JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A PREFORMULATION STUDIES (New)

Laxmi B. Dhotre[1*], Sangram G. Nagargoje, Shubham S. Kshirsagar, Ashok A. Muchandi

Ashwini G. Chintale

[1,2]Department of Pharmaceutical Chemistry, Saraswati Institute of Pharmacy, Kurtadi. Dist.Hingoli - 431701
[3,4]Department of Pharmacology, Saraswati Institute of Pharmacy, Kurtadi. Dist.Hingoli - 431701 [5]Department of Pharmaceutics, Saraswati Institute of Pharmacy, Kurtadi. Dist.Hingoli - 431701

Abstract:

Understanding the physicochemical features of chemicals or biological entities that can affect their development into final products is critical at various stages of development. Preformulation data is crucial for understanding the possible pharmacokinetics of medicine in humans and animals, as well as the opportunities and constraints for process change as the product is scaled up in production. Preformulation studies are also carried out to anticipate the formulation's stability during manufacturing, transportation, and storage, and therefore to establish the marketed product's shelf life. The measurement of solubility and dissolution rate, molecular dissociation, pKa, diffusion, partition, and permeability, as well as how these might be included in a biopharmaceutical classification system, are all discussed in this review. Absorption and absorption of moisture Differential scanning calorimetric (DSC), thermo gravimetric analysis (TGA), and powder X-ray diffraction are used to classify hygroscopicity and evaluate polymorphism and crystallinity. Stress testing is used to evaluate the stability of active components and excipients in isolation and in combination, taking into account the effects of pH, temperature, humidity, light, and oxidizing agents. Finally, the characterization of powders and particle systems is discussed through the measurement of their fundamental and derived properties.

Keywords: Preformulation, Shelf life, Crystallinity, X-ray diffraction.

Objectives:-

1. Determining the physicochemical properties of a new medicinal entity

2. Determining the kinetics and stability of that drug entity

3. To see if it's compatible with commonly used excipients.

4. It reveals how drug items should be prepared and stored in order to maintain their quality.

Major Area of Preformulation Research

BULK CHARACTERS-

- Crystallinity and Polymorphism
- Hygroscopicity
- Fine particle characterization
- Powder flow properties

SOLUBILITYANALYSIS-

- Ionization constant-PKA
- PH solubility profile
- Common ion effect-Ksp
- Thermal effects
- Solubilization
- Partition co-efficient
- Dissolution

STABILITY ANALYSIS-

- Stability in toxicology formulations
- Solution stability
- pH rate profile
- Solid-state stability
- Bulk stability
- Compatibility

BULK CHARACTERS-

1. **Crystallinity and Polymorphism:**

   Depending on their chemical makeup and method of isolation or crystallization, drugs and excipients can exist in a variety of crystalline or amorphous states. During crystallization, molecules may arrange themselves in various geometric configurations, resulting in distinct packing arrangements or orientations in the crystal structure.

The various crystal forms are categorized into six distinct crystal systems based on symmetry.

1. cubic (sodium chloride)
2. tetragonal (urea)
3. hexagonal (iodoform)
4. rhombic (iodine)
5. monoclinic (sucrose)
6. triclinic (boric acid)

Crystalline solids are falling on four categories:

Types of Solid	Forces holding particles together	Properties	Examples
Ionic	Ionic	High Melting Point,Brittle,Hard,Nonconductors as solid,good conductors as liquids or when dissolved in water.	NaCl, Mgo
Molecular	Hydrogen Bonding,Dipole-Dipole,London Dispersion	Low melting point,Nonconductors	H_2, CO_2
Metallic	Metallic bonding	Variable Hardness and Melting Point, Good conductors as solids and liquids	Fe, Mg
Covalent Network	Covalent Bonding	High melting Point,Hard, nonconductors	C (diamond) , SiO_2 (quartz)

Polymorphism: are the names given to these various states. Each polymorphic form may have extremely distinct physicochemical properties (e.g., solubility, melting point), which can have a substantial impact on a drug's bioavailability and stability. Polymorphism can also influence the compression properties of medications (e.g. paracetamol can exist in monoclinic or orthorhombic forms, the latter possessing preferable compaction properties).

