Pharma Pulse - Topper's Tonic

COMPREHENSIVE PHARMACEUTICS

Volume 1

- Pharmaceutical Technology
- Novel and controlled release drug delivery systems
- Physical Phamaceutics
- Biopharmaceutics and Pharmacokinetics
- Pharmaceutical Engineering

Dr. Amit Verma
M. Pharm. Ph.D

A COMPLETE BOOK

Theory and Practice MCQs for GPAT and Other Pharma Competitive Exams

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PART-I: PHARMACEUTICAL TECHNOLOGY

PART-II: NOVEL AND CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

PART-III: PHYSICAL PHARMACEUTICS

PART-IV: BIOPHARMACEUTICS AND PHARMACOKINETICS

PART-V: PHARMACEUTICAL ENGINEERING

PREFORMULATION STUDIES

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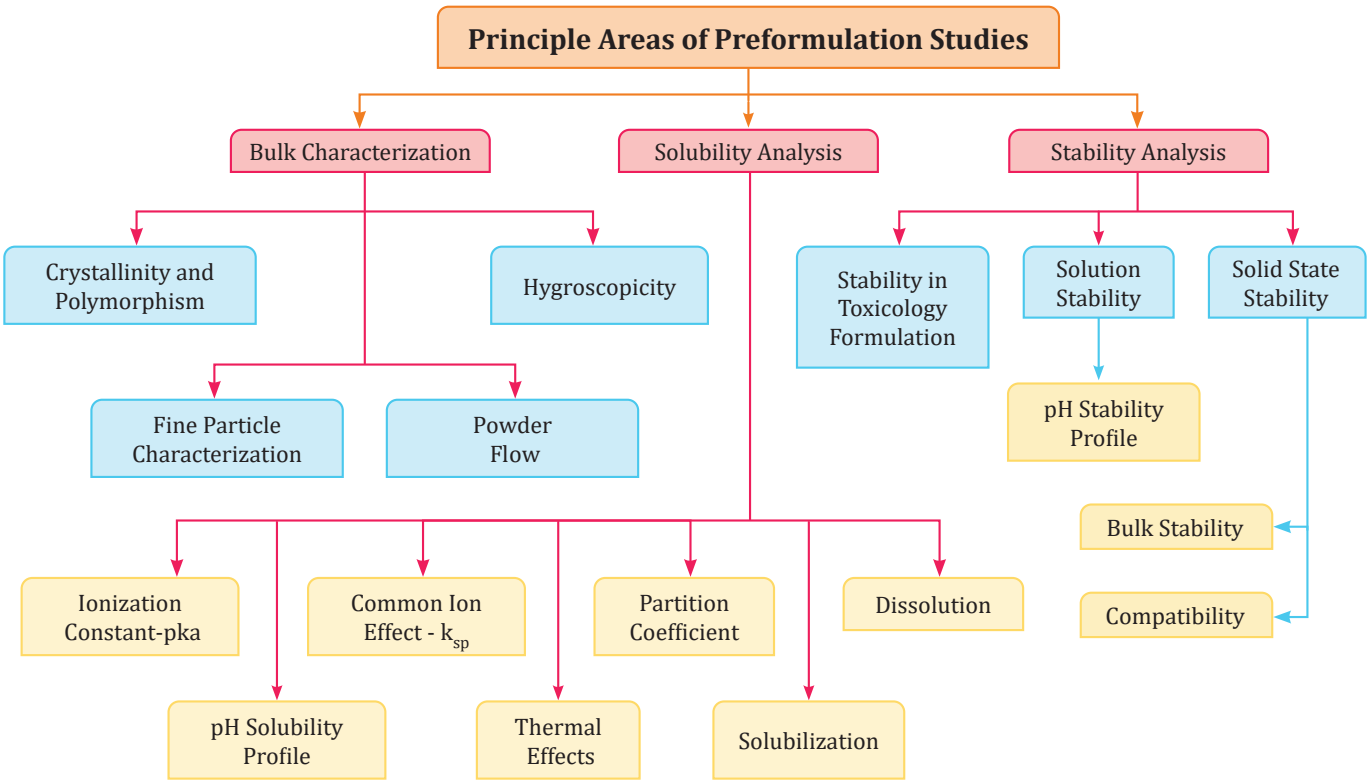
Analysis of **physical chemical properties** either of drug or with excipients to develop safe, effective and stable dosage form.



