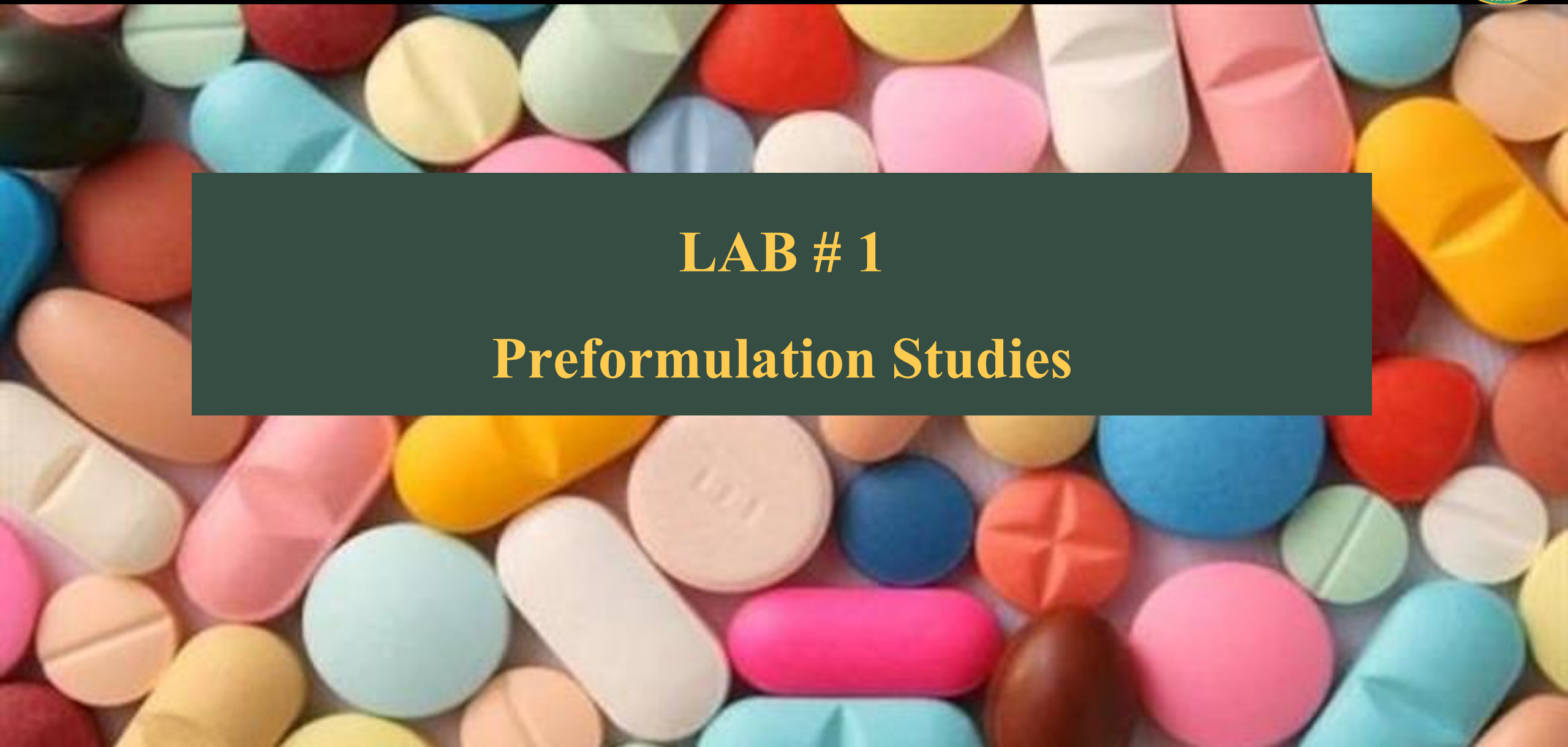
*Industrial Pharmacy II*

*5th stage. - Fall 2021*



# LAB # 1

# Preformulation Studies

# Preformulation Studies

**A- Solubility Studies:**

- Solubility, Dissociation constant (pKa), pH of the solution.
- Partition coefficient.
- Dissolution

**B- Stability Studies:**

- Liquid State stability / solid state stability
- Drug excipient compatibility

**C- Bulk Characterization:**

- Crystallinity and polymorphism.
- Hygroscopicity.
- Micrometric properties:
  - Fine Particle Characterization (particle size)
  - Powder flow properties.