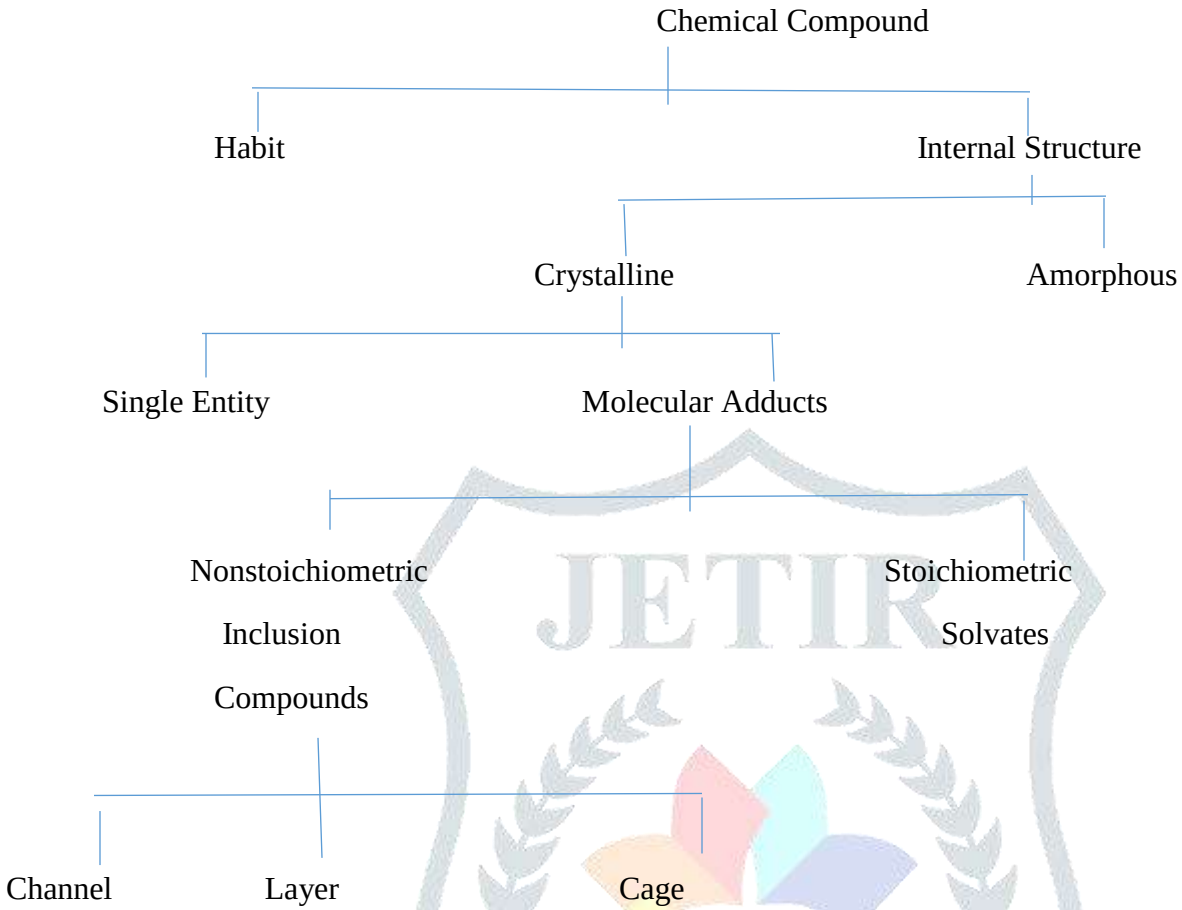
Polymorphisms are categorized as follows:

1.Enantiotropic means that when temperature or pressure are changed, one form transforms into another.

2.The polymorphic form is unstable at all temperatures and pressure when it is monotropic.

Amorphous: Amorphous drug has atoms or molecules randomly placed (without definite structure) within them.The amorphous form is of higher thermodynamic energy, greater solubility as well a higher dissolution rate than the corresponding crystalline form.