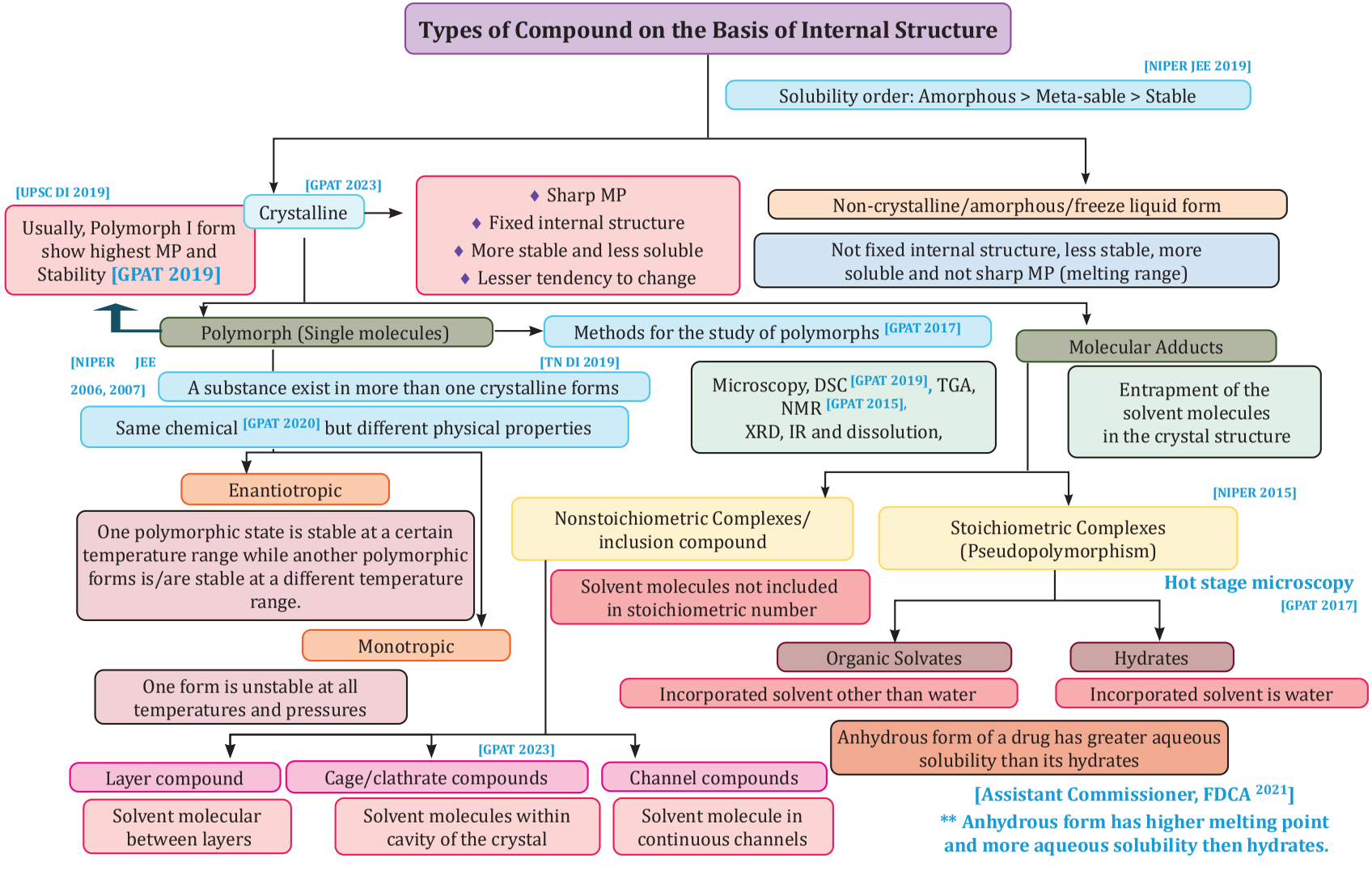
BULK CHARACTERIZATION

A. Crystallinity and Polymorphism

(a) Habit or outer appearance

- **Description of outer appearance** of crystal with same or different internal structures.
- Habit depends upon conditions of process like **degree of saturation, stirring rate, agitation, type of solvent and presence of other solvent.**

  Examples: Acicular, elongated, prism, needle like angular bladed, dendritic, nodular, prismatic, tubular and spherical.


Types of Compound on the Basis of Internal Structure
[NIPER JEE 2019]
Solubility order: Amorphous > Meta-sable > Stable
[UPSC DI 2019]
Usually, Polymorph I form show highest MP and Stability [GPAT 2019]
[GPAT 2023]
Crystalline
♦ Sharp MP
♦ Fixed internal structure
♦ More stable and less soluble
♦ Lesser tendency to change
Non-crystalline/amorphous/freeze liquid form
Not fixed internal structure, less stable, more soluble and not sharp MP (melting range)
Polymorph (Single molecules)
Methods for the study of polymorphs [GPAT 2017]
[NIPER JEE 2006, 2007]
[TN DI 2019]
A substance exist in more than one crystalline forms
Same chemical [GPAT 2020] but different physical properties
Microscopy, DSC [GPAT 2019], TGA, NMR [GPAT 2015], XRD, IR and dissolution,
Molecular Adducts
Entrapment of the solvent molecules in the crystal structure
Enantiotropic
One polymorphic state is stable at a certain temperature range while another polymorphic forms is/are stable at a different temperature range.
Monotropic
One form is unstable at all temperatures and pressures
Nonstoichiometric Complexes/ inclusion compound
Solvent molecules not included in stoichiometric number
[NIPER 2015]
Stoichiometric Complexes (Pseudopolymorphism)
Hot stage microscopy
[GPAT 2017]
Organic Solvates
Incorporated solvent other than water
Hydrates
Incorporated solvent is water
Anhydrous form of a drug has greater aqueous solubility than its hydrates
[Assistant Commissioner, FDCA 2021]
** Anhydrous form has higher melting point and more aqueous solubility then hydrates.
[GPAT 2023]
Layer compound
Solvent molecular between layers
Cage/clathrate compounds
Solvent molecules within cavity of the crystal
Channel compounds
Solvent molecule in continuous channels