# Preformulation studies

- Advantages of conducting a preformulation studies is to help us design **stable, safe and effective dosage form:**

1. Will assist in choosing the best formulation design and storage.
2. Drug solubility will determine the amount available for absorption; so if it has good solubility, this mean its easy to formulate the drug with the required dose.
3. If there is a defect in the molecule such as low solubility; molecule modification may be required such as salt formation to enhance solubility.
4. If drug is amorphous, this probably mean that it will be problematic to formulate it as it will have lower stability.
5. If drug is exist as a polymorph. We need to know which form is optimum for formulation.

# Stability Studies

- Experiments done in a conditions typical to handling, formulation, storage and administration of a candidate drug.
- Early stability studies will indicate the shelf life of the candidate drug.
- **Solution stability** (stability of drug in solution) this can be done via studying Hydrolysis, oxidation, photochemical reaction.
- **Solid state stability**: will help to determine stable storage and packaging conditions for drug in solid state.
- Samples will be stored at each condition and concentration is detected at each time point.
- Data will be used to study the decay kinetic order.

**Example of Solid State Stability Testing**

| Storage conditions | 4 week | 8 week | 12 week |
|---|---|---|---|
| 5 C (refrigerator) | | | |
| 22 C (room temperature) | | | |
| 37 C + Ambient Humidity | | | |
| 37 C + 75% Humidity | | | |
| 50 C ambient Humidity | | | |
| 70 C ambient Humidity | | | |
| 90 C ambient Humidity | | | |
| Light Box | | | |
| Amber Glass | | | |
| Yellow-Green Glass | | | |
| No exposure (control) | | | |

