CHAPTER 1

PREFORMULATION STUDIES ON PARACETAMOL

Aim: To evaluate the Pre-formulation parameters of Paracetamol drug.

Requirements:

1. **Apparatus required**: Beaker, graduated cylinder, hot air oven, sieve no. 10, test tube, pH meter, funnel, stopwatch, bulk density apparatus, weighing balance, burette stand, thermometer, capillary tube, weighing bottle with stopper, oven, desiccator.
2. **Chemicals required:** Paracetamol, water, ethanol, chloroform

Principle: Preformulation studies provide a framework for the qualitative and quantitative estimation of drug before developing dosage form with /without pharmaceutical ingredients. The aim of Preformulation studies is to develop reliable and competent dosage form, by providing the drug's release kinetic profile, its interaction profile with ingredients and the physiochemical parameters of reported drug.

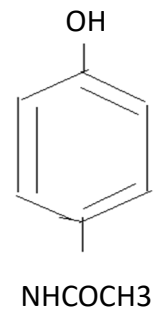
Need and importance of dosage form:

1. To provide reliable & competent delivery of drug.
2. To enhance self-life of drug.
3. To protect drug from degradation by gastric pH. Example: enteric coated tablet.
4. To suppress the odor and taste of the drug.
5. To enhance solubility and stability, for liquid preparations that are unstable or insoluble.
6. Providing rate-controlling drug action. Example: sustained release and controlled release tablet such as aspirin.

Objectives:

1. Determining the physicochemical properties of drug molecules.
2. Determining the kinetics and stability of reported drug molecules.
3. Compatibility with commonly used excipients.
4. Formulation of dosage form and stability studies.

- **Name of the compound:** Paracetamol
- **Chemical name:** N-acetyl-para-aminophenol
- **Molecular formula:** $C_8H_9NO_2$
- **Molecular weight:** 151.165 $g \cdot mol^{-1}$
- **Molecular structure:**
- **Description:** white powder
- **Category:** Nonsteroidal anti-inflammatory drug
- **Dose:** 500 mg
- **Storage:** protected from light and moisture



Preformulation studies/parameters are as follows:

A. Organoleptic properties

B. Bulk characterization

1. Bulk density
2. Hygroscopicity
3. Fine particle characterization
4. Powder flow properties
5. Crystallinity and polymorphism

C. Solubility parameter

1. Ionization constant- pKa
2. pH solubility profile
3. Common ion effect-Ksp
4. Thermal effect
5. Solubilization
6. Partition coefficient
7. Dissolution

D. Stability parameter

1. Stability in toxicology preparation
2. Solution stability
   (a). pH stability
3. Solid state stability
   (a). Bulk stability
   (b). Compatibility

PREFORMULATION STUDIES:

A. Organoleptic Properties:

The organoleptic properties are used for the identification and checking of drug molecules through eye examination method, to compare it with the standards mentioned in the Indian Pharmacopoeia. For identification of sample drug color, odor and taste are observed in day light besides clear background**.** *Color* may be off-white, cream yellow, tan, shiny. *Odor* may be pungent, sulfurous, fruity, aromatic and odorless. *Taste* may be acidic, bitter, bland, intense, sweet and tasteless.

B. Bulk Characterization:

Particle size, density, shape, and environmental conditions are important parameters that affect the flow characteristics of the sample and the formulation process. Following methods can be used for bulk characterization:

1. Bulk density: The bulk density of a powder is equal to the ratio of the mass of an untapped powder sample and its volume and expressed in gm/ml. It is measured by pouring the weighed sample powder/granules into the graduated cylinder using bulk density apparatus (no tapping is required) (Fig. 1.1), record the reading. and perform same procedure three times. Bulk density is used to determine the amount of powder /granules to fill in a space of blender or hopper for tablet formulation, and calculated by the following formula:

$$D_b = M/Vo$$

Where,

D_b = Bulk Density,

M = Mass of powder,

Vo = Bulk volume of sample powder

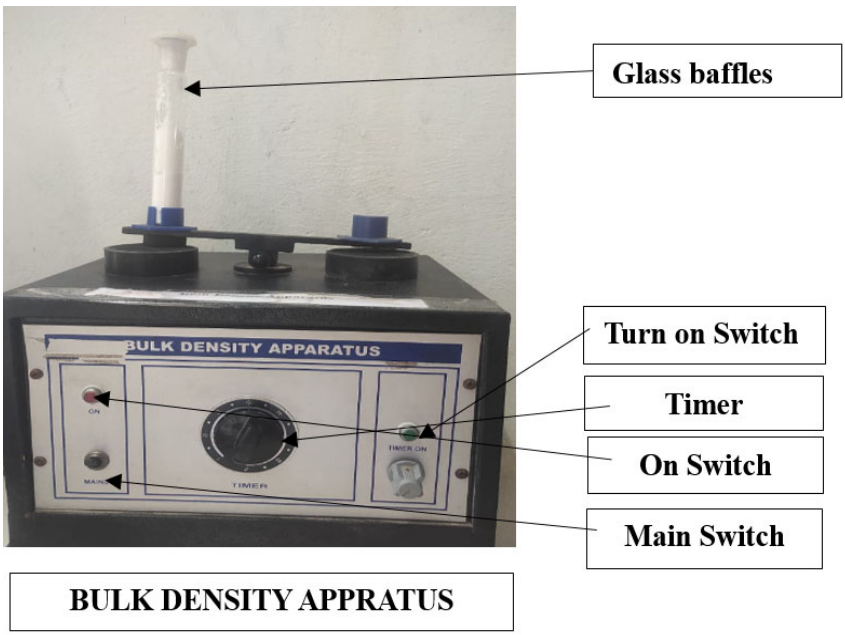


Fig. 1.1 Bulk Density Apparatus.

2. **Tapped density:** To determine the tapped density, a graduated cylinder containing the weighed granules or powder is tapped 100 times using a bulk density apparatus. The minimum volume (Vt) occupied in the cylinder and the weight (m) of the granules/powder are measured and recorded. The tapped density is then calculated using the formula:

$$D_t = M/Vt$$

Where,

M = Mass of powder,

V_t = Tapped volume of powder

3. **Angle of repose:** It is the maximum angle formed between the height of the pile of the powder and the horizontal plane. If, the value of Angle of repose (θ) is large, it indicates irregular shape and rough surface of particle. The lower the value (θ), the better the flow properties. To measure the angle of repose, the test sample is filled into a funnel to the brim (top of the funnel) and allowed to flow downward onto a piece of graph paper.

The cone formed on the graph is taken to measure the surface area of pile by using height of pile and radius of pile, as shown in Fig. 1.2.

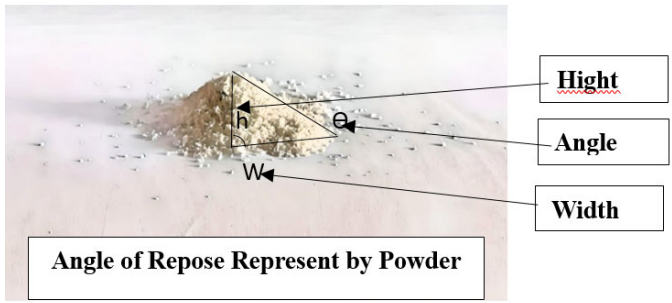


Fig. 1.2 Angle of repose.

Calculate the Angle of repose by the following formula:

$$\theta = \tan^{-1} h/r$$

Where,

Θ = angle of repose
h = height of the powder in cm,
r = radius of heap of powder in cm

Table 1.1 The following are the acceptance criteria for angle of repose.

S. No	Angle of repose (θ)	Type of flow
1.	<25	Excellent
2.	25-30	Good
3.	30-40	Fair/passable
4.	>40	Very poor

4. The Compressibility: It determines the mechanical properties of individual particles of powder or granules, which play an important role in the preparation of tablets.

Compressibility of powder or granule particles can be determined by given methods:

(a) The Hausner's Ratio (Hauser Ratio)

(b) The Carr's compressibility index

(a) Hausner's Ratio: The ratio of the tapped bulk density to the bulk density is known as the Hausner ratio. This ratio serves as a useful cohesiveness indicator since it represents particle friction. Powders with a Hausner ratio greater than 1.4 are considered cohesive and

difficult to fluidize. A powder that flows freely is defined by ratios below 1.20. It is calculated by using formula:

$$\text{Hausner's Ratio} = (Dt / Db)$$

Table 1.2 The following are the acceptance requirements for Hausner's ratio.

