SECTION I

ESSENTIALS OF DOSAGE FORM DESIGN

CHAPTER 1

PREFORMULATION STUDIES

Introduction

Development of a suitable dosage form of a new drug substance involves investigation by several departments or disciplines. The ultimate outcome of the entire program can only bring about a suitable dosage form. Fig. 1.1 presents the names of disciplines involved in this activity. The development of a suitable dosage form of a new drug depends on certain information about the drug molecule. For example, once a new molecule of therapeutic interest is synthesized, it is first subjected to biological screening. When it passes the test, it is sent for clinical trials. To begin this test some basic information about the physicochemical properties of the drug molecule are necessary like chemical structure, molecular formula, molecular weight, solubility, salt forms, approximate dose, interaction with common excipients, etc. These information are generated during preformulation studies.

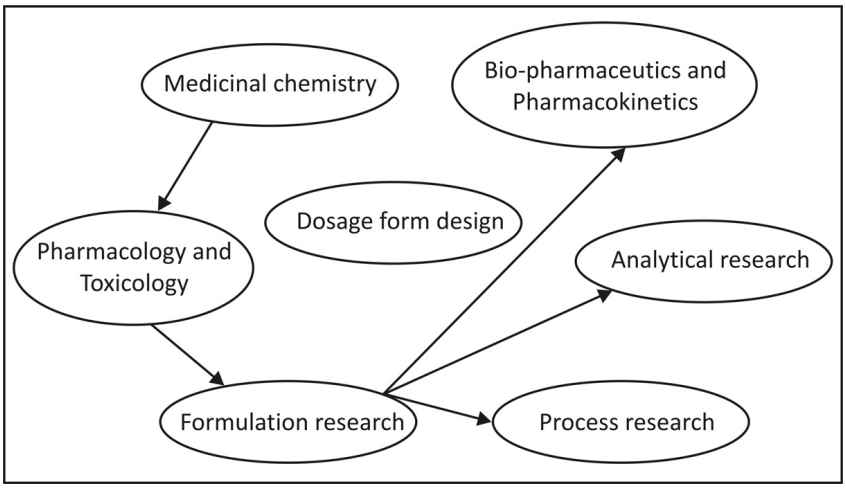


Fig. 1.1 Disciplines involved in dosage form design of a new drug

Hence, preformulation studies may be defined as *testing of physical and chemical properties of a drug substance alone and in combination with excipients proposed to be used in formulation.*

The Table 1.1 presents a list of tests to be carried out during preformulation studies on a new chemical entity (NCE) having therapeutic utility. Most of the new drugs are formulated as solid dosage forms, - tablets and capsules. In fact more than 60% of the marketed formulations are tablet dosage forms. Other dosage forms occupy only 40% or less. More than 45% are tablets and about 15% are capsules.

Table 1.1 List of preformulation tests

Sl. No.	Tests
1.	Fundamental properties of the Molecule; like, Chemical name, Chemical structure, Molecular formula Molecular weight, Solvent used for crystallization and recrystallization,
2.	Organoleptic properties and Skin sensitivity
3.	Microscopic structure
4.	Physical characteristics Particle size and size distribution, Particle shape and surface area, Density, Flow properties, Compressibility, Hygroscopicity, Polymorphism.
5.	Solution characteristics Solubility, pH of 1% solution, Dissociation constant and pK_a, Effect of solubilizing agents Partition coefficient, Dissolution rate: intrinsic and particulate,
6.	Chemical properties Chemical identity UV-visible spectroscopy HPLC Analysis TLC Analysis Purity
7.	Therapeutic information Approximate Human dose Lethal dose Bioavailability

Table 1.1 *Contd…*

Sl. No.	Tests
8.	Stability data: Solid-state stability, Solution-state stability, Physical stability, Chemical stability, Microbiological stability, Therapeutic stability, Toxicological stability,
9.	Recommendation

Organoleptic Properties

The test for description of a drug substance is the first test conducted during preformulation studies. This test provides the information regarding appearance, color, odour and taste of the drug. The description of organoleptic characteristics uses a descriptive terminology as shown in Table 1.2. All these initial data should be recorded, because these can be

- Used as reference for comparison with subsequent lots and for validation,
- Useful to design an acceptable dosage form,
- Used to select the excipients.