# Stability Studies (continue)

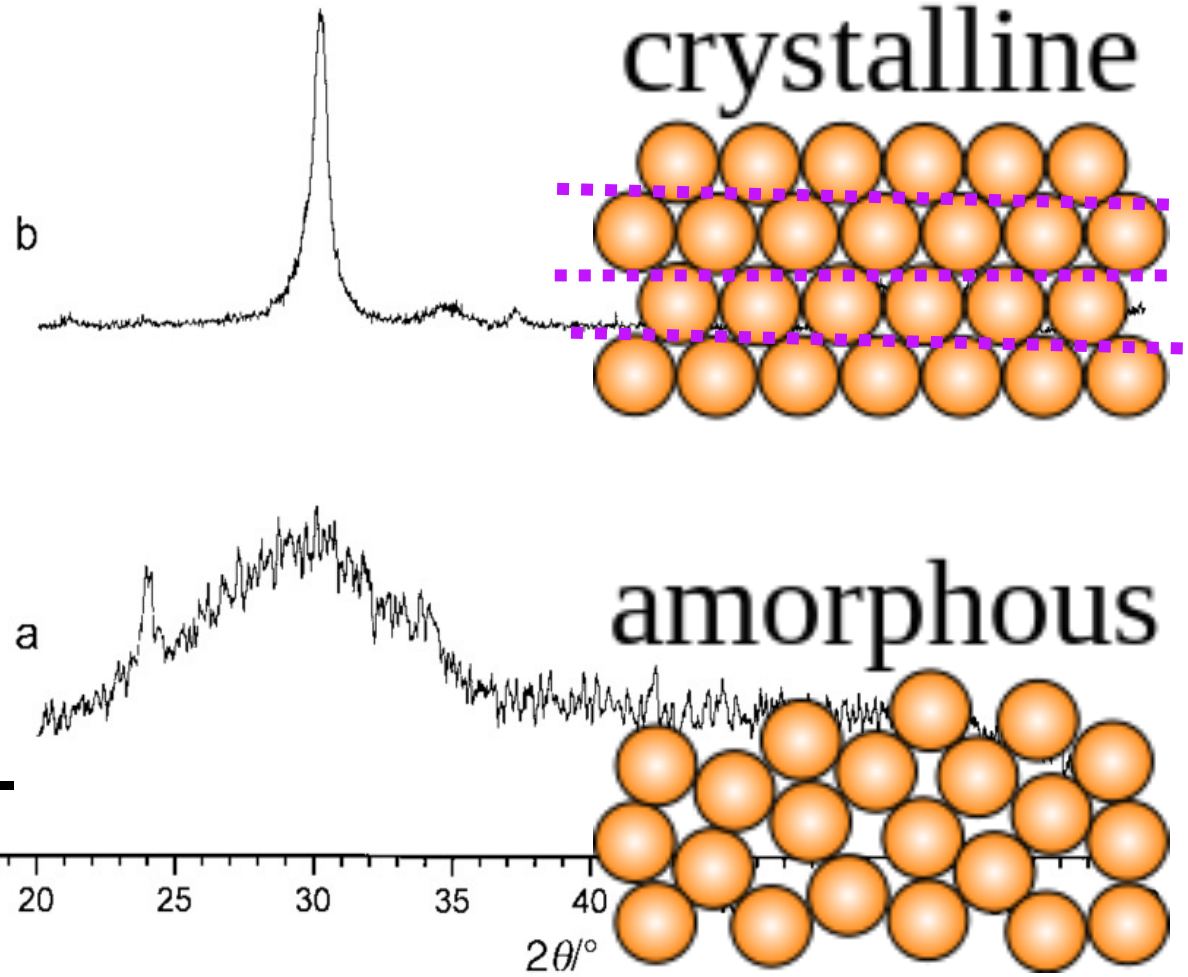
## Drug Excipient Compatibility

- Since excipients are crucial for drug formulation, compatibility testing should be done.
- Done **after** stability testing.
- Drug and excipient are mix into 1:1 ration and stored in various conditions (similar to stability) and analyzed at different time points
- If the excipients were incompatible it might result in:

1. Change in organoleptic properties.
2. Change in dissolution performance.
3. A decrease in potency.
4. Increase in degradation.

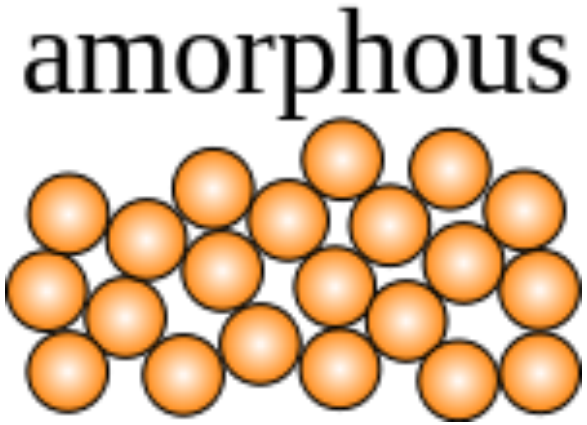
# Bulk Characterization
## Crystallinity and Polymorphism

- Study of crystallinity will assist in understanding of the flowability, solubility and stability.
- Crystal solid: Repetitive spacing of constituent atoms or molecules in a three dimensional structure.
- Amorphous: atoms or molecules are randomly placed as in liquid.
- Crystallinity is determined using **powder x-ray** diffraction and melting point measurements