S. No	Hausner's ratio	Type of flow
1.	1.00–1.11	Excellent
2.	1.12–1.18	Good
3.	1.19–1.25	Fair
4.	1.26–1.34	Passable
5.	1.35–1.45	Very poor
6.	1.46–1.59	Extremely poor

(b) Carr's Index It measures the relationship between interparticle interaction and flow property of powder/granules. The higher the Carr's Index value, the greater the difference between bulk and tapped density of sample. Compressibility index of the granules/powder is determined by using the formula:

$$CI\ (\%) = [(Dt - Db / Db)] \times 100$$

Where,

CI = Carr's index

Dt = tapped density of sample

Db = bulk density of sample

Table 1.3 Table of Car's Index as an indication of powder flow properties.

S. No	Carr's index (%)	Type of flow
1.	5-15	Excellent
2.	12-16	Good
3.	18-21	Fair to passable
4.	23-35	Poor
5.	33-38	Very poor
6.	>40	Extremely poor

5. Hygroscopicity: Hygroscopicity is a general term used to describe the ability of a substance to absorb moisture from its surrounding without any change in physical state, while " hygroscopic" term refers to

substance that retain moisture. Atmospheric moisture is one of the major factors that affects the chemical stability, flow property and compatibility of ingredients used in pharmaceutical preparation.

The hygroscopicity of drug sample is determined by placing glass plate contain thin layer of weighed/given drug sample in an open container with controlled relative humidity prepared with saturated aqueous salt solution. The amount of moisture absorbed by sample can be determined by Karl-fischer titration, Thermogravimetric analysis (TGA), and Gravimetry method.

6. **Sieve Analysis:** The main aim of sieve analysis is to determine the size distribution of different drug particles present. A series of sieves is arranged in the order of their decreasing sieves numbers i.e 85 #, 60#, 40#, 22#, 16 #, 10# and placed over the shaker. Accurately weigh 100 g of drug and transferred to a sieve no.10# which is kept on the top of the sieves. The sieves are shaken mechanically or electrically for about half an hour. Then the drug retained on each of the sieves are taken, weight separately, and expressed in terms of percentage, is calculated by:

$$\%\ \textbf{powder retained} = \frac{\text{Weight of powder that retained on the sieve}}{\text{Weight of total powder taken for experiment}} \times 100$$

C. Solubility Parameter:

Solubility profile is the foundation of preformulation research, which determine effectiveness of drug. Solubility and permeability serve as the cornerstones of the biopharmaceutics classification system. solubility analysis includes, pKa determination, pH solubility profile, partition coefficient.

1. pH: The pH of a solution is an important factor for the solubilization and stability of drug. A solution with a pH of 7 is considered neutral, a pH less than 7 is considered acidic, and a pH greater than 7 is considered basic. The ionic and non-ionic forms of drug depend on the pH of solution. For the measurement of pH, prepare 1% w/v solution of Paracetamol in an appropriate solvent and measure the pH of paracetamol solution using pH meter.

2. Solubility profile in solvent: Solubility are expressed in terms of volume or mass of the solute that dissolves in a given volume or mass of a solvent. In pharmacopoeias, solubility values are expressed as the number of parts by volume of solvent needed to dissolve one part by weight of a solid or one part by volume of a liquid. The solubility of a

drug is a crucial physicochemical feature as it influences the drug's bioavailability, release rate into the dissolving medium, and therapeutic efficacy. This is a crucial phase in the formulation-development process. Solubility is determined by using a range of solvents, including ethanol, chloroform, distilled water, and 0.1 M HCL and analysed at 249nm. The solubility of material is determined by making a saturated solution of the material, where excess quantity of drug is taken in 10 mL of each solvent and occasionally stirring for 24 hrs at room temperature. Afterwards the sample is filtered and filtrate is suitably diluted and analysed spectrophotometrically at 249nm.

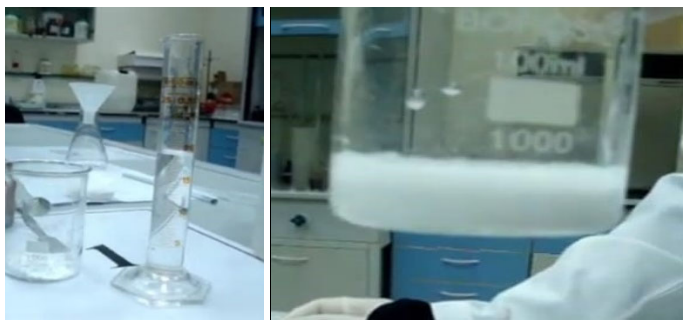


Fig.1.3 Solubility analysis of test drug.

Table 1.4 Solubility criteria as per IP".