Outline of differentiating habit and crystal chemistry of a compound-



2. Hygroscopicity:

Hygroscopicity is a term used to describe the ability of a substance to absorb moisture from its surroundings is known as hygroscopicity. The procedure might take a variety of forms. Water vapors will be physically adsorbed on the exterior surface and within the pores of a porous solid like activated carbon, forming a condensed layer. It's possible that the process starts at "active sites" and then spreads from there. When it comes to other materials, such as silica gel, the surface interaction may not be purely physical, and some loose chemical interactions may form. Many cellulosic materials, such as hair, cotton, and wool, are hygroscopic, meaning they absorb water and change their physical dimensions. This type of material can be used.

Hygroscopicity can be classified as:

1. Deliquescent
2. Very hygroscopic
3. Hygroscopic
4. Non-hygroscopic

Class I:Non-Hygroscopic

At relative humidity below 90%, there are almost no moisture increases. Furthermore, after a week of storage at above 90% relative humidity (RH), the rise in moisture content is less than 20%.

Class II: Mildly Hygroscopic

At relative humidity below 80%, virtually little moisture increases. The increase in moisture content after a week of storage at above 80% RH is less than 40%.

Class III:Moderately Hygroscopic

At relative humidity below 60%, moisture content does not grow more than 5% after storage. The rise in moisture content after a week of storage at above 80% RH is less than 50%.

Class IV:Very Hygroscopic

At relative humidity as low as 40–50 percent, moisture might increase. After a period of storage, the moisture content of the product increases.

3.Characterization of fine particles:

1. Microscopy

2. Microscopy on a hot stage

3. Thermo graphic analysis

4. Diffraction of X-rays

5. Infrared spectroscopy (IR)

6.Proton magnetic resonance (PMR) is a technique for detecting protons (PMR)

7.Nuclear Magnetic Resonance (NMR) (NMR)

8.Scanning electron microscopy (SEM) is the eighth technique (SEM)

4. The properties of powder flow:

Changes in particle size, density, shape, and adsorbed moisture, which might occur during processing or formulation, have a substantial impact on flow characteristics. The following approaches can be used to determine the powder flow properties:

The Angle of Repose:

It is the maximum angle formed by a pile of powder's surface and the horizontal plane.

Tan θ= h/r

The angle of repose will be larger if the particle surface is rougher and more irregular.

The lower the value, the better the flow properties.

The following are the acceptance criteria for angle of repose:-

Table-I

Angle of Repose	Type of Flow
< 20	Excellent flow
20-30	Good flow
30-34	Passable
>40	Poor flow

The Compressibility:

It can be characterized by the following methods

The following approaches can be used to determine compressibility:

1. The Carr's compressibility index
2. The Hauser's Ratio (Hauser Ratio)

1.The Carr's compressibility index

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

Good flow characteristics can be attained by lowering the bulk and tapped density.

The following are the approval criteria for Carr's index:

Table-II

% of Compressibility	Relative Flowability
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
> 40	Extremely poor

2. **Hausner's ratio:**

$$\text{Hausner's ratio} = \frac{\text{Tapped density X 100}}{\text{Bulk density}}$$

The following are the acceptance requirements for Hausner's ratio:

Table-III

Hausner's ratio	Type of flow
1.00–1.11	Excellent
1.12–1.18	Good
1.19–1.25	Fair
1.26–1.34	Passable
1.35–1.45	Poor
1.46–1.59	Very poor

SOLUBILITYANALYSIS

5. pKAionization constant

The ionization properties of a molecule having basic or acidic functional groups influence its solubility at a given pH.In aqueous conditions, a compound's solubility is greater in the ionizedstate than in the neutral state. As a result, the pH of a solution affects the solubility of ionizable substances. The procedure for determining pKa according to the nature of the substance is as follows:

Determining the pKaof a drug based on its nature:

Table-IV

Nature of drug	Ionization	pKa
Very weak acid	Unionized at all pH	> 8
Moderately weak acid	Unionized atgastric pH-1.2	2.5-7.3
Strong acid	Ionize at all pH	< 2.5
Very weak base	Unionize at all pH	<5
Moderately weak base	Unionize at intestinal pH	5-11
Strong base	Ionize at all pH	>11