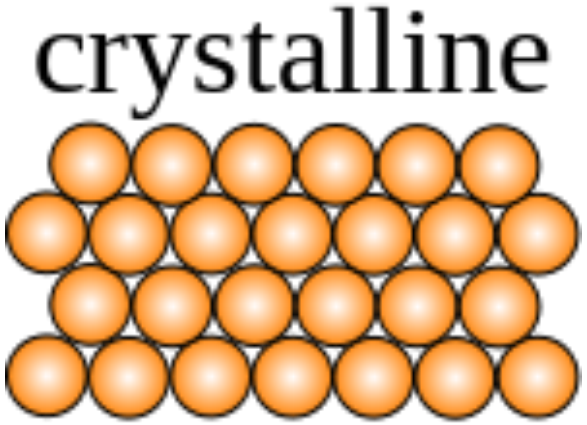
# Amorphous Drugs

- **Advantages:**
- Has **higher** solubility and dissolution than crystal form because water can easily penetrate random amorphous structure than arranged crystal structure.
- **disadvantages:**
- Unstable due to high thermodynamic energy. In storage or sometimes during processing it tends to return to more stable state.
- This thermodynamic instability can cause changes in solubility, flowability compressibility and stability which will be **unpredictable**. This is why amorphous drug are avoided when design a dosage form.