Difference Between Amorphous and Crystalline Compounds

Crystalline Forms	Amorphous Forms
1. Crystalline forms have fixed internal structure	1. Amorphous forms do not have any fixed internal structure
2. Atoms or molecules arranged in definite manner or have highly arranged form and arranged with 3D periodicity.	2. The structural units are arranged randomly in the solid.
3. More stable than its amorphous forms.	3. Amorphous forms are less stable than its crystalline
4. Crystalline form has lesser solubility than its amorphous form.	4. Amorphous forms have greater solubility due to higher thermodynamic energy
5. Crystalline form has lesser tendency to change into other form during storage.	5. Amorphous tend to revert to more stable forms during storage.
6. These are anisotropic	6. These are isotropic
7. These are showing sharp melting point	7. These posses melting range (Not sharp melting point)
8. Prepared by the crystallization method	8. Prepared by rapid precipitation, Lyophilization or freeze drying and rapid cooling of molten liquid

Polymorphs and Polymorphism

Property	Details
Definition	When a substance exists in more than one crystalline form with different internal lattices, these forms are called polymorphs.
Occurrence	Common in organic compounds; inorganic compounds usually have a single crystalline form.
Analytical Methods	Microscopy, Optical crystallography, Fusion method, DSC (Differential Scanning Calorimetry), TGA (Thermal Gravimetric Analysis), XRD (X-ray Diffraction), IR (Infrared Spectroscopy), SEM (Scanning Electron Microscopy), Dissolution and Solubility Analysis

Types of Polymorphs

Feature	Enantiotropic Polymorphs	Monotropic Polymorphs
Stability	Different forms are stable at different temperature ranges	Only one form is stable at all temperatures; others are metastable
Phase Transition	Reversible	Irreversible
Transition Nature	Endothermic	Exothermic
Melting Point Behaviour	Lower MP form is stable below transition temp, higher MP form is stable above	Higher melting form is always thermodynamically stable
Thermodynamic Relation	Equilibrium exists between forms at a specific transition temperature	No equilibrium; direct conversion to stable form
Examples	Carbamazepine, Acetazolamide	Metolazone

B. Hygroscopicity

Tendency to **adsorb atmospheric moisture** (Especially water-soluble salt forms).

Methods for the determination of hygroscopicity:

- **Gravimetry** – Measures weight change over time due to moisture gain/loss
- **Thermogravimetric Analysis (TGA)** – Tracks weight changes with temperature
- **Karl-Fischer Titration (KF Titration)** – Precise measurement of water content
- **Gas Chromatography (GC)** – Used indirectly when analyzing moisture-sensitive compounds