For acidic compounds:

PH = pKa + log ([ionized drug]/[un-ionized drug])

For basic compounds:

PH = pKa + log ([un-ionized drug]/[ionized drug])

6. Solubility profile at pH:

The rate of drug release into the dissolving media, and thus the therapeutic efficacy of the pharmaceutical product, is affected by drug solubility, which is an essential physicochemical attribute. The equilibrium solubility method, which uses a saturated solution of the material created by swirling an excess of material in the solvent for a long time until equilibrium is reached, is commonly used to determine a substance's solubility.

Rules of thumb –

1. In polar liquids, polar solutes dissolve.

2. In non-polar liquids, non-polar solutes dissolve.

Determination of solubility.

Table-V

Description	Approximate weight of solvent(g) necessary to dissolve 1g of solute	Solubility(%w/v)
Very soluble	<1	10-50
Freely soluble	1-10	3.3-10
Soluble	10-30	1-3.3
Sparingly soluble	30-100	0.1-1
Slightly soluble	100-1000	0.01-.1
Very slightly soluble	1000-10000	0.01-0.1
Poorly soluble	>10000	<0.01

7.Ksp (common ion action)

The common-ion effect refers to the decrease in solubility of an ionic precipitate when a soluble compound with an ion in common with the precipitate is added to the solution.

This behavior is a result of Le Chatelier's principle for the ionic association/dissociation equilibrium reaction. The effect is most typically perceived as a reduction in the solubility of salts and other weak electrolytes. Increasing the concentration of one of the salt's ions leads to increased precipitation, which lowers the concentration of both ions until the salt's solubility equilibrium is reached. The result is due to the fact that both the original salt and the additional chemical contain one ion.

8.Thermal Effect:

The heat of solution can be used to determine the influence of temperature on a prospective therapeutic molecule. The heat generated or absorbed when a solute dissolves fully in a significant quantity of solvent is known as heat of solution, also known as enthalpy of dissolution or enthalpy of solution. This is significant because temperature affects the solubility of a medicinal ingredient in a specific solvent. The amount of energy necessary to break the bonds present in the solutes, as well as the amount of energy generated from the solid-solvent bond formation, determine whether the heat of solution is positive (endothermic) or negative (exothermic). Increasing the temperature of solutions with positive heat of solution (endothermic) can increase medication solubility.

9.Solubilization:

Solubilization is the process of increasing the apparent solubility of a sparingly soluble chemical by incorporating it into micelles and forming a thermodynamically stable solution. The ability of a surfactant solution to dissolve or solubilize water-insoluble or partially soluble compounds begins at the critical micelle concentration (CMC) and grows as the micelles grow. To achieve a stable dosage form with adequate absorption and enhanced bioavailability, it is necessary to fully understand the solubility behavior and likely mechanism for solubilization of a proposed drug molecule over the pH range encountered in the gastrointestinal system.

APIs with low solubility profile are very difficult to design into solid oral dosage forms due to their poor dissolution rate.Most of the available drugs are weakly acidicand weekly basic in nature and their solubilities increase in basic and acidic pH respectively depending on their ionization state shows in figure.