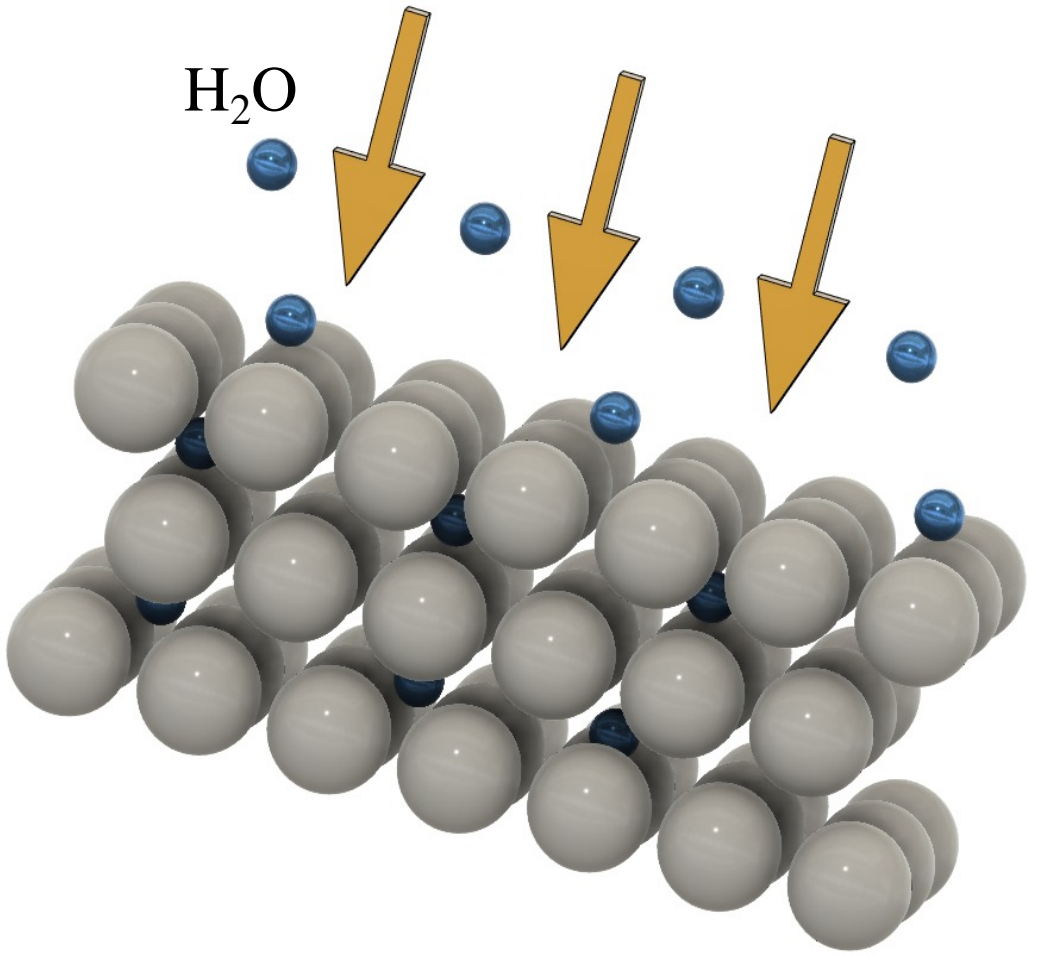
# Crystalline Drugs

- Less soluble and more stable than amorphous drugs so its widely used in drug formulation of dosage forms.
- Some crystal contain water molecules inside their structure which is called **hydrate** and if no water present the powder is called **anhydrous**.
- Anhydrous has more solubility than hydrate.
- Crystals of each material can be form in different internal structure. This called **polymorphism** and they might have different properties.
- Polymorphism can affect chemical stability and solubility which can affect bioavailability.
- Example is chloramphenicol found in A, B and C polymorph. C is unstable and A more stable. But **B** has better solubility so is has better bioavailability.
- This is why it is important to study crystal structure.



# Bulk Characterization
## Hygroscopicity

- Many drugs particularly water-soluble salts, have a tendency to adsorb atmospheric moisture.
- Change in moisture level can greatly influence many important parameters, such as chemical stability, flowability and compactibility.
- Hygroscopicity studies are required to detect storage requirements and packaging of the candidate dosage form.



# Bulk Characterization

## Fine Particle Characterization

- Particle size characterization will help in understanding the flow properties and compressibility of the powder.
- Measured using multiple sieve method: (https://youtu.be/WOKgItPBmR8)
- Powders with more percentage of fine particles may have poor flow properties.
- Powders with homogenous particle size distribution will have better content uniformity after formulation.
- Drugs with more fine particles will have greater surface area and will have faster dissolution.

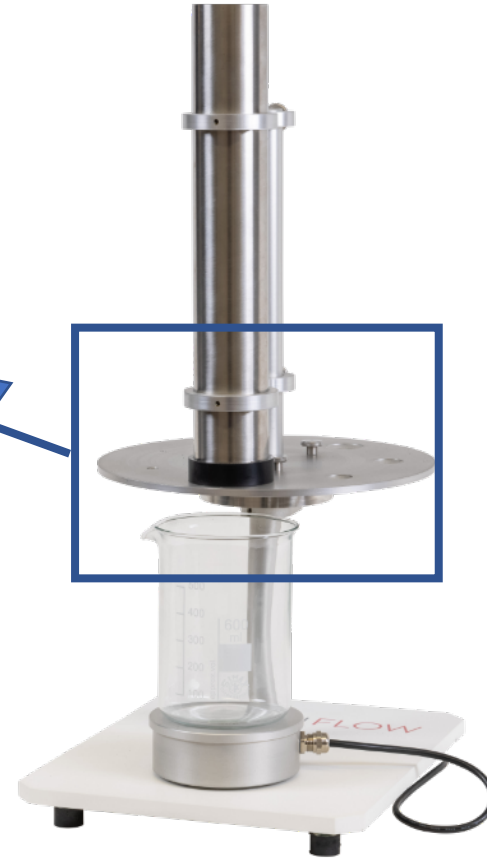
# Bulk Characterization

## Powder Flow Properties

- Powder flow is an important measurement to be consider during dosage form formulation and it will affect content uniformity.
- Powder flow is controlled by forces that act between particles such as frictional forces, surface tension forces, electrostatic forces, and cohesive forces (Van der Waals).
- Flow properties is affected by particle size, shape, electrostatic charge and adsorb moisture during processing.
- These factors can be changed during processing and powder flow may change during formulation.