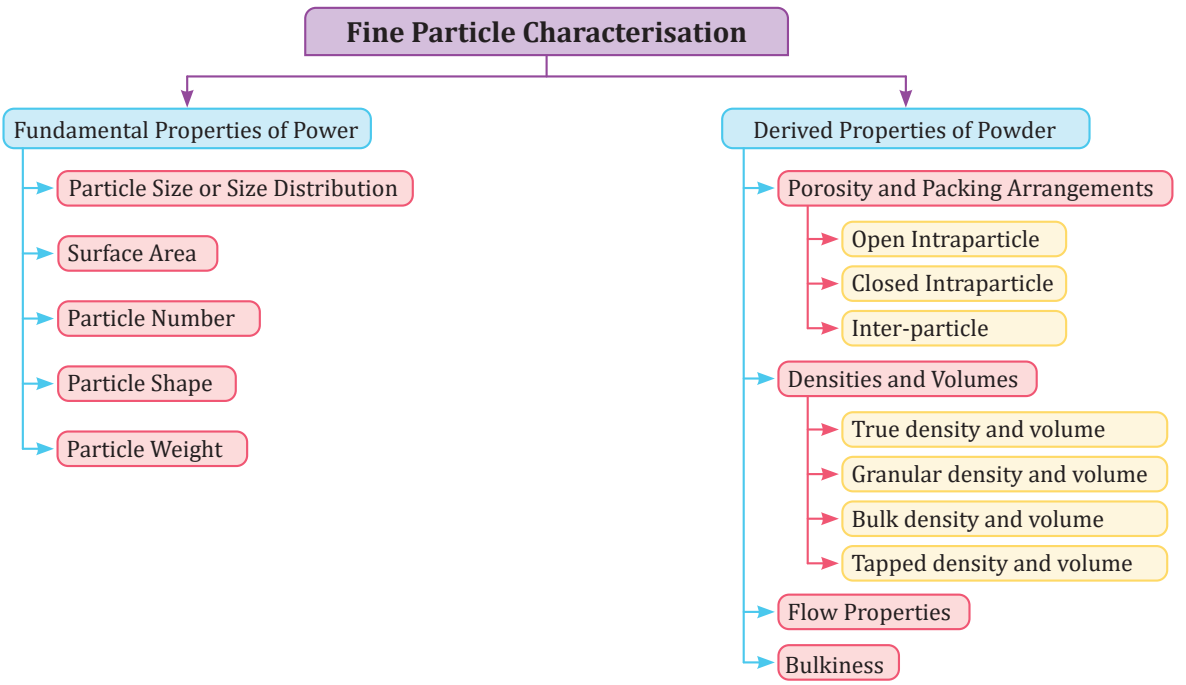
Types of Hygroscopic Compounds

Hygroscopicity Level	% Water uptake (w/w) at 25oC temperature and 80% RH	Remarks
Non-Hygroscopic	0 - 0.12	Do not noticeably absorb moisture under normal conditions
Slightly Hygroscopic	0.2- 2	Absorb small amounts of moisture; generally stable
Moderately Hygroscopic	2 - 15%	Moisture absorption increases with humidity; may cake or clump
Highly Hygroscopic	>15	Strongly absorb water; often deliquescent (can dissolve in absorbed water)