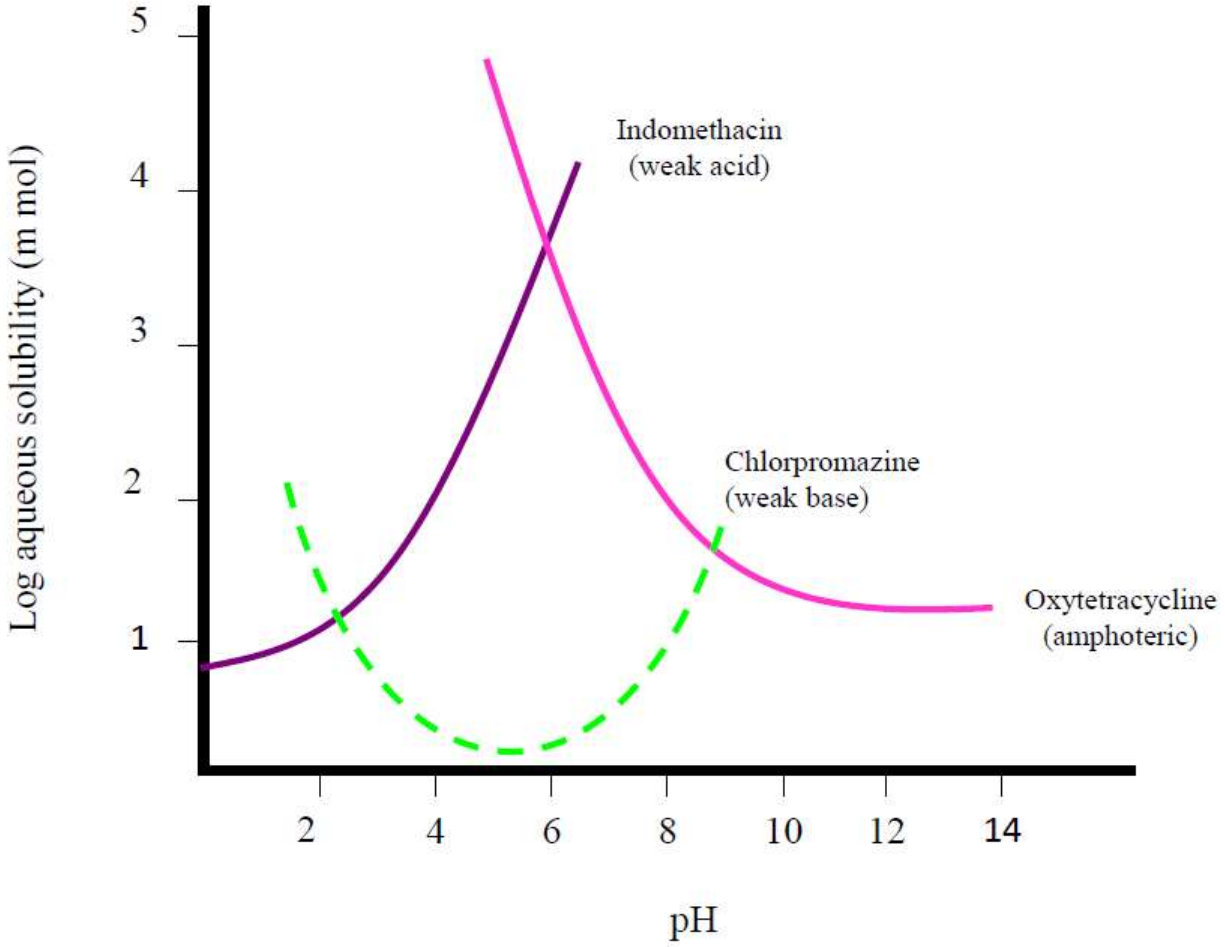


Figure .1: Solubility of drugs as a function of pH, plotted as logarithm of the solubility.

According to Biopharmaceutical Classification System (BCS), based on solubility and permeability, drugs are classified into the following four groups:

Class I: High Permeability, High Solubility

Class II: High Permeability, Low Solubility

Class III: Low Permeability, High Solubility

Class IV: Low Permeability, Low Solubility

According to the above classification, a dosage form is termed as highly soluble if the highest dose is soluble in less than 250 mL water within a pH range of 1 to 7.5. Additionally, a dosage form is considered highly permeable if more than 90% dose is absorbed in human. On the other hand, the dosage form is termed rapidly dissolving if more than 85% of labelled amount of drug substance dissolves within 30 minutes. Compounds which show aqueous solubility of more than 1% w/v are not considered to exhibit dissolution-related absorption problems.

10.Coefficient of partition:

The ratio of unionized drugs dispersed between the organic (n-octanol) and aqueous (water) phases at equilibrium is known as the partition coefficient (P), sometimes known as the distribution coefficient (D). Mathematically it is represented as

Po/w = (Conc. of thedrug in organic phase/ Conc. of the drug in water) equilibrium.