# Study of Powder Flow Properties

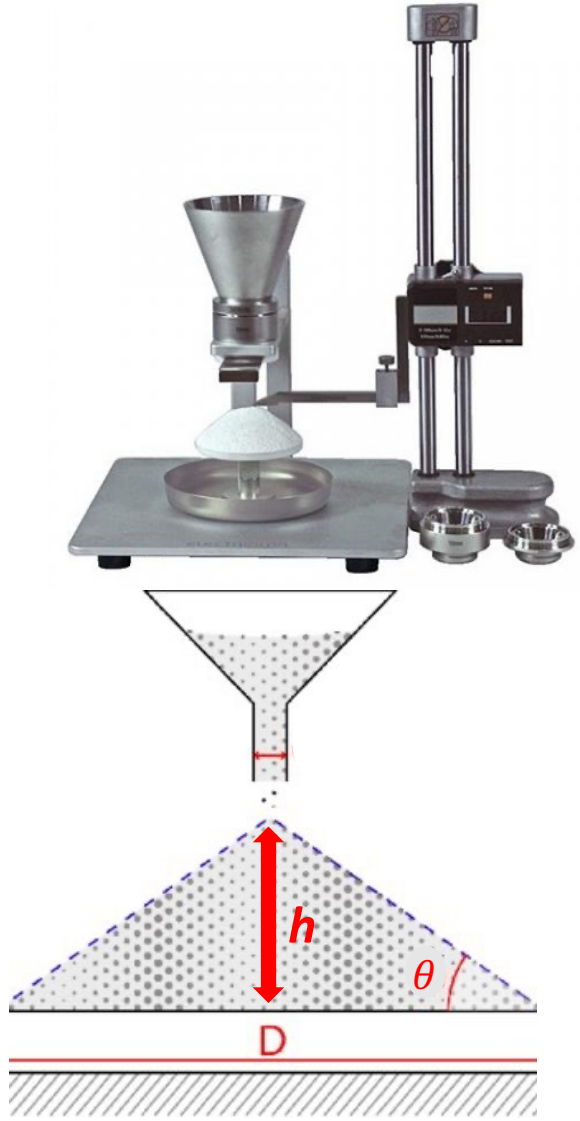
- **Simple flow rate apparatus**. Cylinder and a disk containing different diameter orifices. It's connected to a balance that connected to a computer to measure the weight at given time (flow rate g/s)
- The computer analyze the flow rate at different orifices and the deviation in flow rate will indicate weight variation in dosage form formulated using that powder
- https://youtu.be/3j4xct3-Z9E



# Study of Powder Flow Properties

- **Angle of repose ($\theta$):**
- Measure resistance of powder to flow. It's the maximum angle between the freestanding surface of a powder heap and the horizontal plane
- This give a qualitative assessment powder flow properties.
- Measured by **fixed funnel method or fixed cone method.**
- Powder is carefully poured in the funnel then heap height (h) and diameter (D) is recorded:

$$\boldsymbol{Tan\,(\theta) = \frac{2h}{D}}$$



# Angle of Repose Experiment

- You will need stand, clamp, funnel, spatula and paper or filter paper.
- Make sure everything is clean and dry
- Fix funnel on stand at 2 cm over paper.
- Close funnel lower opening with a spatula.
- Carefully and slowly pour the powder (40 gm) in the funnel and let it flow.
- Stop if the top of the heap touched the lower tip of the funnel or when you pour all the powder.
- Measure the height and diameter of the cone
- https://youtu.be/yQ3VGjEFI8M

| Angle of Repose | Flowability |
|---|---|
| < 25 | excellent |
| 25 - 30 | Good |
| 30 - 40 | Moderate flow |
| > 40 | Poor flow |

# Lab Report (due in the beginning of the next week lab)

- Choose the powder type (A, B or C) (record it)
- **Next week** each students needs to submit a report (you will work in group but submit individual report)
- Report should contain the following:

1. Name /group/ lab date and time.
2. Experiment name
3. Brief description of the experiment.
4. Calculation and results
5. Your conclusion
6. What is the importance of the experiment?

**Answer these two question**:

1- Why it is important to study crystallinity of the candidate drug?

2- How to study equilibrium solubility?