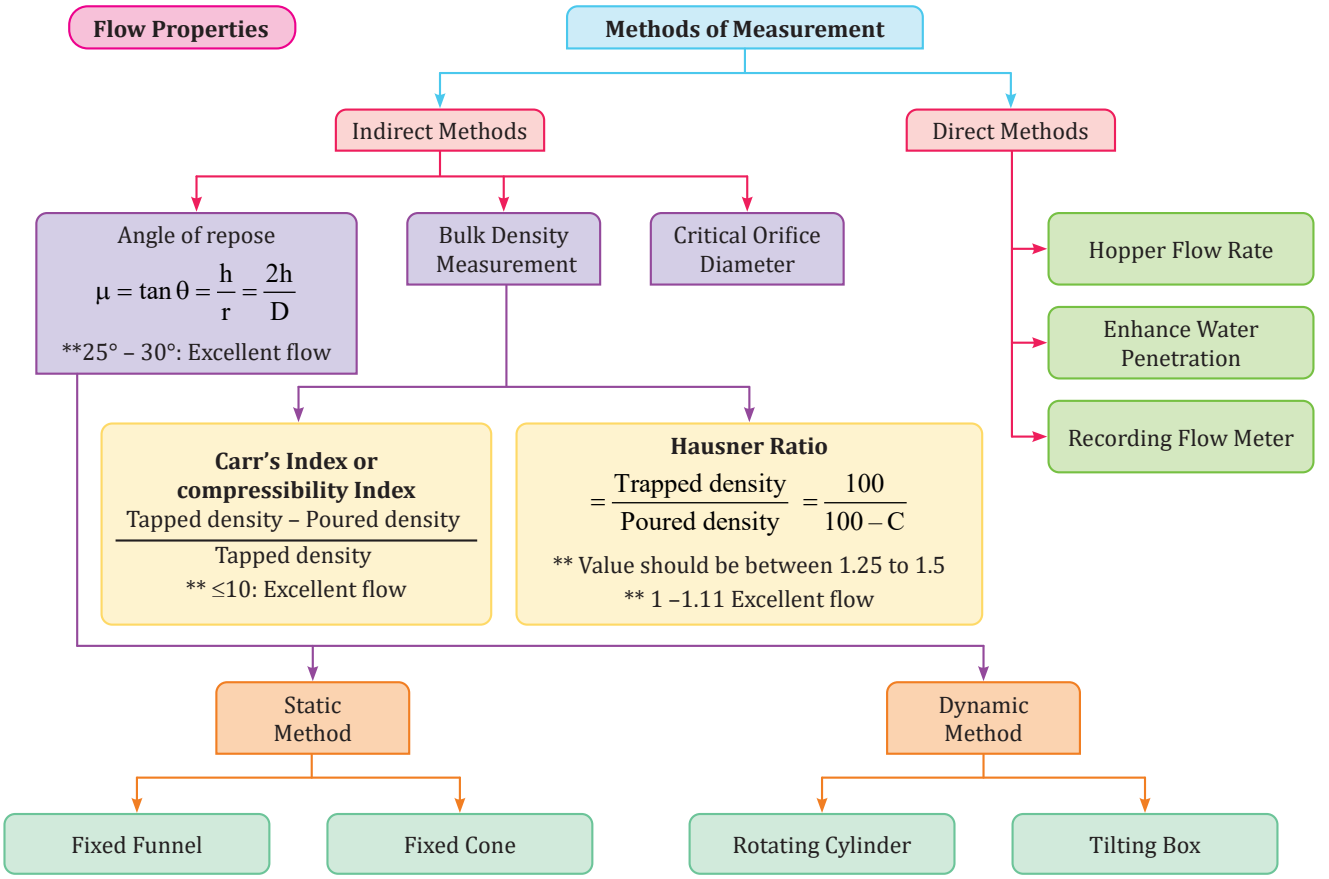
Deliquescent Vs. Efflorescent compounds

Type	Definition	Behaviour	Examples
Deliquescent	Substances that absorb sufficient moisture from the air and dissolve in it	Form a solution by absorbing atmospheric moisture (Often >50% water uptake)	Anhydrous $CaCl_2$, $MgCl_2$, KOH
Efflorescent	Substances that lose water of crystallization to the atmosphere	Become dry, powdery, or lose their crystalline form	$Na_2CO_3 \cdot 10H_2O$, $CuSO_4 \cdot 5H_2O$

C. Fine Particle Characterisations



D. Flow Properties



Solubility Analysis

Solubility means **concentration at which the solution phase is in equivalent with a given solid** at static temperature and pressure.

Or **Amount of solid/solute/drug present in the solvent at saturated condition** at stated temperature and pressure.

(a) Types of solubility

Type of Solubility	Definition	Conditions
1. **Intrinsic Solubility** (Inherent/Absolute Solubility)	Equilibrium solubility of the **unionized (free acid or base)** form of a compound.	Measured at a pH where the compound is **fully unionized.**
2. **Apparent Solubility**	Equilibrium solubility of the **ionized** form of a compound at a specific pH.	Depends on **pH** and degree of **ionization** of the compound.

(b) pKa Concept

Aspect	Details
Definition	**pKa = $-\log_{10}$(Ka); negative logarithm of the acid dissociation constant (Ka).**
Significance	Indicates **degree of ionization at a specific pH**; essential for predicting **drug absorption and solubility.**

Absorption Relevance	According to **pH partition hypothesis**, only **unionized form** is **lipophilic** enough to cross biological membranes effectively.
Henderson-Hasselbalch Equation	**For weak acid** $pH = pka + \log \frac{[\text{ionized form}]}{[\text{unionized form}]}$ **For weak base** $pH = pka + \log \frac{[\text{unionized form}]}{[\text{ionized form}]}$
Methods of Determination	1. **Conductometric Method** – Measures conductivity changes with ionization 2. **Potentiometric Method** – pH titration method 3. **Chromatographic Method** – Liquid-liquid partitioning 4. **Dissolution Method** – Solubility at various pH 5. **Spectrophotometric Method** – UV absorbance vs. pH

(c) Partition coefficient (K, Pc, P, π)

Aspect	Details
Definition	Ratio of concentration of **unionized drug** distributed between **two immiscible phases** (usually aqueous and organic).
Formula (Unionized drug)	$K_{o/w} = \frac{C1}{C2}$ $K_{o/w} = \frac{\text{Concentration of drug in organic or oil phase}}{\text{Concentration of drug in aqueous or water phase (inorganic)}}$ $K_{o/w} = \frac{\text{Concentration of drug in n-octanol}}{\text{Concentration of drug in water}}$
Formula (In case of drug will be ionised)	Distribution coefficient $\left(K_{o/w}\right) = \frac{(C1)^n}{C2}$ n = no. of ions
Interpretation of Value	**P > 1** Lipophilic drug **P < 1** Hydrophilic drug
Common Organic Solvents	n-Octanol, Ether, Ethyl Oleate, Ethyl Acetate, Chloroform
Methods of Determination	1. **Shake Flask Method** – Traditional and widely used 2. **Chromatographic Method** – HPLC/TLC analysis 3. **Coulter Counter Method** – Particle counting 4. **Filter Chromatographic Method** – Filtration and analysis

(d) Common ion effect

Aspect	Details
Definition	Decrease in the **solubility** or **ionization** of a compound when a **common ion** is added to the solution.
Mechanism	Based on **Le Chatelier's Principle** – the equilibrium shifts to **suppress further ionization** of the compound.

Effect on Solubility	Solubility of a **sparingly soluble salt** is reduced when a solution already contains one of its **common ions**.
Effect on Ionization	Presence of a common ion **reduces the ionization** of weak electrolytes (like weak acids or bases).
Example	❍ **NaCl + HCl:** Addition of HCl (provides Cl^-) reduces ionization of NaCl. ❍ **Acetic acid + Sodium acetate:** Addition of sodium acetate (common ion CH_3COO^-) reduces ionization of acetic acid.
Pharmaceutical Relevance	Used to **control solubility, precipitate drugs,** or **modify release rates** in drug formulations.