For example, if a drug possesses an unacceptable color and odour, it may be necessary to mix with a suitable dye and flavor to make it acceptable. If the taste is unpalatable, suitable taste masking agent can be used to make it palatable.

Table 1.2 Terms used to describe color, odour and taste

Property	Descriptive terms
Color	White,off-white,cream, light-cream, slightly cream, yellow, light-yellow, pale-yellow, light-brown, brown, pink, maroon, chocolate, etc.
Odour	Odorless, pungent, aromatic, sulphurous, fruity, etc.
Taste	Bland, sweet, bitter, bitter-after, acidic, etc.

Skin sensitivity test is another important test. If a drug causes irritation to the skin, appropriate measures can be recommended for handling it.

Purity and Impurity

It is necessary to know the purity of the drug substance and the type and extent of impurity it contains. This information is important with respect to,

- Design and validation of the clinical studies,
- Standardization of specifications,

- Analytical method development and validation,
- Stabilization of the drug and its formulation.

Impurities may be named as by-product, degradation product, interaction product, intermediate, penultimate intermediate, related product and transformation product. The sources of impurities may be related to,

- Crystallization,
- Stereochemistry(isomers),
- Residual solvent,
- Synthesis(synthetic intermediates and by-products),
- Interaction between drug and excipients of the formulation,
- Ageing (during storage of the drug/formulation).

The most commonly used methods for measurement of purity of a drug are Thin Layer Chromatography (TLC) and High Performance Liquid Chromatography (HPLC). Paper Chromatography and Gas Chromatography are also useful for some drugs.

Impurity index (II) and *homogeneity index (HI)* are useful measures and can be calculated from the HPLC chromatographs. The chromatograph indicates the responses of the principal component (drug) and of other components (impurities). The area of each type of responses are calculated and with these values both impurity index II and homogeneity index, HI can be calculated as follows,

$$II = \frac{\text{Responses due to other components}}{\text{Total response}}$$

The homogeneity index, $$HI = \frac{\text{Response due to principal component}}{\text{Total response}}$$

The USP has introduced a test for impurity with a maximum limit of 2%. The test uses the TLC chromatograph. According to the USP,

Impurity index =

$$\frac{\text{response due to impurity}}{\text{response due to a specified concentration of standard main component}}$$

However, none of these indices is an absolute measure of the impurity. Each of the impurity should be identified and estimated.

Differential and gravimetric thermal analyses can be used to characterize impurity of a substance. These provide qualitative information about the homogeneity of the drug and also directly indicate the presence of solvates. Sometimes the test for melting point

can characterize purity of a substance. Similarly, other tests, like solubility, X-ray powder diffraction, etc.., can indicate the purity of a substance.

Particle Size, Shape and Surface Area

Particle size distribution and shape can influence various physical as well as biopharmaceutical properties of a drug substance. For example,

- The difference among sizes of powder particles of a drug and other excipients in a mixture can cause mutual sieving (demixing) affecting the homogeneity of the powder mix (*uniformity of content*).
- If the powders are too fine, the particles become sticky and their flow ability may decrease (*physical property*).
- Size distribution, the shape of the powders can influence the flow and mixing efficiency. Bioavailability of certain drugs, e.g., griseofulvin, phenacetin, etc. depends directly on the particle size distribution[1,2].

Usually the absorption of poorly soluble drug is dissolution rate limited. Thus, the absorption of such drugs can be improved by decreasing their particle size (*Biopharmaceutical property*). The stability of a powder drug depends on the particle size. Due to large surface area fine powders are more susceptible to atmospheric oxygen, moisture, light, heat and other interacting materials than coarse powders.

In general, for most formulations the optimum particle size range is 10-30 µm. If the particles are more than 100 µm in size, grinding is required. Otherwise grinding should be avoided; because grinding develops a static electricity, which subsequently develops a tendency to aggregation; as a result apparent hydrophobicity is produced. Grinding damages the solvates and causes polymeric transformation of the substance. Moreover, handling of fines is also difficult. When a drug is administered orally as its solid dosage form, various processes are involved to complete the absorption of the drug. Fig. 1.2 shows these sequential processes of absorption.

