor

\*Can be improved by using a glidant, e.g. 0.2% Aerosil.

### 3- 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 "flowability" 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 (Figure 4), which is set to tap the powder at a fixed impact force and frequency. The methods for

measurement in the U.S. pharmaceutical industry are specified in the U.S. Pharmacopeia (USP). Tapped density by the USP method is determined by a linear progression of the number of taps.



FIGURE 4. TAPPED DENSITY TESTER. <sup>(4)</sup>

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

$$\text{Bulk Density} = \text{Weight} / \text{Volume} = \text{g/mL}$$

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:

$$\text{Tapped Density} = \text{Weight} / \text{Tapped Volume} = \text{g/mL}$$

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 be filled with the small particles upon tapping and consequently large reduction in the volume is expected. This concept is illustrated in Figure 5.

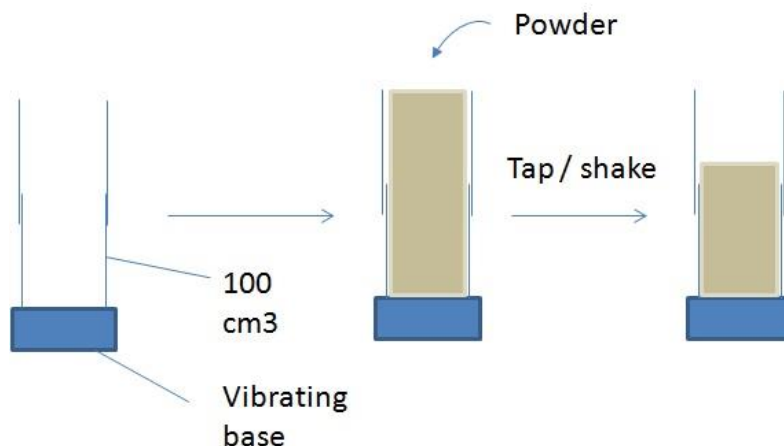


FIGURE 5. MEASURING TAPPED BULK DENSITY <sup>(5)</sup>

In Summary; if our granules have 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 the **Compressibility Index** as the following:

$$\text{Compressibility Index} = ((\text{Bulk Density} - \text{Tapped Density}) / \text{Tapped Density}) * 100\%$$

Now, for the previous two granulations, which one would have higher compressibility index. Of course, B will. Now the name of this index indicates that it 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 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 3. CARR'S INDEX AS AN INDICATION OF POWDER FLOW<sup>(6)</sup>**

Carr's Index (%)	Type of Flow
0 - 10	Excellent
11 - 15	Good
16 - 25	Fair to passable *
26 - 31	Poor *
32 - 37	Very Poor
> 40	Extremely Poor

\*Can be improved by using a glidant, e.g. 0.2% Aerosil.

#### 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, which can range from 0 (completely dry) to the value of the materials' porosity at saturation.

##### 1- Loss on Drying (LOD):

It determines the amount of volatile components that are released from a sample under specific temperature, it is calculated as follows:

$$\% \text{ LOD} = \text{weight of water in sample} / \text{total weight of wet sample} * 100\%$$

A weighed sample is placed on the balance and allowed to dry until it is at constant weight. The water lost by evaporation is read directly from the percent LOD scale.

##### 2- Moisture Content:

$$\% \text{ MC} = \text{weight of water in sample} / \text{total weight of dry sample} * 100\%$$

Example:

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

$$\text{MC} = ((5-3)/3) * 100\% = 66.7\%$$

Whereas:

$$\text{LOD} = ((5-3)/5) * 100\% = 40\%$$

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 surface tension 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 and capping 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.

**EXPERIMENTAL PART:****a. Materials:**

Granules A, B, & C from Experimental Granulation.

**b. Apparatus:**

Flow Rate Apparatus, Funnel, Bulk Density Apparatus, Jolting Sieving Apparatus, Moisture Content Determination Apparatus.

**c. Method:****. Method:**

Figure 1. Powders flowability apparatus representation. <sup>(7)</sup>

For the **three batches** of granules, determine the following:

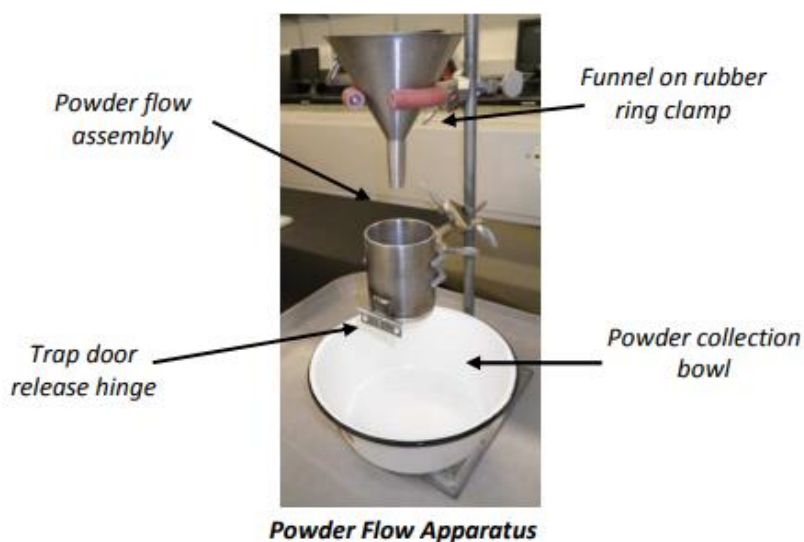
**1. Flowability index & Flow Rate:**

Setting up the Powder Flow Apparatus: (TA performs this set-up)

1. The powder flow apparatus will be set up in the fume hoods using the following procedure:
2. Obtain a series of disks and a ruler from your instructor or TA. As these disks are custom made, take special care not to lose them.
3. Place the powder collection beaker on the top of the balance.
4. adjust the shutter mechanism such the lower surface of the shutter is approx.. 40mm above the top of the beaker.
5. Now adjust the cylinder attachment such the bottom plate of the cylinder is resting on the top of the shutter( the shutter should cover the hole)



6. Finally adjust the funnel assembly that the bottom of the powder funnel is no more than 2cm above the upper rim of the cylinder, The final assembly should look like this:.



Note: Altering the position of the funnel during the test sequence may affect the results.

- The apparatus should be high enough so that the shutter open freely. the body of the powder flow apparatus cylinder should be ~10 cm from the bottom of the beaker.
- 7. The disks are labelled with their **hole diameter in millimeters** stamped on the disk.
- 8. **Insert the 16 mm disk into the powder flow apparatus.** Make sure the disk is flush with the bottom of the powder flow apparatus cylinder.
- 9. Close the shutter knob.

## ***Test Procedure:***

### **Determining Flowability:**

1. Fill a clean, dry 400 mL beaker with 100g of the powder test.
  2. Pour the powder test mix into the funnel, until the powder flow apparatus is filled ~1 cm from the top. If the powder becomes trapped in the funnel, tap the funnel gently with a spatula until all of the powder falls loosely into the center of the cylinder of the powder flow apparatus. Pouring the powder in the funnel disrupts powder aggregates due to long term storage or sitting.
- NOTE: Be careful not to touch the sides of the powder flow apparatus or tap it once it is loaded.



**Positive Result** (hole visible from above)



**Negative Result** (hole not visible)

3. After the cylinder is filled, allow 30 seconds for possible formation of individual flocculi or mass flocculation of the whole powder mass.

NOTE: in case of poorly flowing powder, it may be necessary to spoon in small amount of powder through the funnel.

4. Gently and smoothly but rapidly move the knob of the shutter arm to the right to release the powder from the funnel.
5. A “positive” result is deemed if the powder flows through the hole, and the hole is visible from the top of the cylinder. A “negative” result is deemed if the hole is not visible from the top of the cylinder:
6. For positive results, repeat the test with smaller and smaller disks until a negative result is obtained. For negative results, repeat the test with larger and larger disks until a positive result is obtained.



- The Flowability Index is the diameter of the smallest hole through which the sample will give 3 successive positive results. Free flowing powders will generally form an inverted cone with a consistent plane.
- The Flowability index is the inverse of the flow characteristics thus a positive test of 10 on powder suggests better flow characteristics than 16 on different form of powder.
- The index thus determined will generally repeat between one of two numbers.

7. Three positive results in a row are required to determine flowability. Repeat the test two more times on the smallest disk that produces a positive result. If a negative result is obtained, advance to the disk having the next largest diameter, and proceed testing.

- Calculate and record the viscosity of the two formulations.
- Comment on the flowability of the samples (Flowability index)

### **Determining Flow rate:**

- Weigh 100g of the granules and determine the time to flow through funnel using stopwatch.  
( Remove the Cylinder Attachment and replace it with funnel attachment)
- Repeat three times and determine the average flow time.
- Calculate the Flow Rate:

Flow Rate = weight/ flow time= (g/1sec)

Flow Rate = 100g/ average flow rate = (g/1sec)

## 2. Angle of Repose:



### **\* Setting up the Angle of repose attachment: (TA performs this set-up)**

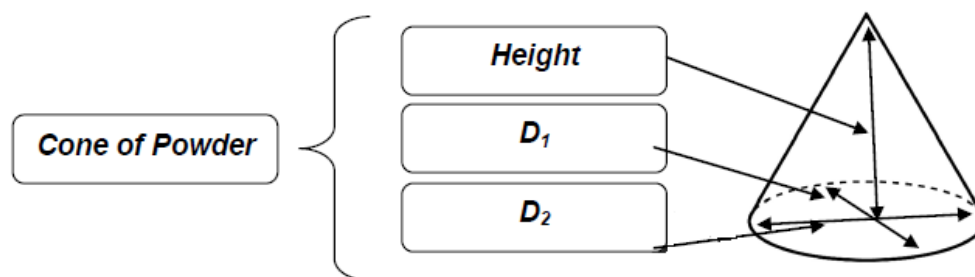
- Assemble the stainless steel funnel with the special 10 mm nozzle (marked 'AOR') and secure with a locking nut.
- position the shutter mechanism and the assembled funnel in their approximate operating position on the base upright and secure using the black knurled knobs provided on each assembly for this purpose.
- Now position the height gauge to the right of the base plate and adjust the tip of the scribe ( the pointer) such that it's over the center of the hole in the base plate.
- Then screw the alignment pin for the powder collection tray( and test platform) into position in the central hole in the base plate provided for this purpose and zero the height gauge on the test platform by lowering the bottom of the pointer onto the test platform and pressing the origin button for more than one second.
- Remove the height gauge.
- Adjust the funnel such that the bottom of the nozzle of the funnel is 75mm above the test platform.