(e) Effect of pH on solubility

Aspect	Details
Description	The solubility of a drug can change **depending on the pH** of the solution, especially for **weak acids and weak bases**.
Determination Method	Add **excess drug to solvent gradually alter pH** using acid or base observe solubility changes.
Roll of pH	Weak acids and bases ionize depending on pH. Since **ionized forms** are usually more water-soluble, **pH affects solubility** significantly.
Weak Acid Behavior	Solubility **increases** at **high pH** (alkaline), where the acid is more **ionized**.
Weak Base Behavior	Solubility **increases** at **low pH** (acidic), where the base is more **ionized**.
Examples	❍ **Aspirin (weak acid):** more soluble in alkaline pH ❍ **Lidocaine (weak base):** more soluble in acidic pH
pH Range Impact	No significant effect on solubility for **non-ionizable (neutral)** drugs.
Pharmaceutical Application	Adjusting pH can improve **drug solubility, bioavailability,** and **formulation stability**.

(f) Thermal effect

Aspect	Details
Description	Solubility of most drugs **increases with rise in temperature**, as solubility is typically a **temperature-dependent process**.
Nature of the Process	Most solubility processes are **endothermic** (absorb heat).
Temperature Dependence	❍ **Endothermic:** ↑ Temperature → ↑ Solubility ❍ **Exothermic:** ↑ Temperature → ↓ Solubility
Heat of Solution Effect	**Higher heat of solution** → greater influence of temperature on solubility.
Pharmaceutical Importance	Helps improve solubility of drugs during formulation; key factor in designing **hot vs. cold processes**.
Examples	**Endothermic:** Potassium nitrate (KNO_3), Benzoic acid → solubility increases with temperature **Exothermic: Calcium hydroxide ($Ca(OH)_2$), Lithium carbonate (Li_2CO_3)** → solubility decreases as temperature increases

(g) Dissolution

- Transfer of solid particles into the solution
- It is the **mass transfer process** from solid to the solution Or

- Amount of **drug substance that goes in the solution per unit time** under standard conditions
- Rate of drug dissolution is related to Noyes Whitney Equation –

$$\frac{dc}{dt} = \frac{DA(C_s - C_o)}{h}$$

Where,
D = Diffusibility (Diffusion coefficient),
A = Surface area of diffusion layer
Cs-Co = Concentration gradient,
h = Path length (thickness of diffusion layer)

Lipinski's Rule of Five [Gujrat DI 2024; GPAT 2013]

This rule used in drug discovery to predict if a chemical compound can be orally active in humans.

Rule	Limit	Why?	Effect of Violation	Example
Molecular Weight	≤ 500 Da	Small molecules absorb better	Larger molecules = Poor absorption	Paracetamol (151 Da) – Good absorption Cyclosporine (1202 Da) – Poor absorption
logP (Lipophilicity)	≤ 5	Balance between lipid & water solubility	High logP = Poor solubility	Ibuprofen (logP ~3.5) – Good absorption Vitamin D (logP ~7) – Poor oral absorption
Hydrogen Bond Donors	≤ 5	Less polarity = Better membrane permeability	Too many donors = Poor absorption	Aspirin (2 HBD) – Well absorbed Vancomycin (7 HBD) – Poor absorption
Hydrogen Bond Acceptors	≤ 10	Less polarity = Better absorption	Too many acceptors = Poor absorption	Caffeine (3 HBA) – Good absorption Streptomycin (12 HBA) – Poor absorption

Exceptions to Lipinski's Rule

Some drugs violate Lipinski's rule but are still orally bioavailable:

- **Antibiotics (e.g., Vancomycin, Rifampicin) –** Transported via specific carriers.
- **Natural products (e.g., Cyclosporine, Digoxin) –** Have active transport mechanisms.
- **Peptides & Proteins –** Often too large but may use transporters.

IMPORTANT MCQS FOR PRACTICE

1. Which of the following statement is correct
   (*a*) Periodic arrangement of molecules create amorphous compound
   (*b*) Habit means outer appearance of a crystal
   (*c*) Crystal form has high energy than amorphous
   (*d*) Amorphous form is more soluble than crystalline

2. Which of the following is most appropriate to crystalline solid [GPAT 2023]
   (*a*) Give diffraction bands
   (*b*) Characteristics geometrical shapes
   (*c*) Sharp melting point
   (*d*) All of these

3. Assertion: Metastable polymorph is more soluble than stable form
   Reason: Metastable form has high energy than stable and show more interaction with solvent molecules
   (*a*) Both [A] and [R] are true and [R] is the correct reason for [A].
   (*b*) Both [A] and [R] are true but [R] is not the correct reason for [A].
   (*c*) Both [A] and [R] are false.
   (*d*) [A] is true but [R] is false.