S. No	Solubility	Parts of solvent required for 1 part of solute
1.	Very soluble	Less than 1
2.	Freely soluble	1 to 10
3.	Soluble	10 to 30
4.	Sparingly soluble	30 to 100
5.	Slightly soluble	100 to 1000
6.	Very slightly soluble	1000 to 10000
7.	Practically insoluble	10000 or more

3. **pKa Determination**: The solubility of a molecule at a particular pH is determined by its ionization characteristics, or pKA (ionization constant), which can be affected by basic or acidic functional groups. The dissociation constant of a drug that can ionize within a pH range of 1 to 14 must be determined, as pH changes can affect a drug's solubility and, in the meantime, its absorption. The ionized and unionized drug concentration at a given pH can be estimated using the Henderson-

Hasselbach equation.

For acidic compounds: pH = pKa + log [ionized drug] / [un-ionized drug]

For basic compounds: pH = pKa + log [un-ionized drug] / [ionized drug]

Table 1.5 pKa determination table.

S. No	Nature of drug	Ionization	pKa
1.	Very weak acid	Unionized at all pH	> 8
2.	Moderately weak acid	Unionized at gastric pH-1.2	2.5-7.3
3.	Strong acid	Ionize at all pH	< 2.5
4.	Very weak base	Unionize at all pH	<5
5.	Moderately weak base	Unionize at intestinal pH	5-11
6.	Strong base	Ionize at all pH	>11

4. **Partition coefficient**: Partition coefficient is defined as the ratio of un-ionized drug concentrations between the organic and aqueous phases, at equilibrium, where aqueous phase is water and organic phase is octanol. Drug with high partition coefficient will be able to cross the lipid cell membrane.

$$\text{Partition coefficient (Po/w)} = \frac{\text{Concentration of drug in oil phase}}{\text{Concentration of drug in aqueous phase}}$$

D. Stability Studies: Stability of active pharmaceutical ingredient is performed at different temperature and humidity, as per the below table:

Table 1.6 Stability studies.

S. No	Study	Storage condition	Minimum time period covered by data at submission
1.	Long term	25^0 C to 30^0C ± 2 ^{0} C/60 % to 65% RH± 5% RH	12 months
2.	Intermediate	30^0C ± 2 ^{0}C/ 65% RH± 5% RH	6 months
3.	Accelerated	40^0C ± 2 ^{0}C/ 75% RH± 5% RH	6 months

Observation and evaluation tables of Preformulation studies

Organoleptic Properties:

S. No	Test	Specification	Observation
1.	Color	White Crystalline powder	
2.	Odor	Odorless	
3.	Taste	Slightly bitter	

Solubility profile of Paracetamol drug:

S. No	Chemical (Solvent)	Specification	Observation
1.	Water	Sparingly soluble in water	
2.	Alcohol	Freely soluble in alcohol	
3.	Acetone	Freely soluble in alcohol	
4.	Ether	Very slightly soluble	

Solubility profile in different solvents:

S. No	Chemical (solvent)	Absor bance	Dilution factor	Concentrati on(mg/mL)	Solubility observed as (partsrequired to dissolve 1g of drug)
1.	Water			mg/mL	
2.	Ethanol			mg/mL	
3.	0.1 N HCl			mg/mL	
4.	Chloroform			mg/mL	

Result: The Preformulation parameters of the prepared Paracetamol drug were found to be:

S. No	Test	Specification	Observation
1.	Color	white amorphous powder	
2.	Odor	Slightly bitter	
3.	Taste	bitter taste, no distinct odour	
4.	Solubility	Sparingly soluble in water, freely soluble in alcohol, acetone, very slightly, soluble in ether and methylene chloride	

contd..

5.	pH	5.5-6.5	
6.	Bulk density g/ml		
7.	Tapped density g/ml		
8.	Angle of Repose	<25	
9.	Carr's Index	5-15	
10.	Hausner's ratio	1.00-1.11	
11.	Partition coefficient	>1<	

QUESTIONS

Q.1 What are the objective of pre-formulation studies?

Q.2 Why physicochemical estimation of a drug is required?

Q.3 What do you understand by Bulk characterization?

Q.4 What do you understand by 'organoleptic properties'?

Q.5 Define Hygroscopy?

Q.6 Describe techniques used to identify crystalline or amorphous nature of drug?

Q.7 Define 'Density' and its type?

Q.8 What is partition coefficient?

Q.9 Why angle of repose is important in the performulation studies?

Q.10 What is the role of tapped density in drug formulation?

Answers on page.no: 84