The formulator can use knowledge of how drug substances partition in the hydrophilic or lipophilic phase to select appropriate extraction solvents, conduct drug stability studies, measure drug absorption from dosage forms (e.g., ointments, suppositories, transdermal patches), measure the hydrophobic bonding ability of drug substances to serum albumin, and also permeation of drug substances across biological membranes, among other things.

11.DISSOLUTION BEHAVIOR:

Dissolution rate may be defined as the amount of drug substance that goes in solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. It may be estimated by the Noyes-Whitney Equation given below.

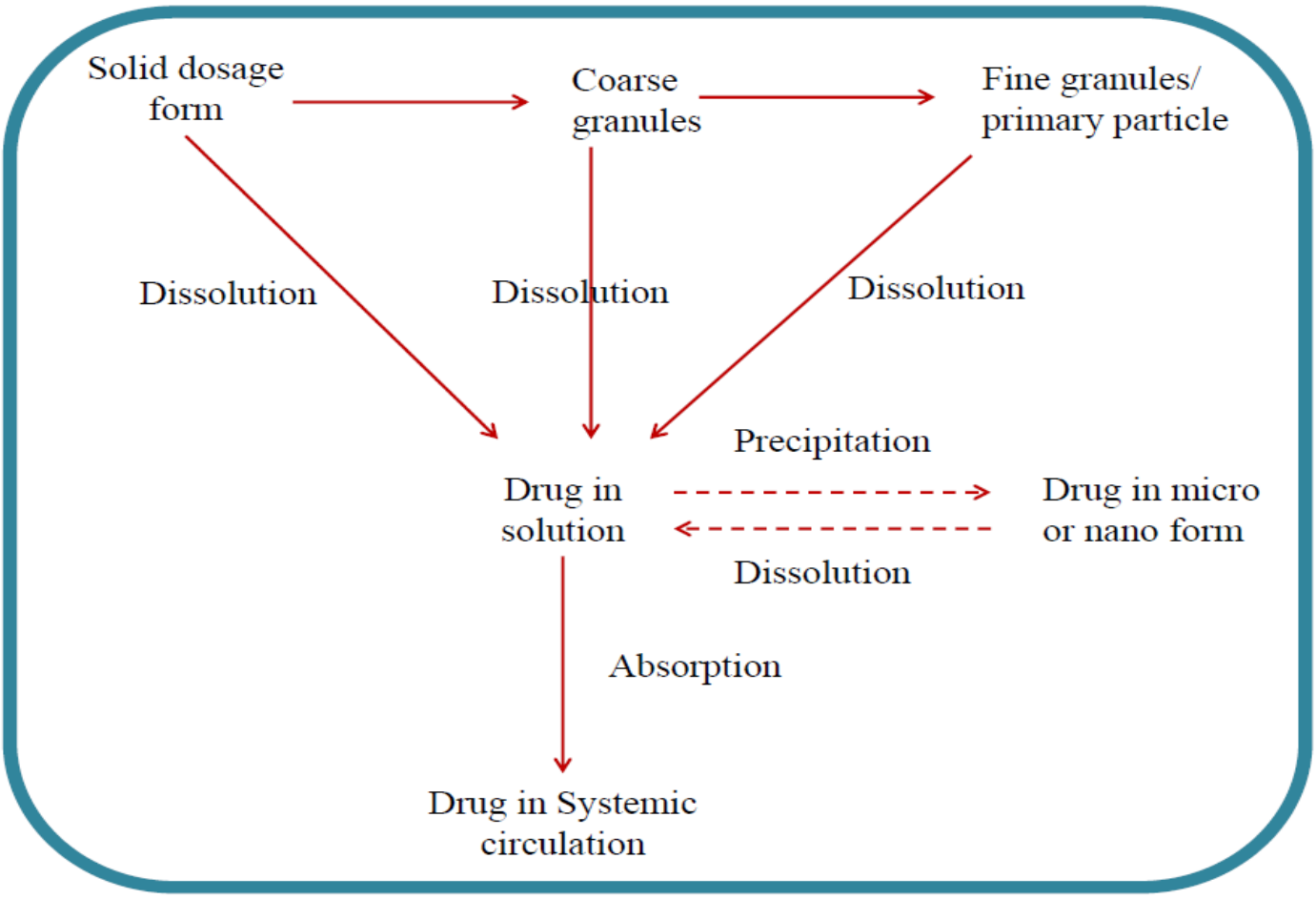


Figure 1.1: Dissolution and absorption of a drug from its solid dosage form.