### Test procedure :

- Allow 100g of granules to flow freely through the nozzle such that it forms a conical pile on the test platform.
- the tangent of the angle of repose  $\Theta$  can be determined by reading off the height of the powder cone in mm from the digital display of the height gauge and dividing it by 50. Take the *inverse tangent* of this figure to obtain the angle in degrees.

$$\tan \Theta = \frac{\text{Height Of Cone (Mm)}}{\text{Half Of The Cone Base Diameter}} \quad \therefore \quad \Theta = \tan^{-1} \left( \frac{\text{Height Of Cone (Mm)}}{50} \right)$$

the **three batches** of granules, determine the following:



**FIGURE 7. ANGLE OF REPOSE OF POWDERS REPRESENTATION<sup>(8)</sup>**

- Repeat three times and determine the average

### 3. Bulk Density and Tapped Density:

- Weigh 50g 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).  
Bulk Density = weight/bulk volume = 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).  
Tapped Density = weight/tapped volume = grams per 1 ml

### 4. Moisture Content:

- Of one of the three batches weigh (using a foil paper) 1.0 gm of the dried granules (Wet Weight) on the Moisture Content Determination Apparatus, and record the moisture content  
Moisture Content (MC%) = (granules wet weight - granules dry weight) / granules dry weight \* 100%
- Loss on Drying (LOD%) = (granules wet weight - dry weight / granules wet weight) \* 100%

**RESULTS AND DATA ANALYSIS:****1- Flow Rate**

Flow Rate Analysis: Granules	Amount Tested (g)	Flow Time (Seconds)				Flow Rate (g/sec)
Granules		Trial 1	Trial 2	Trial 3	Average	
A		a1	a2	a3	a\	
B		b1	b2	b3	b\	

Amount Tested (g) = Sample Weight which is equal to 100 grams

Flow Rate = amount/ flow time = gm/second

Here; Flow Rate = 100(gm) /average flow time (second)

Example; Granules A Flow Rate = 100gm/a\second

**2- Angle of Repose:**

Granules	Trial	Radius (cm)	Height (cm)		Angle of Repose	
Code			H	Average	Tan $\theta$	$\theta$
A	1					
	2					
	3					
B	1					
	2					
	3					

Average  $T = (D1 + D2) / 2$

Average Height = (Trial 1 + Trial 2 + Trial 3) / 3

Average Diameter = (Average T1 + Average T2 + Average T3) / 3

Radius = (Average Diameter) / 2

Tan  $\theta$  = Average Height / Radius

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

**3- Bulk and Tapped Densities:**

Granules	Amount Tested (g)	Volume (mL)		Density (g/mL)		Compressibility Index (%)
Binder	50	Bulk	Tapped	Bulk	Tapped	
A		X	Y	B	T	
B						

Bulk Density= Amount Tested/Bulk Volume = (gm/mL)

Here, Bulk Density=50 g/ x mL = B (g/mL)

Tapped Density= Amount Tested/tapped Volume = (g/mL)

Here, Bulk Density= 50 g/Y mL= T (g/mL)

Compressibility Index= tapped density- bulk density/tapped density \*100%

Here, CI %= (T-B)/T\*100%

**4- Moisture Content Analysis:**

Granules	Wet Weight (g)	Dry Weight (g)	MC %	LOD %
Code				
A				
B				

MC% = (sample wet weight -sample dry weight)/ sample dry weight\* 100%

LOD% = (sample wet weight -sample dry weight)/ sample wet weight \* 100%

**DISCUSSION:**

Record your results and compare the findings between the three granules, justifying the differences

**REFERENCES:**

<sup>(1)</sup> EGYPTEX CO.(Mahmoud El-Tallawi).2018 EGYPTEX Co. *FLUIDIZER PADS* . [online] Available at <http://www.egyptex.com/Fluidizer%20Pads.html> (11 Feb.2020)

<sup>(2)</sup> L. Lachman. July 09, 2017. *Practical: Determination of Angle of repose, Carre's Index & Hausner ratio of given powder*. [online] Available at <https://knowledgeofpharma.blogspot.com/2017/07/practical-determination-of-angle-of.html> (11.Feb.2020)

<sup>(3)</sup> Kleinhans, M. G.; Markies, H.; de Vet, S. J.; in 't Veld, A. C.; Postema, F. N. (2011). "Static and dynamic angles of repose in loose granular materials under reduced gravity". *Journal of Geophysical Research* **116**. Bibcode:2011JGRE..11611004K. doi:10.1029/2011JE003865 (11 Feb.2020)

- <sup>(4)</sup> Geneq Inc. 2018. *BIOTECHNOLOGY*. [online] Available at <https://geneq.com/biotechnology/en/product/geneq/tap-density-tester-11755> (11.Feb.2020)
- <sup>(5)</sup> Power process Co. June 03,2018. *Tapped and loose bulk density : Definition, calculation, application*. [online] Available at [https://www.powderprocess.net/bulk\\_density.html](https://www.powderprocess.net/bulk_density.html) (11.Feb 2020)
- <sup>(6)</sup> Catherine Sheehan. B.Sc., scientist. *Carr,R.L. Evaluating Flow Properties Of Solids. Chem. Eng. 1965,72. 163-168*. [online] Available at [http://www.pharmacopeia.cn/v29240/usp29nf24s0\\_c1174.html](http://www.pharmacopeia.cn/v29240/usp29nf24s0_c1174.html) (11. Feb 2020)
- <sup>(7+8)</sup> Hamzah M. Beakawi Al-HashemiOmar S. Baghabra Al-Amoudi. (27 February 2018). A review on the angle of repose of granular materials. *Powder Technology*, Volume 330, 1 May 2018, Pages 397-417. [online] Available at: <https://www.journals.elsevier.com/powder-technology>. (11 Feb 2020)

## EXPIREMENT 5

### TABLETS PREPARATION AND TESTING

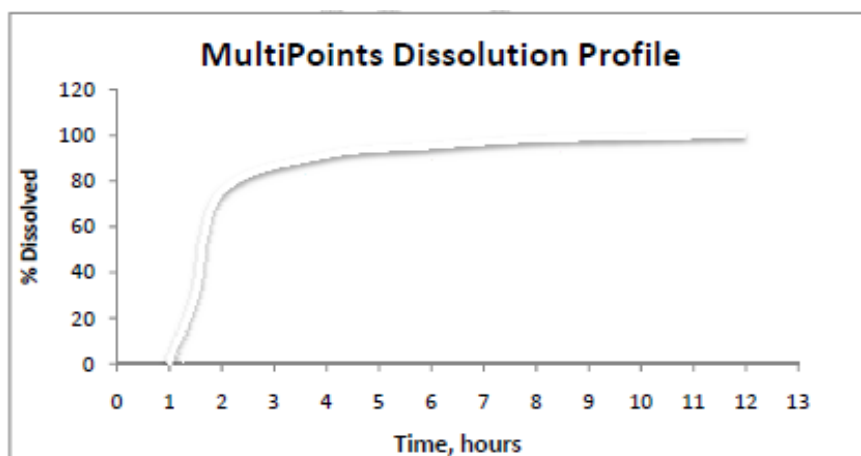
#### Introduction

After you have been exposed to various pharmaceutical operations (mixing, granulation, size reduction and particle size analysis), and to quality control tests of tablets (hardness, weight variability etc.), In this cycle, you will apply the knowledge you gained from the previous two cycles in suggesting direct compression formulation, a procedure to manufacture the formulation and after the tablet manufacturing you need to test the tablet specifications (Weight variability, hardness, disintegration and multipoint dissolution)

#### Objective

- Preparation of four different direct compression formulae using different diluents.
- Using “Hydraulic Press” to compress at least three tablets of each formula.
- Constructing a “Multipoint Dissolution Profile” for the collected data.

Dissolution Profile showing Percent Dissolved vs. Time:



graph draw the dissolution curves for each formulation.

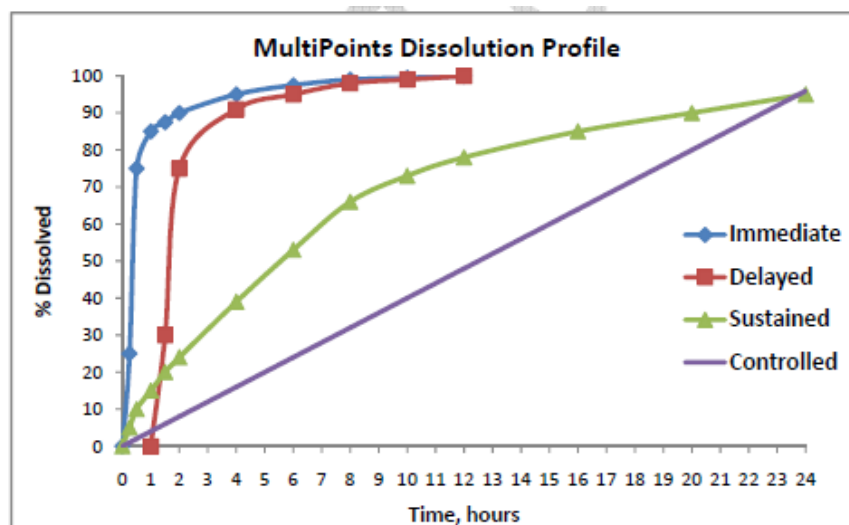
NB. On the same

### Functions of Excipients:

Avicel: .....  
 Lactose: .....  
 Starch: .....  
 Mg-Stearate: .....  
 HPMC: .....  
 DCP (Di-Calcium Phosphate): .....

### Concepts

- **Immediate-Release:** drug is released rapidly from the dosage form (Solution (instantaneous release), Suspension, Disintegrating Tablets, etc.)
  - **Delayed Release:** delay in the onset of drug release; e.g. enteric-coated tablets
  - **Sustained /Extended-Release:** prolonged (slowed down) release from dosage form.
- Controlled-Release:** special type of S.R. where release is zero-order.