4. Hot stage microscopy is an important tool in Preformulation studies for the study of [GPAT 2017]
   (*a*) Pseudopolymorphism
   (*b*) Particle size measurement
   (*c*) Microbial contamination
   (*d*) Compaction behaviour

5. Choose the correct sequence in concern of solubility
   (*a*) Amorphous > Stable > Metastable
   (*b*) Metastable > Amorphous > Stable
   (*c*) Amorphous > Metastable > Stable
   (*d*) Amorphous = Metastable > Stable

6. When the solvent in association with the drug is water, the solvate is known as
   (*a*) Anhydrous
   (*b*) Amorphous
   (*c*) Hydrate
   (*d*) All

7. The pH dependence of the solubility of weak acids and weak bases can be expressed by
   (*a*) Noyes- Whitney's equation
   (*b*) BET equation
   (*c*) Fick's Firs law
   (*d*) the Henderson-Hasselbalch equation

8. Which is measured for the neutral form of a drug? [Deputy Commissioner, FDCA 2021]
   (*a*) Log P
   (*b*) Log D
   (*c*) Both (*a*) and (*b*)
   (*d*) None of the above

9. The solubility of a weak base
   (*a*) Decrease with pH
   (*b*) increases with pH
   (*c*) constant at all pH
   (*d*) Increase with decrease in H+ ions concentration

10. Strong acid
   (*a*) Has low Ka value
   (*b*) Has High pKa value
   (*c*) Has low pKa value
   (*d*) show more ionization at low pH

11. Which of the following is one of the rules in Lipinski's rule of five? [Gujrat DI 2024]
   (*a*) A molecular weight equal to 500
   (*b*) No more than five hydrogen bond acceptor groups
   (*c*) No more than 10 hydrogen bond donor groups
   (*d*) A calculated logP value less than + 5

12. Intrinsic solubility means
(a) Equilibrium solubility of the free acid or free base form of an ionisable compound at a pH where it is fully ionised.
(b) Equilibrium solubility of the free acid or free base form of an ionisable compound at a pH where it is fully unionised.
(c) Equilibrium solubility of the free acid or free base form of an ionisable compound at a pH where it is partially ionised.
(d) Both (a) and (c)

13. Which of the following is Stoichiometric compound
P. Cage Q. Layer R. Channel S. Solvates
(a) Only P, Q & R (b) Only P
(c) Only Q & S (d) Only S

14. Freeze liquid form is the another name of
(a) Crystalline form (b) Hydrates form
(c) Both (a) & (b) (d) Amorphous form

15. Select the correct statement [GPAT 2018]
(a) Acid salt corresponding to an insoluble salt will be more water soluble than original salt
(b) Hydroxides and oxides of compounds other than alkali metal cations and the common ions are generally water soluble
(c) Sulphides are water soluble except for their alkali metal salts
(d) Ammonium and Quaternary ammonium salts are water insoluble

16. Drug-drug/drug-excipients/excipient-excipient interaction can by determine by which of the following method
(a) DSC (b) TLC
(c) Both (a) and (b) (d) TEM

17. All of the following properties are the different among the all polymorphs except
(a) Melting point (b) Solubility
(c) Both (a) and (b) (d) Chemical reaction

18. Choose the correct type of compound which has highest solubility
(a) Amorphous (b) Meta-stable
(c) Stable (d) Hydrates

19. Clathrates or inclusions compounds belong to which category
(a) Amorphous (b) Stoichiometric
(c) Non-stoichiometric (d) Solvates

20. If drug has partition coefficient > 1, the drug will be
(a) Ionized (b) Polar
(c) Water soluble (d) Lipophilic

ANSWER KEY

1. (d)	2. (d)	3. (a)	4. (a)	5. (c)	6. (c)	7. (d)	8. (a)	9. (a)	10. (c)
11. (d)	12. (b)	13. (d)	14. (d)	15. (a)	16. (c)	17. (d)	18. (a)	19. (c)	20. (d)

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- Drug regulatory affairs
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Dr. Amit Verma
M. Pharm. Ph.D