In vitro dissolution testing provides information regarding the behaviour of the drug product

in vivo, especially how the drug is going to be released from the dosage form. In many

circumstances, it may predict the bioavailability if the drug belongs to BCS Class I or Class

III. A pre-formulation scientist can use this study to investigate the effects of particle size, surface area, and excipients on the dissolving of prospective therapeutic molecules. It also allows him to determine whether dissolution is a rate-limiting phase in the absorption of medicinal compounds. Apart from intravenous drug administration, which provides immediate drug substance access to the systemic circulation, other drug administration routes necessitate an absorption stage before pharmaceuticals reach the systemic circulation. The dissolving rates of pharmacological compounds determine the extent to which they are absorbed into the systemic circulation. This is true for both oral solid dose forms (such as tablets, capsules, and suspensions) and intramuscular dosage forms (such as pellets or suspensions). The start and intensity of the medication effect are also influenced by the rate of dissolution.

ANALYSIS OF STABILITY

12.Toxicology formulations' stability

Because toxicological studies are generally started early in the drug development process, it's common to test samples of toxicological preparations for stability and potential homogeneity issues.

The drug is given as a feed as an oral gavage of a solution or as a suspension in an aqueous medium.

Minerals, vitamins, enzymes, and a variety of functional groups included in feed lower the drug's shelf life.

- ✓ To be used a fresh sample of feed.
- ✓ Checked for ease of production of solutions or suspensions
- ✓ At varying temperatures, store in flame-sealed ampoules.
- ✓ Shaking every now andDispersibility.

13.Stability of the solution:

Effects of pH, Ionic strength, Co-solvent, Light, Temperature, and Oxygen are all investigated.

Experiments were carried out at pH and temperature extremes to see what would happen.

Assay specificity and maximal degradation rates.

The pH rate profile in its whole – the pH of maximum stability.

Aqueous buffers are utilized to give a wide range of medication concentrations, cosolvent concentrations, and ionic strength.

Physiological media are compatible.

14. pH rate profile:

- ✓ Data on stability for each pH and temperature
- ✓ Kinetic analysis – apparent decay constant
- ✓ Arrhenius plot - log apparent degradation is constant vs absolute temperature reciprocal Activation energy.

15.Solid-state stability:

Changes in purity and crystallinity affect solid-state stability.

To be researched are the initial bulk lots as well as recent lots.

Solid-state TLC, UV-Vis, and fluorescence are slower and more difficult to interpret than solution state TLC, UV-Vis, and fluorescence.

DSC, IR, or visual changes such as oxidation – surface discoloration – are examples of polymorphic alterations.

Storage condition:

Refrigerator - 5°C

Room temperature - 22°C

Ambient humidity, 70 % RH, 90% RH

25°C / 60% RH, 40°C/75 % RH

Light – Clear, Amber, yellow-green-glass, control sample

Ambient humidity – O2 headspace, N2 headspace

The information obtained may help determine whether an amber-colored container is required or whether color masking should be utilized in the formulation.

Stability to Oxidation: The sensitivity of a drug to oxidation can be tested by exposing it to a high oxygen atmosphere. Rapid evaluation is usually possible in a 40 percent oxygen environment. Desiccators with three-way stop cocks are used to store samples, which are alternately evacuated and inundated with the desired environment. The technique is done three or four times to guarantee that the desired environment is achieved. The results could help determine whether an antioxidant is needed in the formulation or whether the finished product should be packaged in an inert atmosphere.

16. Bulk stability

During the development phase, bulk parameters for the solid form, such as particle size, bulk density, and surface shape, are likely to change. The following are the various physical and bulk characteristics:

Preformulation goals:

1. Gather information throughout the preformulation stage in order to generate a stable product.
2. Determine the maximum shelf life/expiration date
3. To improve the storage situation
4. To figure out what goes inside the packaging.