**EXPERIMENTAL:****a. Materials:**

Paracetamol

Avicel 101:

Mg-Stearate:

Starch:

Lactose:

HydroxyPropylMethylCellulose (HPMC):

DiCalciumPhosphate (DCP):

**b. Apparatus:**

- Hydraulic Press  
Single Punch press machine, for research purposes mainly.
- Dissolution Apparatus.
- Rotary Multi-Station Tableting Machine

**c. Method:****• Targets:**

- Batch Size = 10 grams
- Tablet Weight = 600 mg
- Drug Potency= 200 mg (Active Ingredient per tablet)
- Tablet Diameter = 12 mm
- Compression Force = 10 KN

**• Sampling Methodology:**

- Sample Volume: 5 mL
- Time Points: 15 minutes, 30 minutes, 45 minutes, 1 hour, 1.50 hour, 2 hours
- Method: with replacement of equal volume from fresh medium kept at the same temperature.

• **Formula:**

**General Formula**

Ingredients	% w/w	Amount per tablet (per 600 mg)	Amount per Batch (per 10 gm)
Paracetamol	200 mg per tablet	200 mg	3.333 gm
Starch	5% w/w	30 mg	0.500 gm
Avicel 101	10% w/w	60 mg	1.000 gm
Mg-Stearate	1% w/w	6 mg	0.100 gm
<b>Diluent</b>	q.s 100%	304 mg	5.067 gm

You are about to prepare the following **four** formulas:

**Formula A**

Paracetamol	200 mg per tablet
Starch	5% w/w
Avicel 101	10% w/w
Mg-Stearate	1% w/w
<b>Lactose</b>	q.s 100%

**Formula B**

q.s 100%	200 mg per tablet
Starch	5% w/w
Avicel 101	10% w/w
Mg-Stearate	1% w/w
<b>DCP</b>	q.s 100

**Formula C**

Paracetamol	200 mg per tablet
Starch	5% w/w
Avicel 101	10% w/w
Mg-Stearate	1% w/w
<b>HPMC</b>	q.s 100%

**Formula D**

Paracetamol	200 mg per tablet
Starch	5% w/w
Avicel 101	10% w/w
Mg-Stearate	1% w/w
<b>Lactose : HPMC in 1:1 ratio</b>	q.s 100%

**Procedure:**

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

**• Tablets Preparation:**

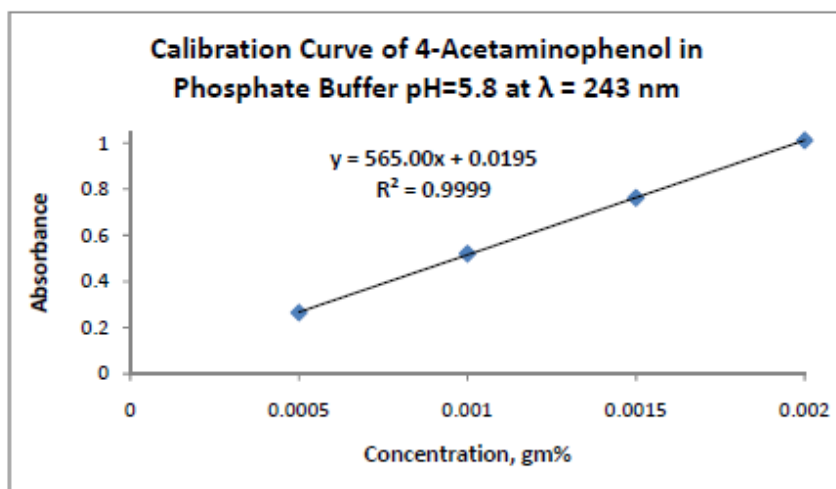
1. Sieve all ingredients using 1.4 mm mesh.
2. Weigh the required amounts to prepare 10 grams mixture.
3. Mix all ingredients, except Mg-stearate, together in a plastic bag for three minutes.
4. Add Mg-Stearate and mix for 30 seconds (maximum 1 minute), why?
5. Weigh 600 mg of the mixture prepared above (three weights each of 600 mg).
6. Compress the three tablets using **hydraulic press** (follow the instructions of your instructor).
7. Reserve the prepared tablets for dissolution testing (next practical session).

**• Tablets Testing (Dissolution Testing):**

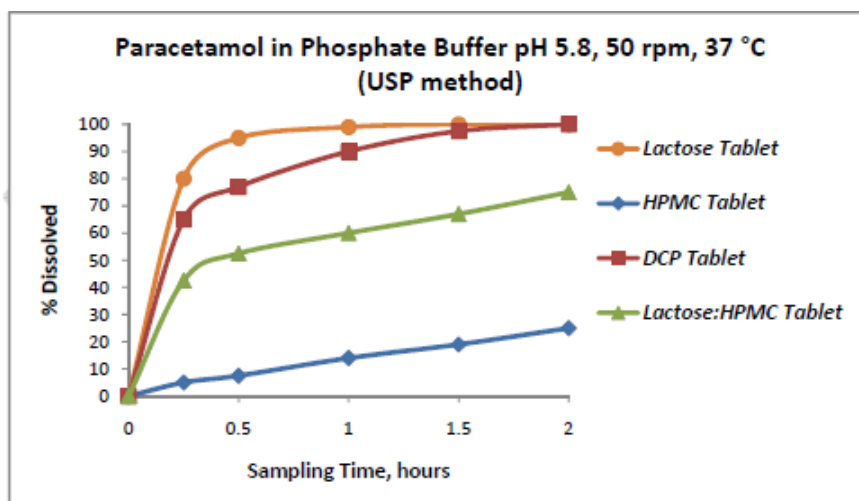
1. Weigh each tablet and record its weight.
2. Perform dissolution testing using the same procedure parameters in **experiment 3**.
3. Use the sampling methodology described above.

## Results and Data Analysis

- Use the following **calibration curve** to do find out the samples concentrations



- Calculate % Dissolved for each sample as described in table next page.
- Construct a Multipoint Dissolution Profile as follow:



### Dissolution Samples Analysis

Sampling Time		Absorbance	Dilution Factor	Concentration mg%, w/v		Amount Dissolved, mg			Percent age Dissolved
Minutes	Hours			Diluted	Before Dilution	in 5 mL sample	in 900 mL	Total	
0	0	0	0	0	0	0	0	0	0
15	0.25	Abs <sub>1</sub>	DF <sub>1</sub>	C <sub>1</sub> =A <sub>1</sub> /E%	CV <sub>1</sub> =C <sub>1</sub> *DF <sub>1</sub>	as <sub>1</sub> =CV <sub>1</sub> *5mL/100 mL	Am <sub>1</sub> =CV <sub>1</sub> *900mL/100mL	T <sub>1</sub> =Am <sub>1</sub>	
30	0.5	Abs <sub>2</sub>	DF <sub>2</sub>	C <sub>2</sub> =A <sub>2</sub> /E%	CV <sub>2</sub> =C <sub>2</sub> *DF <sub>2</sub>	as <sub>2</sub> =CV <sub>2</sub> *5mL/100 mL	Am <sub>2</sub> =CV <sub>2</sub> *900mL/100mL	T <sub>2</sub> =Am <sub>2</sub> +as <sub>1</sub>	
45	0.75	Abs <sub>3</sub>	DF <sub>3</sub>	C <sub>3</sub> =A <sub>3</sub> /E%	CV <sub>3</sub> =C <sub>3</sub> *DF <sub>3</sub>	as <sub>3</sub> =CV <sub>3</sub> *5mL/100 mL	Am <sub>3</sub> =CV <sub>3</sub> *900mL/100mL	T <sub>3</sub> =Am <sub>3</sub> +as <sub>1</sub> +as <sub>2</sub>	
60	1.00	Abs <sub>4</sub>	DF <sub>4</sub>	C <sub>4</sub> =A <sub>4</sub> /E%	CV <sub>4</sub> =C <sub>4</sub> *DF <sub>4</sub>	as <sub>4</sub> =CV <sub>4</sub> *5mL/100 mL	Am <sub>4</sub> =CV <sub>4</sub> *900mL/100mL	T <sub>4</sub> =Am <sub>4</sub> +as <sub>1</sub> +as <sub>2</sub> +as <sub>3</sub>	
90	1.30	Abs <sub>5</sub>	DF <sub>5</sub>	C <sub>5</sub> =A <sub>5</sub> /E%	CV <sub>5</sub> =C <sub>5</sub> *DF <sub>5</sub>	as <sub>5</sub> =CV <sub>5</sub> *5mL/100 mL	Am <sub>5</sub> =CV <sub>5</sub> *900mL/100mL	T <sub>5</sub> =Am <sub>5</sub> +as <sub>1</sub> +as <sub>2</sub> +as <sub>3</sub> +as <sub>4</sub>	
120	2.00	Abs <sub>6</sub>	DF <sub>6</sub>	C <sub>6</sub> =A <sub>6</sub> /E%	CV <sub>6</sub> =C <sub>6</sub> *DF <sub>6</sub>	as <sub>6</sub> =CV <sub>6</sub> *5mL/100 mL	Am <sub>6</sub> =CV <sub>6</sub> *900mL/100mL	T <sub>6</sub> =Am <sub>6</sub> +as <sub>1</sub> +as <sub>2</sub> +as <sub>3</sub> +as <sub>4</sub> +as <sub>5</sub>	

Active ingredient in the tested tablet (mg)  
= tablet weight \* ratio of the active in the tablet  
Here.....

Active ingredient in the tested tablet  
= tablet weight \*  $\frac{1}{3}$  mg

$$\% \text{Dissolved} = \frac{\text{Total amount Dissolved,mg}}{\text{Claimed amount,mg}} * 100\%$$

Here.....

$$\% \text{Dissolved} = \frac{\text{Total amount Dissolved in 900mL,mg}}{\text{Claimed Amount,mg}} * 100\%$$

Example at 1.5 hour:

$$\% \text{Dissolved}_{1.5} = \frac{T_5}{\text{Active ingredient quantity in the tablet,mg}} * 100\%$$

### DISCUSSION:

- Co-relate each profile to the components of different formulas.
- Compare the resulted dissolution profiles to each other.
- Comment on your results.

## EXPERIMENT 6

### QUALITY CONTROL OF TABLETS

#### OBJECTIVES:

1. To be familiar with the official and non-official quality control tests for tablets.
2. To perform some of the quality control tests on tablets.

#### INTRODUCTION:

The manufacturer must give his assurance that the final product is of suitable quality. Several **Quality Control Test** are performed for each batch of tablets produced, and such tests may include: Weight Uniformity, Content Uniformity, Friability Test, Disintegration, and Dissolution Test.

These tests categorized as following:

##### A. Official Pharmacopial Tests:

1. Uniformity of Weight (BP).
2. Uniformity of Drug Content (BP & USP).
3. Disintegration Test (BP & USP).
4. Dissolution Rate (BP & USP).