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Dr. Supriya Mishra
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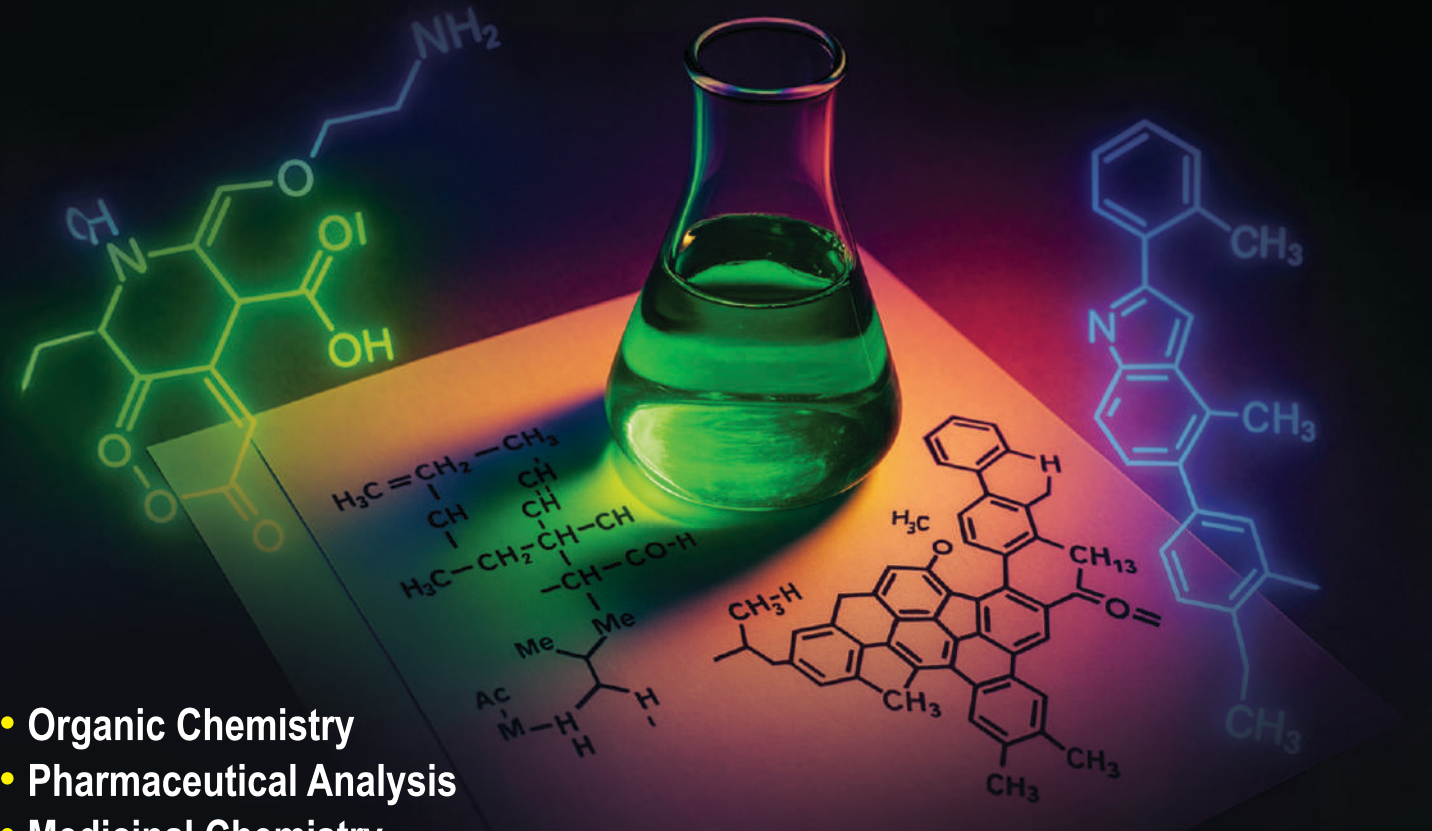

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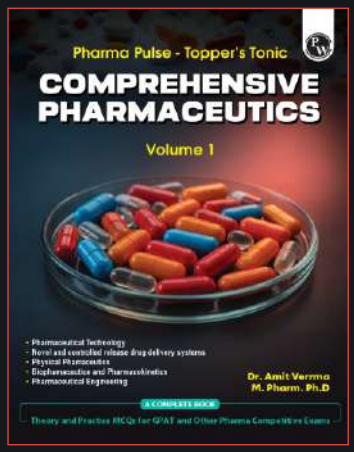

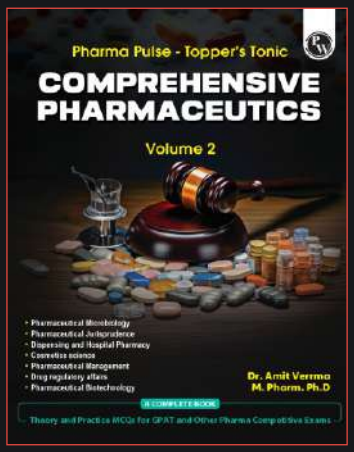

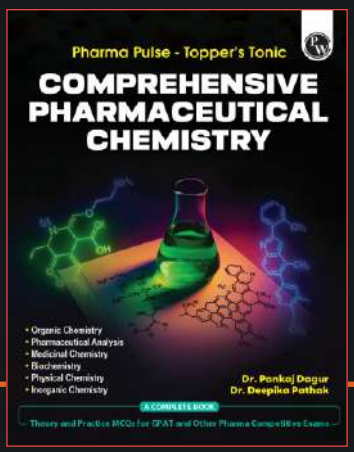

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