CONCLUSION:

PREFORMULATION IMPACTS: Preformulation has an impact on the selection of the drug candidate, formulation components, API & drug product manufacturing processes, determining the most appropriate container closure system, development of analytical methods, API retest periods, API synthetic route, and toxicological strategy. Preformulation studies support the guidance's scientific foundation, provide regulatory release and save resources in the drug development and evaluation process, improve public safety standards, improve product quality, facilitate the implementation of new technologies, and facilitate policy development and regulatory decision making.Preformulation studies provide instructions for formulation creation in terms of drug form, excipients, content, and physical structure, as well as pharmacokinetic and biopharmaceutical properties adjustment. This review article summarises the findings of the preceding investigations, demonstrating that no pharmacological preparation can be developed without first conducting pre-formulation trials.

References:

1.L. Allen and H. Ansel (2014). Pharmaceutical Dosage Forms and Drug Delivery Systems by Ansel (10th ed). Lippincott Williams & Wilkins, Philadelphia: 34-75.

2.M. E. Aulton and M. M. Taylor (2013). Pharmaceutics: The Design and Manufacture of Medicines, by Aulton. Churchill Livingstone Elsevier, Amsterdam, Netherlands: 367-394.

3.G. Chaurasia (2016). Preformulation Studies in Pharmaceutical Formulation and Development of New Drug Molecules: A Review 2313-2320 in International Journal of Pharmaceutical Science and Research.

4.M. Gibson, M. Gibson, M. Gibson, M. Gibson, M. Gibson, M. Gibson (2004). Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form is a practical guide to pharmaceutical preformulation and formulation. CRC Press LLC is based in Florida.

5.S. Kulkarni, S. Sharma, and Agrawal, Agrawal, Agrawal, Agrawal, Agrawal, Agrawal, Agrawal, Agrawal, Agrawal (2015). Preformulation is a foundation for the development of formulations. 5(2): 403-406 in International Journal of Pharmaceutical, Chemical, and Biological Sciences.

6.P. Kumar, G. Vaishnavi, K. Divya, and U. Lakshmi (2015). Preformulation Studies in Context. 2(10): 1399-1407 in Indo American Journal of Pharmaceutical Science.

7.A. Leo, C. Hansch, and D. Elkins (1971). The Uses of Partition Coefficients Chemical Reviews, vol. 71, no. 6, pp. 525-616.

8.I. V. Onyishi (2015). Preformulation is the subject of this lecture.

9. https://www.slideshare.net/bknanjwade/thermalanalysis-42770949 Onyishi's personal collection, University of Nigeria, Nsukka, Enugu State.

10.A Textbook of Professional Pharmacy, edited by NK Jain and SN Sharma. 317-333 in VallabhPrakashan, Pitampura, Delhi, 2004.

11. G T Kulkarni, B Gowthamarajan, and B Suresh: An overview of stability testing of pharmaceutical products. Indian Journal of Pharmaceutical Education, vol. 38, no. 4, pp. 194–198, 2004.

12.Lachman L, Lieberman H A, and Joseph L K: Industrial Pharmacy Theory and Practice. Bombay: Varghese Publishing House, 1990, Edition 3: 171-196.

13.Brahmankar DM, Jaiswal SB: Drug absorption in: A treatise on biopharmaceutics and pharmacokinetics. 5-75 in VallabhPrakashan, 1st Edition, 1995.

14.Vilegave K, Vidyasagar G and Chandankar P: Preformulation studies of pharmaceutical novel drug molecule and products: An Overview. 1–20 in American journal of pharmacy and health research, 2013.

15.Trends in polymorph solubility, M. Pudipeddi and A.T. Serajuddin. 94, 929–939. J. Pharm. Sci., 2005

16.A. Martin, J. Swarbrick, and A. Cammarata. Physical Pharmacy is a branch of pharmacy that deals with physical chemical principles. 3rd edition Philadelphia: Lea and Febiger, 1983.