##### B. Non-Official (Non-Pharmacopial) Tests:

1. Hardness (Crushing Strength).
2. Friability (become official in USP 1995).
3. Uniformity of Thickness.

#### 1. Friability Test:

It is another measure of tablet's **strength** and it is related to a tablet's ability to withstand both shock and abrasion without crumbing during the handling of manufacturing, packaging, shipment, and consumer use.

Tablets friability may be influenced by the **moisture content** of the tablets granulation in the finished tablets. A low but acceptable moisture level frequently serves to act as a binder. Very dry granulation that contain only fractional percentages of moisture will often produce more friable tablets than will granules containing 2 to 4 % moisture.

This test is performed using a friabilator (Figure 1), this device subjects a number of tablets (minimum weight = 6.5 gm) to the combined effects of abrasion & shock utilizing a plastic chamber which revolves at 25 rpm dropping the tablets a distance of 6 inches with each

revolution. Normally, a pre-weighed tablets sample is placed in the friabilator, which is then operated for 100 revolutions. The tablets then are dusted & reweighed.

Conventional compressed tablets that lose **less than 0.5 to 1.5%** in weight are generally acceptable. So me chewable tablets & most effervescent tablets would have higher friability weight losses, which accounts for the special stack packaging that may be required.

When **capping** is observed during friability testing, the tablet should not be considered acceptable, regardless of what the percentage weight loss result in.



FIGURE 1. FRIABILATOR <sup>(1)</sup>

## 2. Disintegration Time:

For most tablets the first important steps in order to enter the solution is the **breakdown of the tablet in to smaller particles or granules**, this process is known as disintegration. The time that it takes a tablet to disintegrate is measured in a device described in the Pharmacopeias.

### Apparatus:

The USP has long had a device to test disintegration. The device uses six glass tubes, three inches long; open at the top & held against a 10-mesh screen at the bottom end of the basket rack assembly (Figure 2).

To test for disintegration time, one tablet is placed in each test tube, and the basket rack is positioned in one-liter beaker of 1-water, or 2-simulated gastric or 3-intestinal fluid at  $37 \pm 2^\circ\text{C}$  such that the tablet remain 2.5 cm below the surface of the liquid on their upward movement and descent not closer than 2.5 cm from the bottom of the beaker.

Perforated plastic disks may also be used in the test. These are placed on the top of the tablets and impart an abrasive action to the tablets. The disks may or may not be meaningful or impart more sensitivity to the test, but they are useful for tablets that float.

To be in compliance with USP standards the tablets must disintegrate, and all particles pass through the 10-mesh screen in the time specified. If any residue remains, it must have a soft mass with no palpably firm core.

**Factors that affect disintegration time:**

It has been established that one should not expect a correlation between Disintegration & Dissolution. However, since the dissolution of a drug from the fragmented tablet appears to partially or completely control the appearance of the drug in the blood, disintegration is still used as a guide to the formulator in the preparation of an optimum tablet formula and as in-process control test to ensure lot-to-lot uniformity.

The formulator should be aware that:

- 1- The medium used.
- 2- The temperature of the medium.
- 3- The operator recording the results.

All can have a significant effect on disintegration time.

In addition, many factors involved with a tablet's formula and method of manufacture can affect the disintegration such factors are:

- 4- The nature of the drug.
- 5- The diluents used.
- 6- The binder and its amount.
- 7- The type and amount of disintegrating agent.
- 8- The type of amount of lubricant.
- 9- The method of incorporation for all these additives. (The compaction pressure used to make the tablets also influences the disintegration, in general disintegration time's increase with an increase in pressure).





FIGURE 2. DISINTEGRATION APPARATUS.<sup>(2)</sup>

### 3. Thickness Uniformity:

Tablets thickness should be controlled **with 5% or less of the relative standard value.**

Any variation in tablet thickness should not be apparent to the unaided eye to maintain product acceptance by consumer as well as to facilitate packaging. At constant compressive load, tablet thickness varies with changes in die fill and tablet weight. Whereas, with a constant die fill, thickness varies in variation in compressive load.

#### Three set of factors influence tablet thickness and tablet thickness control:

1. The physical properties of raw materials including crystal form and true bulk density.
2. Control of upper and lower punch lengths, which should be standardized.
3. The granulation prosperities including bulk density, tapped density, particle size, and particle size distribution.

### 4. Tablet Hardness:

Tablet hardness is defined as the force required to break a tablet in a diametrical compression test. A tablet requires a certain amount of strength or hardness to withstand mechanical shocks of handling in its manufacturing, packaging, and shipping. More recently, the relationship and importance of hardness as it may influence disintegration and perhaps more significantly, drug dissolution rate, become apparent.

#### 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 (Figure 3). Hardness is thus sometimes termed "Tablets Crushing Strength".



FIGURE 3. TABLET HARDNESS TESTER.<sup>(3)</sup>

#### Factors that Affect Tablet Hardness:

The hardness of a tablet is a function of many things all working together. The three factors that were noted in the tablet thickness may also produce variation in tablet hardness.

Hardness is a function of the applied pressure and is therefore a function of those factors which cause the force to vary. As additional pressure is applied to make a tablet, the hardness values increase, this relationship holds up **the maximum value beyond which increases in pressure cause the tablet to laminate or cap, thus destroying the integrity of the tablet.**

**Time:** Tablets generally are harder several **hours after** compression than they are immediately after compression.

**Lubricant:** can affect the tablet hardness when used in too high concentration or mixed for too long period. The lubricant will coat the granules and interfere with tablet bonding.

**Size:** Larger tablet require a greater force to cause fractures (harder) than small tablet.

An appropriate balance between a minimally acceptable tablet hardness to produce an adequate friability value and a maximum acceptable tablet hardness to achieve adequate tablet dissolution may be required.

#### 5. Weight Variation:

In manufacturing of tablet our aim is to produce tablet product that can be validated as to its safety, efficacy, and reliability. In a way that each tablet is designed to have certain weight and to check the uniformity of weight we find in different pharmacopeias a method for weight variation as follows:

**Method:**

The test is run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average (as a percent of the average weight of the sample).

The tablets meet the USP weight variation test if no more than two tablets are outside the percentage limit and no tablet differs by more than twice the percentage limit. The weight variation tolerance for uncoated tablets differs depending on average tablet weight:

**Table 1. The weight variation tolerance<sup>(4)</sup>**

<b>Average Weight of Tablets (mg)</b>	<b>Maximum Percentage Difference Allowed</b>
<b>130 or less</b>	<b>10 %</b>
<b>130 to 324</b>	<b>7.5 %</b>
<b>More than 324</b>	<b>5 %</b>

The weight variation test is a satisfactory method of determining content uniformity of tablets if

1. The tablet is all-drug or essentially (90-95%) all-active ingredient, or
2. The uniformity of drug distribution of the granulation or powder from which the tablets are made is perfect.

The weight variation test is not sufficient to assure uniform potency of moderate to low-dose drugs, in which excipients make up the bulk of the tablet weight.

**Causes of Weight Variation:**

Causes of weight variation can be separated into:

- a. Granulation problems.
- b. Mechanical problems.

The actual weight of the tablet is determined by geometry of the die and the position of the lower punch in the die as dictated by the weight adjustment cam. If everything is working well mechanically, the weight can be caused to vary by poorly flowing granules, which causes a spasmodic filling of the dies. The improper mixing of the Glidant into the granulation can influence the weight variation by not allowing for uniform flow. If the granule particle size is too great for the die size, the dies will not be uniformly filled, causing weight variation. Granulation that have a wide particle size distribution which is resulted when a granulation has been thoroughly mixed or when the granulation has been stored in an area where vibrations were present to cause segregation of particles. Can have a localized non-uniformity of density in the granulation and with fixed geometry this will cause varying amounts of granulation to fill the

dies, causing weight variation. Furthermore, as the particle shape became more angular, the weight variation increased.

Mechanical problems can cause weight variation with a good granulation. A set of lower punches of non-uniform length will cause weight variation, as will lower punches that are dirty enough to restrict their movement to their lowest point during die fill. A cupped lower punch that gets filled in with a sticking granulation will cause weight variation.

### **6. Content uniformity test:**

The content uniformity test is performed to ensure that every dosage form contains equal amount of drug substance. Normal testing is confirmed by performing specific assay to determine the content of drug material contained in a particular dosage form.

According to USP, the procedure for content uniformity includes two stages:

Stage one; perform the **assay test** to 10 randomly taken units.

It passes if the relative standard deviation is less than 6% and no value outside 85-115%. If one or more value is outside 75-125% the test fails.

Stage two: perform assay test to an extra 20 dosage units, if the relative standard deviation for the 30 units (20 from stage 2 and 10 from stage 1) is less than 7.8 %, not more than one value is outside 85-115% and no value is outside 75-125% the batch passes the test.

## **EXPERIMENTAL PART:**

**a. Materials:** Paracetamol Tablets.

**b. Apparatus:** Hardness Tester, Friability tester, analytical balance, hardness tester, digital caliper, UV-visible spectrophotometer

### **1. FRIABILITY TEST:**

- Place 6.5 grams of tested tablets (record this weight as tablets initial weight) in the drum of the friabilator.
- Operate the instrument for 4 minutes using 25 rpm as rotational speed.
- After the time elapsed remove the tablets and dust them using a brush.
- Examine the tablets for any sign of capping, lamination or breakage.
- Weigh the tablet and record the weight as tablets final weight.
- Calculate the Percentage Weight Loss using the following equation:

Percentage Weight Loss

$$= (\text{tablet initial weight} - \text{tablet final weight}) / (\text{tablet initial weight}) * 100\%$$

**2. HARDNESS TEST:**

- a. Using the Hardness Tester measure the hardness for 10 tablets.
- b. Calculate the mean, standard deviation, and relative standard deviation of the tested values.

**3. WEIGHT VARIATION TEST:**

- a. Measure the weight of 20 tablets of the tested tablets, weight should be measured in milligrams.
- b. Calculate the Average Tablets Weight in grams.
- c. For each tablet of the 20 tested tablets calculate the Maximum Percentage Difference Allowed.  
Maximum Percentage Difference Allowed  
= ((tablet weight-average tablets weight)/average tablets weight)\* 100%
- d. Interpretation of the results should be done according to table underweight variation section above.

**4. THICKNESS VARIATION TEST:**

- a. Measure the thickness of 10 tablets of the tested tablets using the Caliber as directed by your instructor.
- b. Calculate the mean, standard deviation, and relative standard deviation of the tested values.

**RESULTS:**

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

**1. FRIABILITY TEST:**

Initial Weight (grams)	Final Weight (grams)	Observation (Yes or No)		
		Breakage	Lamination	Capping

**2. WEIGHT VARIATION TEST:**

Tablet Number	Tablet weight (g)	Maximum Percentage Difference Allowed
1		
2		
3		
...		
20		
Average Weight (g)		

**3. HARDNESS TEST:**

Tablet Number	Tablet Hardness (N)
1	
2	
3	
...	
10	
Average Hardness (N)	
Standard Deviation	
RSD	

**4. THICKNESS VARIATION TEST:**

Tablet Number	Tablet Thickness (mm)
1	
2	
3	
...	
10	
Average Thickness (mm)	
Standard Deviation	
RSD	

**5. CONTENT UNIFORMITY TEST:**

Tablet Number	Content of Acetaminophen
1	
2	
3	
...	
10	

**DISCUSSION:**

Discuss your findings in accordance to pharmacopoeia specifications.

**REFERENCES:**

- <sup>(1)</sup> <https://www.erweka.com/> (2016). *Tablet Friability/Abrasion Tester TAR 120 / 220*. [online] Available:[https://www.erweka.com/images/downloads/manualsENG/otherphysicalsENG/TAR%20120-220\\_Manual\\_21842\\_En\\_V1.3-web.pdf](https://www.erweka.com/images/downloads/manualsENG/otherphysicalsENG/TAR%20120-220_Manual_21842_En_V1.3-web.pdf). [Accessed 20 Feb. 2020].
- <sup>(2)</sup> [pharmapproach.com](https://www.pharmapproach.com) (2019). *Quality Control Tests for Tablets*. [online] Available at: <https://www.pharmapproach.com/quality-control-tests-for-tablets/2/> [Accessed 20 Feb. 2020].

<sup>(3)</sup> <https://www.erweka.com/> (2019). *HARDNESS TESTERS* . [online] Available at:

<https://www.erweka.com/hardness-testers/item/tbh-125.html>. [Accessed 20 Feb. 2020].

<sup>(4)</sup> avinder Kumar, Jasbir Singh, Mamta Antil, Virender Kumar.(2016). QUALITY CONTROL OF TABLETS: A REVIEW. *International Journal of Universal Pharmacy and Bio Sciences* 5(4), [online]

[https://www.researchgate.net/publication/315671284\\_INTERNATIONAL\\_JOURNAL\\_OF\\_UNIVERSAL\\_PHARMACY\\_AND\\_BIO\\_SCIENCES\\_IMPACT\\_FACTOR\\_296\\_ICV\\_513\\_Pharmaceutical\\_Sciences\\_QUALITY\\_CONTROL\\_OF\\_TABLETS\\_A\\_REVIEW](https://www.researchgate.net/publication/315671284_INTERNATIONAL_JOURNAL_OF_UNIVERSAL_PHARMACY_AND_BIO_SCIENCES_IMPACT_FACTOR_296_ICV_513_Pharmaceutical_Sciences_QUALITY_CONTROL_OF_TABLETS_A_REVIEW) [Accessed 20 Feb. 2020].

## EXPERIMENT 7

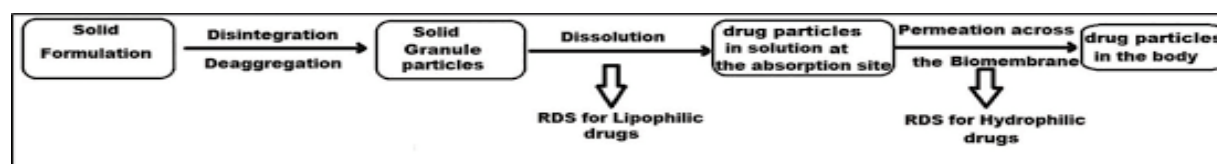
### DISSOLUTION TEST OF TABLETS

#### OBJECTIVES:

To study and evaluate the dissolution test of tablets and capsules.

#### INTRODUCTION

The effectiveness of tablet or capsule dosage forms relies on the drug dissolving in the fluid of GIT prior to Absorption into systemic circulation. **Tablet Dissolution** is a standardized method for measuring the rate of drug release from a dosage form. (Dissolution defined as the process by which a known amount of drug substance goes into solution per unit of time under standardized conditions.)



**Figure 1.** Disintegration and dissolution of solid drugs<sup>(1)</sup>

The principle function of the dissolution test may be summarized as follows:

1. Optimization of therapeutic effectiveness during product development and stability assessment.
2. Routine assessment of production quality to ensure uniformity between production lots.
3. Assessment of "Bioequivalence", that is to say, production of the same biological availability from discrete batches of products from one or different manufacturers.
4. Prediction of "in-vivo" availability i.e. bioavailability (where applicable).

The rate at which a solid dissolves in a solvent was proposed by "**Noyes and Whitney**" in 1897 and elaborated subsequently by other workers. The equation can be written as:

$$\frac{dC}{dt} = \frac{AD(Cs - C)}{h * V}$$



**A:** surface area of exposed solid.

**D:** diffusion coefficient.

**C<sub>s</sub>:** drug concentration in the diffusion layer (solubility of solid).

**C:** drug concentration in the bulk.

**h:** thickness of diffusion layer.

**V:** volume of the dissolution medium. It is in the equation to make unit of the dissolution rate per unit volume.

During early phase of dissolution,  $C_s \gg C$  (sink condition) and  $C_s$  is set to equal solubility in the dissolution medium (S), also A is considered constant thus the above equation becomes:

$$\frac{dC}{dt} = KS, \text{ Where } K \text{ is } AD/hV.$$

**K** is called the intrinsic dissolution rate constant. Hydrophilic drugs have high intrinsic dissolution rate as they have high **S**, while hydrophobic drug has low intrinsic dissolution rate.

When  $K > 1$ , absorption process is not dissolution limited.

When  $K < 1$ , absorption process is dissolution limited.

## EXPERIMENTAL PART:

### a. Materials:

Revanin ® 500 mg tablets, Paracetamol powder, Monobasic Potassium Phosphate, Sodium Hydroxide.

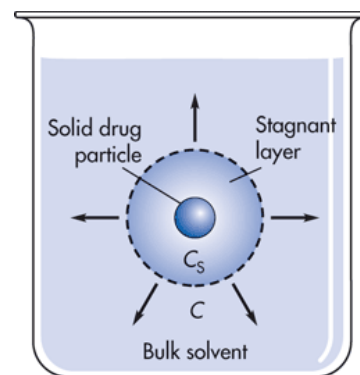
### b. Apparatus:

Dissolution Apparatus, UV/VIS Spectrophotometer, pH meter.

### c. Method:

#### I. Dissolution Parameters:

Medium	: Phosphate Buffer pH 5.8
Apparatus	: Paddle
Time	: 30 minutes
Volume	: 900 mL
RPM	: 50 rpm
Wavelength	: 243 nm
Temperature	: 37 °C ± 0.5 °C
Tolerance (Q)	: 80%



**FIGURE 2. DISSOLUTION OF TABLET IN THE MEDIA<sup>(2)</sup>**

## II. Preparation of Phosphate Buffer pH 5.8 Solution:

1. Solution 1: Weigh accurately 20.42 grams of Monobasic Potassium Phosphate ( $\text{KH}_2\text{PO}_4$ ) and place it in 500 mL volumetric flask and adjust enough distilled water to completely dissolve the powder then complete the volume up to the 500mL mark using distilled water.
2. Solution 2: Weigh accurately 0.43 grams Sodium Hydroxide ( $\text{NaOH}$ ) and place it in 250mL volumetric flask and adjust enough distilled water to completely dissolve the powder then complete the volume up to the 250mL mark using distilled water.
3. Transfer solution 1 and solution 2 to 3-liter volumetric flask and complete the volume up to the 3 liter mark with distilled water then mix well.
4. Adjust the pH of the solution to achieve  $\text{pH} = 5.8 \pm 0.1$ , using Phosphoric acid (if pH value where  $> 5.8$ ) or  $\text{NaOH}$  solution (if pH value where  $< 5.8$ ).

## III. Procedure:

1. Turn the heater of the dissolution apparatus on and control the temperature to achieve the specified value ( $37^\circ\text{C}$ ).
2. Clean two vessels and in each of them place 900 mL of medium using measuring cylinder.
3. Fix the paddles to be  $25 \pm 2$  mm away from the bottom of vessel.
4. Start operating the paddles at 50 rpm rotational speed.
5. Place one Revanin<sup>®</sup> 500 mg tablet in each vessel (only two vessels will be used) and immediately start timing.

**NB: dissolution vessels should be covered to prevent evaporation of the dissolution medium and hence affecting the concentration.**

6. After 30 minutes elapsed withdraw 3mL sample from each vessel using a volumetric pipette. Filter each sample to get rid of any undissolved particles that may present in the sample) using Syringe filter (always discard the first milliliter).
7. Dilute each sample using the medium up to 100ml.
8. Read the absorbance of the diluted samples solutions at  $\lambda = 243$  nm using the medium (Phosphate Buffer pH = 5.8) as a blank.

## IV. Preparation of Standard Solution:

### Calibration Curve:

- a. Prepare 0.050gm% w/v of Acetaminophen in Phosphate Buffer pH 5.8 (place 50 mg Acetaminophen in 100 mL Volumetric Flask, dissolve using few 10 mL of the solvent then complete volume up to the 100 mL mark with Phosphate Buffer pH 5.8) → **Standard Stock Solution**

b. Withdraw 1, 2, 3 & 4 mL from the Standard Stock Solution and place each in 100 mL volumetric flasks and complete the volume up to 100mL mark with Phosphate Buffer pH 5.8 →

### Standard Solutions

c. Measure the standard solutions absorbance using Phosphate Buffer pH 5.8 as a blank at  $\lambda=243\text{nm}$ .

## RESULTS AND DATA ANALYSIS

### Calibration Curve:

- Plot solutions absorbances vs their concentrations in mg%.

e.g. Standard solution no. 1 concentration = 50mg% / D.F= 0.5mg%

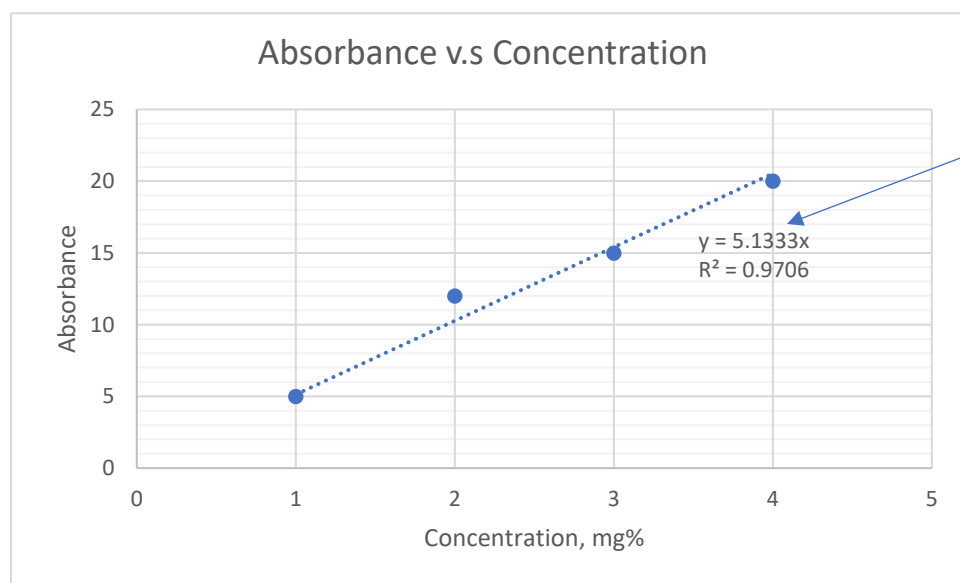
**D.F(Dilution Factor)**

$$= \frac{\text{Final Volume}}{\text{Initial Volume}}$$

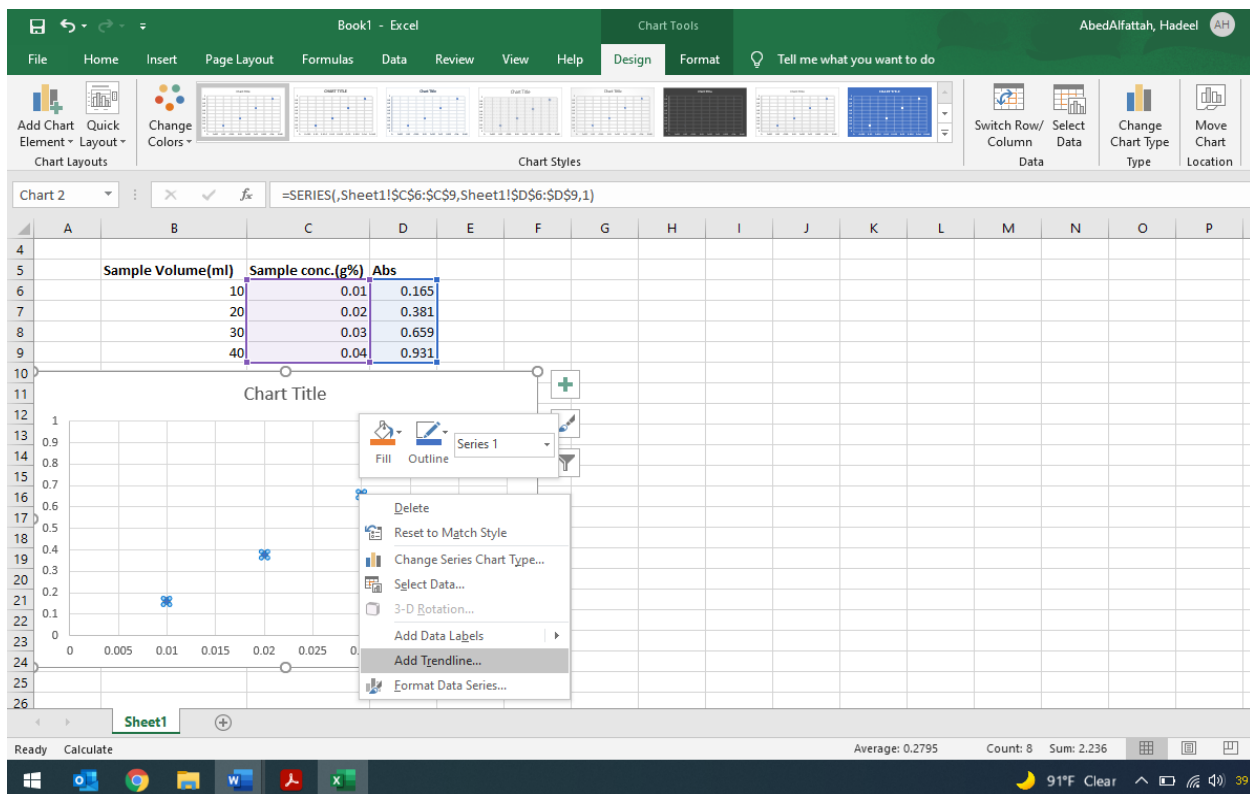
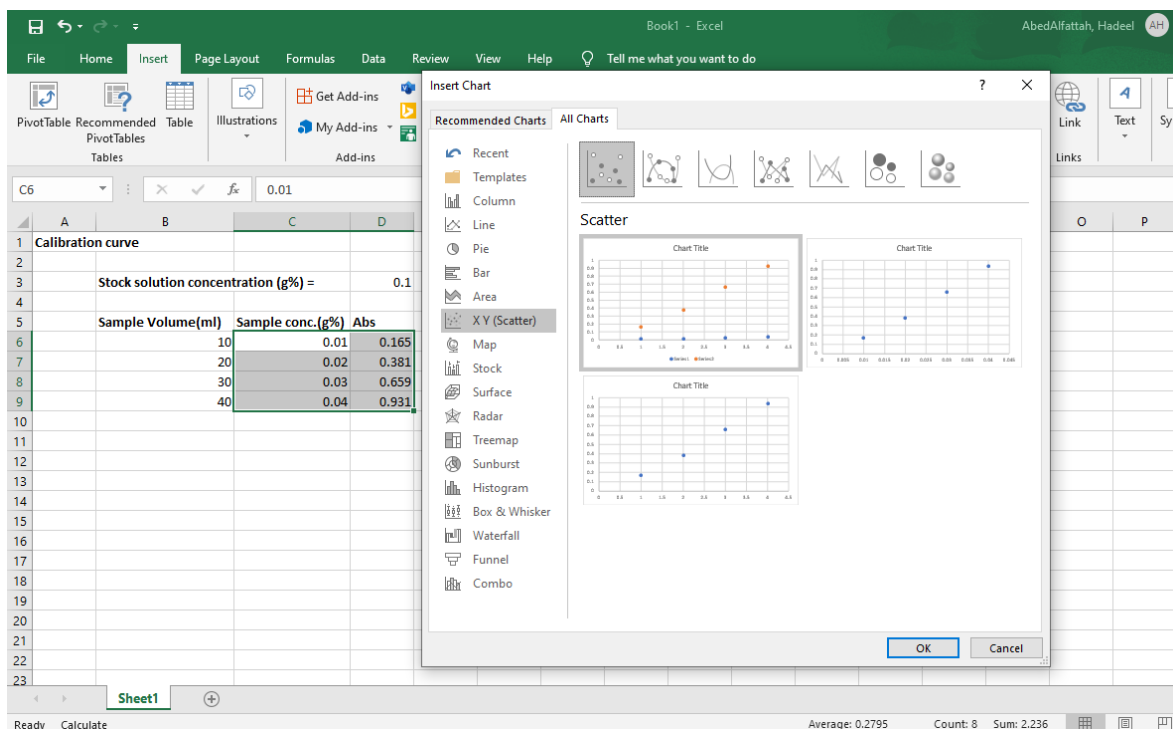
- Apply Beer's Law to the calibration curve straight line equation as following:

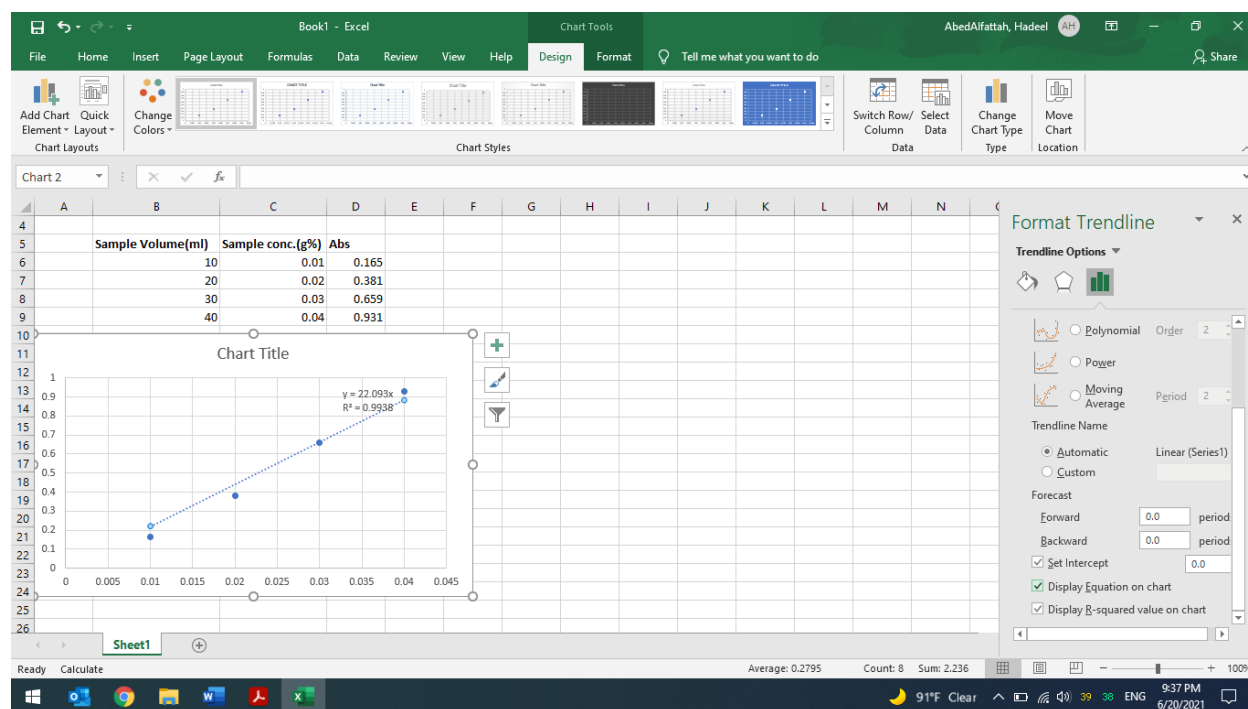
$$A = a \cdot b \cdot C$$

Where A is the Absorbance, A is absorptivity (slope of the straight line equation), b is cell bath (=1 cm), and C is the concentration of the substance of interest.



Slope = absorptivity, here absorptivity is  $E\%$  since the concentration unit is mg%, the  $E\%$  unit is  $(\text{mg}\%^{-1} \cdot \text{cm}^{-1})$





### Dissolution Samples Analysis

- Use E% (absorptivity) value from calibration curve to calculate concentrations in mg% w/v of the mixing samples.

$$\text{Sample no. 1 concentration mg\% w/v (diluted sample concentration)} = \frac{\text{sample absorbance}}{E\%} \text{ mg\%}$$

$$\text{Sample no. 1 concentration mg\% w/v (vessel concentration)} = \frac{\text{sample absorbance}}{E\%} * D.F$$

- Calculate the total amount (in mg) dissolved in each vessel.

$$\text{E.g. Vessel no. 1 amount (mg)} = \text{Vessel Concentration} * \frac{900 \text{ ml}}{100 \text{ ml}}$$

Calculate the % Dissolved for each tablet using the following ratio:

$$\% \text{ dissolved} = \frac{\text{total amount dissolved in 900 ml}}{\text{claimed amount}} * 100\%$$

Note: claimed amount is the labeled amount, which is equal to 500 mg.

## DISCUSSION:

Interpretation of the data must be done according to the USP criteria.

Acetaminophen Tablets

» Acetaminophen Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of acetaminophen ( $C_8H_9NO_2$ ).

**Packaging and storage—** Preserve in tight containers, and store at controlled room temperature.

**Labeling—** Label Tablets that must be chewed to indicate that they are to be chewed before swallowing.

**USP Reference standards** [{ 11 }](#) —

[USP Acetaminophen RS](#) .

**Identification—**

**A:** The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

**B:** Triturate an amount of powdered Tablets, equivalent to about 50 mg of acetaminophen, with 50 mL of methanol, and filter: the clear filtrate (test solution) responds to the [Thin-layer Chromatographic Identification Test](#) [{ 201 }](#), a solvent system consisting of a mixture of methylene chloride and methanol (4:1) being used.

**Dissolution** [{ 711 }](#) —

*Medium:* pH 5.8 phosphate buffer (see *Buffer Solutions* in the section [Reagents, Indicators, and Solutions](#)); 900 mL.

*Apparatus 2:* 50 rpm.

*Time:* 30 minutes.

**Procedure—** Determine the amount of  $C_8H_9NO_2$  dissolved by employing UV absorption at the wavelength of maximum absorbance at about 243 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium*, if necessary, in comparison with a Standard solution having a known concentration of [USP Acetaminophen RS](#) in the same *Medium*.

**Tolerances—** Not less than 80% (Q) of the labeled amount of  $C_8H_9NO_2$  is dissolved in 30 minutes.

Q= 80%

Interpretation—Unit Sample—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to the accompanying **Acceptance Table**. Continue testing through the three stages unless the results conform at either S1 or S2. **The quantity Q** is the amount of dissolved active ingredient specified in the individual mono-graph, expressed as a percentage of the labeled content; the 5%, 15%, and 25% values in the Acceptance Table are percentages of the labeled content so that these values and Q are in the same terms.

**Acceptance Table<sup>(3)</sup>**

<b>Stage</b>	<b>Number Tested</b>	<b>Acceptance Criteria</b>
S <sub>1</sub>	6	Each unit is not less than $Q + 5\%$ .
S <sub>2</sub>	6	Average of 12 units (S <sub>1</sub> + S <sub>2</sub> ) is equal to or greater than Q, and no unit is less than $Q - 15\%$ .
S <sub>3</sub>	12	Average of 24 units (S <sub>1</sub> + S <sub>2</sub> + S <sub>3</sub> ) is equal to or greater than Q, not more than 2 units are less than $Q - 15\%$ , and no unit is less than $Q - 25\%$ .

Please refer to Appendix for acetaminophen monograph sented by email.

## **REFERENCES**

- <sup>(1)</sup> G. Thirumurugan and M.D. Dhanaraju (2017). *Marine Polysaccharides as Multifunctional Pharmaceutical Excipients, Biological Activities and Application of Marine Polysaccharides*, Emad A. Shalaby, IntechOpen, DOI: 10.5772/66191. [online] Available from: <https://www.intechopen.com/books/biological-activities-and-application-of-marine-polysaccharides/marine-polysaccharides-as-multifunctional-pharmaceutical-excipients> [Accessed 26 FEB. 2020].
- <sup>(2)</sup> Shargel L, Wu-pong S, Yu ABC: *Applied biopharmaceutics and pharmacokinetics*, 6<sup>th</sup> edition. [online] Available from: [www.accesspharmacy.com](http://www.accesspharmacy.com) [Accessed 26 FEB. 2020].
- <sup>(3)</sup> ERWEKA® Total Laboratory Services. (2018) *DISSOLUTION*. Available at: <https://totallaboratoryservices.co.uk/dissolution-testers-usp-guidelines>. [Accessed 26 FEB. 2020].

## EXPERIMENT 8

# CONSISTENCY OF FORMULATED PREPARATIONS: CAPSULES COMPOUNDING AND UNIFORMITY OF ITS WEIGHT

### OBJECTIVES:

The purposes of this experiment are to develop a proficiency in formulating and compounding capsules as solid dosage forms and to perform weight variation test on the capsule as one of the quality control measures to devise the relationship between angle of repose and capsule weight variation using hand packing capsule technique.

### INTRODUCTION:

Hand packing capsules has been a standard practice of pharmacists for decades. A firm grasp of the skill and relevant calculations is necessary for this technique, especially when small number of capsules is needed.

To ensure the consistency of the 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 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, which can be demonstrated by either content uniformity or weight variation method.



FIGURE 1. CAPSULES COMPOUNDING EQUIPMENT. <sup>(1)</sup>

### EXPERIMENTAL PART:



**Part I: Capsule compounding**

<b>Formulation A</b>	<b>Weight</b>
Acetaminophen USP (powder)	295 mg
Lactose	450 mg
Magnesium Stearate	154 mg
Corn Starch (Diluent)	375 mg
	<b>Total<sup>*</sup>: 1274mg</b>
<b>Formulation B</b>	
Acetaminophen USP (powder)	295 mg
Lactose NF	450 mg
Corn Starch	375 mg
Magnesium Stearate	154 mg
Avicel	230 mg
	<b>Total<sup>*</sup>: 1504mg</b>

\*Adjust the content of each capsule to weigh up to 400mg.

After adjusting the weights, don't forget to calculate an extra amount of powder compounded to account for the losses due to leakage and processing error in filling (around 10%).

For each blend carefully pour the blend into a plastic laboratory bag and twist or seal the bag shut with at least as much air trapped in the bag as product, then shake the sealed bag for 5 minutes by repeatedly inverting the bag.

Dispense 20 capsules of each blend using the capsule machine.

**Part II: Weight variation evaluation**

Weigh an intact capsule. Open the capsule without losing any part of the shell and remove the contents as completely as possible. Weigh the shell. The mass of the contents is the difference between weighing. Repeat the procedure with another 19 capsules.

**RESULTS AND DISCUSSION**

The following test provides for the permissible variations in the weight of individual dosage units, expressed in terms of the allowable deviation from the average weight of a sample. Weigh 20 intact capsules individually, and determine the average weight.

(a) Record individual weight of each capsule:

Sample number	Weight
1.	
2.	
3.	
...	
20.	

(b) Total weights of 20 capsules ( $W$ ) =

(c) Average weight of the capsules ( $w$ ) =  $W / N$ , where  $N$  is number of capsules

(d) Calculate 90% of the average weight ( $w$ )  $\times 0.90$  =

(e) Calculate 110% of the average weight ( $w$ )  $\times 1.10$  =

(f) Record the number of capsules whose weight meet the compendia requirements

(g) Record the number of capsules whose weight are less than 90% of the average weight and greater than 110% of the average weight

## **CONCLUSIONS**

Interpret your results with relation to weight variation test and mention the differences between the preparations that you made.

## **REFERENCES**

<sup>(1)</sup> Capsuleconnection.com/ (1973). *Capsule connection*. [online] Available at: <https://capsuleconnection.com/profiller-3600>. [Accessed 20 Feb. 2020].

## EXPERIMENT 9

# DISINTEGRATION OF TABLETS AND CAPSULES

### OBJECTIVES:

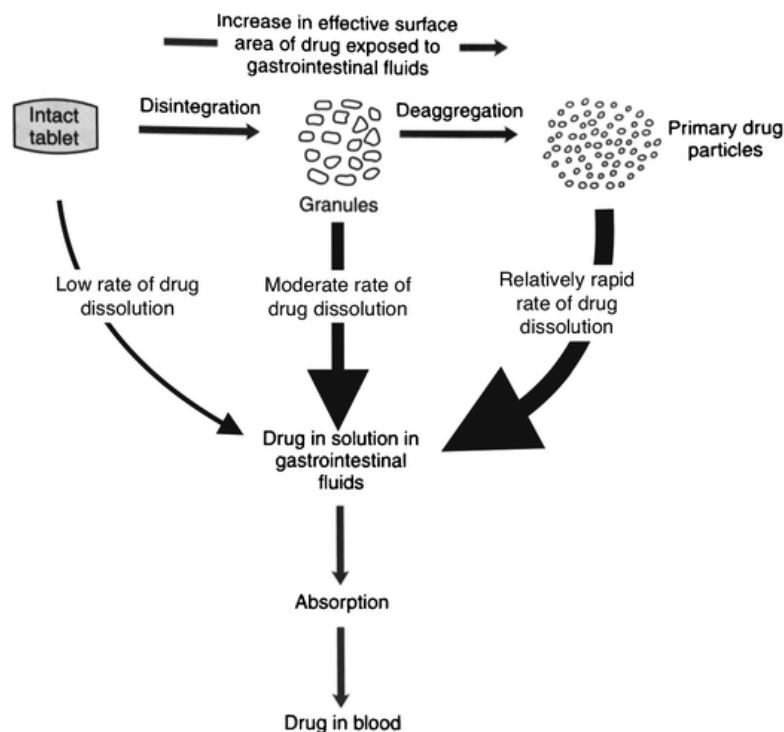
- 1- To study and evaluate the disintegration test of enteric coated tablet and capsules.
- 2- To assess the quality of different brands of Paracetamol tablets in Jordanian market.

### INTRODUCTION:

When a powdered drug is granulated and compressed into a tablet, the effective surface area of the medicinal compound is decreased. An immediate-release tablet must break up or disintegrate in the gastrointestinal fluids into granules, which then must disintegrate into primary particles. The drug needs to dissolve from the primary particles before the molecules or ions of the medicinal compound can be absorbed by the gastrointestinal mucosa. Improperly formulated and improperly processed compressed tablets may retard drug release with a decrease in bioavailability. If a tablet does not disintegrate, the surface available for dissolution is restricted only to the surface area of the tablet.

This test determines **whether dosage forms such as tablets or capsules disintegrate within a prescribed time when placed in a liquid medium under the prescribed experimental conditions.**

For the purpose of this test, disintegration does not imply complete solution of the dosage unit or even of its active constituent. Disintegration is defined as that state in which no residue of the unit under test remains on the screen of the apparatus or, if a residue remains, it consists of fragments of disintegrated parts of tablets component parts such as insoluble coating of the tablets or of capsule shells, or of any melted fatty substance from the pessary or suppository or is a soft mass with no palpable core. If discs have been used with capsules, any residue remaining on the lower surfaces of the discs consists only of fragments of shells.



**FIGURE 1. DISINTEGRATION AND DISSOLUTION OF TABLETS AND THEIR RELATIONSHIP TO DRUG ABSORPTION <sup>(1)</sup>**

When a powdered drug is granulated and compressed into a tablet, the effective surface area of the medicinal compound is decreased. An **immediate-release tablet** must break up or disintegrate in the gastrointestinal fluids into granules, which then must disintegrate into primary particles.

The drug needs to dissolve from the primary particles before the molecules or ions of the medicinal compound can be absorbed by the gastrointestinal mucosa. Improperly formulated and improperly processed compressed tablets may retard drug release with a decrease in bioavailability. If a tablet does not disintegrate, the surface available for dissolution is restricted only to the surface area of the tablet.

Disintegration time specification is a useful tool for quality control, but disintegration of a tablet does not imply that the drug has dissolved. A tablet may pass a disintegration test and yet the drug may be biologically unavailable. The disintegration time is a rapid indicator of the effect caused by changes in formulation parameters or stability of the final dosage form.

In the lab, we use disintegration apparatus to determine the disintegration time. A basket travels up and down in a 37 °C water bath. The basket holds six vertical glass tubes. At the bottom of each glass tube is a 10- mesh screen. A tablet is placed in each tube to start the test. The disintegration time is expressed as the time it takes for the last piece of tablet to fall through the 10-mesh screen.

**Factors that affect disintegration time:**

It has been established that one should not expect a correlation between Disintegration & Dissolution. However, since the dissolution of a drug from the fragmented tablet appears to partially or completely control the appearance of the drug in the blood, disintegration is still used as a guide to the formulator in the preparation of an optimum tablet formula and as in-process control test to ensure lot-to-lot uniformity.

The formulator should be aware that:

- 1- The medium used.
- 2- The temperature of the medium.
- 3- The operator recording the results.

All can have a significant effect on disintegration time.

In addition, many factors involved with a tablet's formula and method of manufacture can affect the disintegration such factors are:

- 4- The nature of the drug.
- 5- The diluents used.
- 6- The binder and its amount.
- 7- The type and amount of disintegrating agent.
- 8- The type of amount of lubricant.
- 9- The method of incorporation for all these additives. (The compaction pressure used to make the tablets also influences the disintegration, in general disintegration time's increase with an increase in pressure).

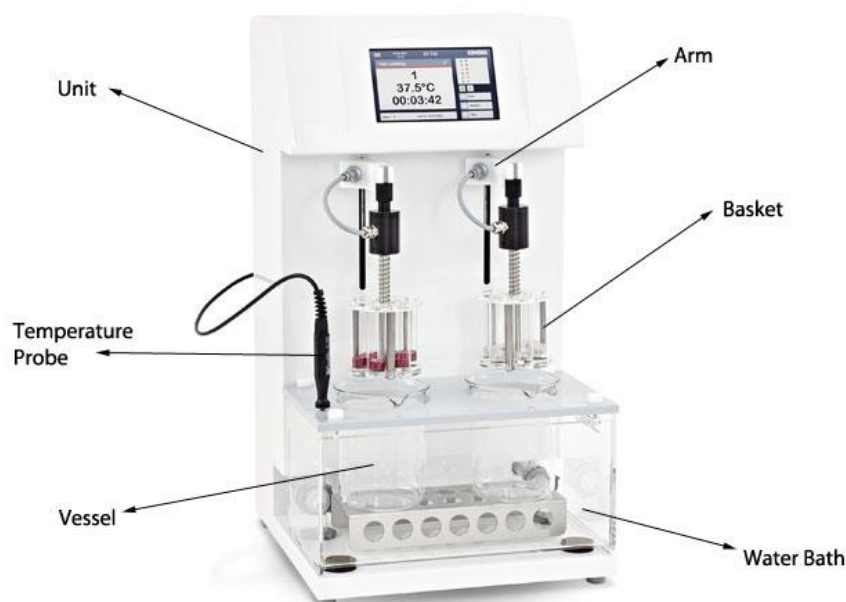


FIGURE 2. DISINTEGRATION APPARATUS<sup>(2)</sup>

### Disintegration Apparatus

Disintegration Apparatus for tablets and capsules of normal size. The apparatus consists of a basket-rack assembly, a 1-litre beaker, a thermostatic arrangement for heating the fluid and a mechanical device for raising and lowering the basket in the immersion fluid at a constant frequency rate. Fig. 2.5.1-1: Apparatus for Disintegration of Tablets and Capsules

**Basket-rack assembly:** The basket-rack assembly is rigid and supports **six cylindrical glass tubes**,  $77.5 \pm 2.5$  mm long, 21.5 mm in internal diameter and with a wall thickness of about 2 mm. The tubes are held vertically by two superimposed transparent plastic plates,  $90 \pm 2$  mm in diameter and  $6.75 \pm 1.75$  mm thick perforated by six holes having the same diameter as the tubes. The holes are equidistant from the center of the plate and are equally spaced from one another. Attached to the underside of the lower plate is a woven stainless steel wire cloth with a plain square weave with  $2.0 \pm 0.2$  mm **mesh apertures** and with a wire diameter of  $0.615 \pm 0.045$  mm.

The upper plate is covered with a **stainless steel disc perforated by six holes**, each about  $24 \pm 2$  mm in diameter, which fits over the tubes and holds them between the plastic plates. The holes coincide with those of the upper plastic plate and the upper open ends of the glass tubes. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis. The plates are held rigidly in position and 77.5 mm apart by vertical metal rods

at the periphery and a metal rod is also fixed to the center of the upper plate to enable the assembly to be attached to the device for raising and lowering it smoothly at a constant frequency of between 28 and 32 cycles per minute through a distance of 50 to 60 mm.

The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction should be smooth and not abrupt. There should be no appreciable horizontal motion or movement of the axis from the vertical.

The design of the basket-rack assembly may be somewhat different provided specifications for the glass tubes and the screen mesh size are unchanged.

**Discs:** A cylindrical disc for each tube, each  $20.7 \pm 0.15$  mm thick in diameter and  $9.5 \pm 0.15$  mm thick, made of transparent plastic with a relative density of 1.18 to 1.20, and pierced with five holes, each 2 mm in diameter, one in the center and the other four spaced equally on a circle of radius 6 mm from the center of the disc. Four equally-spaced grooves are cut in the lateral surface of the disc in such a way that at the upper surface of the disc they are 9.5 mm wide and 2.55 mm deep and at the lower surface 1.6 mm.

**Medium:** The assembly is suspended in the liquid medium in a suitable vessel, preferably a 1-litre beaker. The volume of liquid is such that the wire mesh at its highest point is at least 25 mm below the surface of the liquid, and at its lower point is at least 25 mm above the bottom of the beaker. At no time should the top of the basket rack assembly become submerged. There is a thermostatic arrangement for heating the liquid and maintaining the temperature at  $37^\circ \pm 2^\circ$ .



**FIGURE 3. PARTS OF THE DISINTEGRATION APPARATUS (DISCS AND MESH).<sup>(3)</sup>**

**EXPERIMENTAL PART:****a. Materials:**

- 4 tablets having the same API (Paracetamol) with different brands.
- 1 enteric coated Aspirin tablet
- 1 plain coated aspirin
- 4 capsules

0.1 M Hydrochloric acid. (immersion fluid)

**b. Apparatus:**

Disintegration Tester.

**c. Method****1- Test method for Paracetamol tablets and Aspirin Tablet:**

- Place 1 tablet in each of the 6 tubes of the basket, add a disk to each tube.
- Use the immersion fluid maintained at 37 °C.
- Suspend the assembly in the beaker containing the specified liquid and operate the apparatus, observe the time needed for each tablet to disintegrate and record it.

**2- Test Method for capsules :**

- Place 1 capsule in each of the 6 tubes of the basket (prepared in the previous lab) , add a disk to each tube.
- Use the immersion fluid maintained at 37 °C.
- Suspend the assembly in the beaker containing the specified liquid and operate the apparatus for the specified time, remove the assembly from the liquid. The capsules pass the test if all six have disintegrated.
- If one or two tablets from the 6 tablets fail to disintegrate completely within 30 min repeat the same test on another 12 tablets. (i.e. the whole test will consume 18 tablets)
- Not less than 16 tablets disintegrate completely within the time.

**DISCUSSION**

Discuss your findings in accordance to pharmacopoeia specifications.

Please refer to the link below :

<https://www.usp.org/sites/default/files/usp/document/harmonization/gen-chapter/april-2019-m99460.pdf>



## References:

- (1) (Markl and Zeitler, 2021): Markl, D. and Zeitler, J., 2021. *A Review of Disintegration Mechanisms and Measurement Techniques*
- (2) LTD, T., (2021) Disintegration tester. [ONLINE]. Available at: <https://totallaboratoryservices.co.uk/anatomy-of-disintegration-testers/> [Accessed 22 June 2021].
- (3) Pharma, A., (2021) *Disintegration tester discs and mesh*. [ONLINE]. Available at: <https://www.icapsulepack.com/tablet-manufacturing/> [Accessed 22 June 2021].