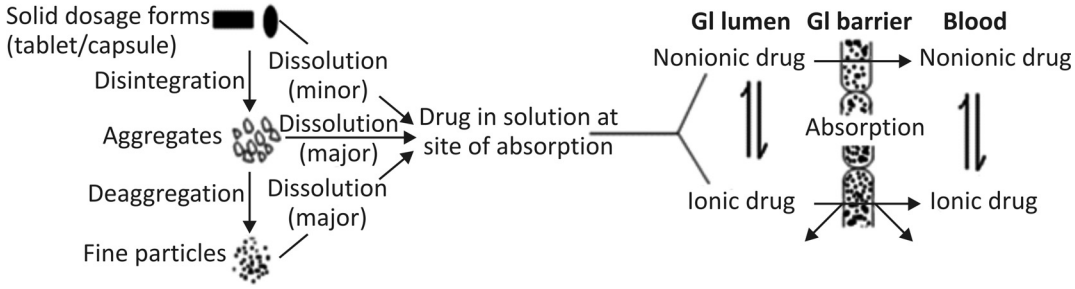


Fig. 1.2 Sequence of steps involved in absorption of drug from orally administered solid dosage form

There are various methods for determination of particle size and each method has certain advantages as well as limitations with respect to minimum size of the particle, accuracy and ease of operation of the instrument. The Table 1.3 provides some common methods and measurable particle size range.

Table 1.3 Methods of particle size measurement

Method	Particle size range(μm)
Light scattering	0.5-50
Permeability	More than 1
Sedimentation	More than 1
Centrifugal	Less than 50
Elutriation	1-50
Sieving	More than 50
Microscopic	1-100

Microscopy, although tedious, is useful for determining both size and shape of the particles. The flow property, surface area, packing and compaction characteristics of powders depend on the shape of the particles. A sphere has minimum surface area per unit volume.

Solubility

Whatever may be the route of administration, a drug must have some aqueous solubility for systemic absorption and pharmacological response. Drugs having aqueous solubility of less than 10 mg/mL show incomplete, erratic and/or slow absorption.

Usually a drug is either a weak acid or weak base. The solubility of a weakly acidic drug is more in alkaline medium and that of a weakly basic drug is more in acidic medium. In both cases the drug will dissociate with a measurable dissociation constant, pK_a. Thus the solubility will change with change of pH. A drug which is either amorphous or zwitterions, will be soluble in both acidic and alkaline medium. A non-ionizable neutral drug will not show any change in its solubility due to change in pH. The fundamental solubility is the *intrinsic solubility*, C_o. *The solubility of a weakly acidic drug in acidic medium and that of a weakly basic drug in alkaline medium are called as intrinsic solubility*, because this indicates the solubility of unionized drug only.

The solubility has a great influence on the therapeutic efficacy of a drug and its product. This must be considered during formulation development. When a solid drug is administered orally, the drug is to be dissolved in the gastrointestinal fluid first for its absorption. The rate and extent of absorption of the drug depends on its rate of dissolution in gastrointestinal fluid. The absorption of poorly soluble drugs is dissolution rate-limited. If 1 g of a drug dissolves in 100 mL of water, its absorption will not be affected by its dissolution. At the same time the drug in solution in gastrointestinal fluid must remain stable until it is absorbed. If a drug is very soluble in gastrointestinal fluid but not stable, the absorption of the drug will decrease. In any of the two situations, efforts should be made to modify the solubility of the drug and/or its stability in solution state at pH ranging from 1 to 8.

Determination of Solubility

The solubility can be determined quantitatively as follows: At a particular temperature a definite volume of solvent is taken. To this the solute is added gradually in small amounts and the mixture is shaken vigorously after each addition. At each time sample (solution of drug) is withdrawn and analyzed to determine the concentration. The process is continued until the consecutive samples show same concentration and a small amount of solute remains undissolved.

In case of poorly soluble drugs, problem may occur during determination of solubility. While investigating the solubility of poorly soluble drugs it has been found that due to the presence of soluble impurities in the drug, the solubility may appear more than the actual[3]. This can be overcome by using facilitated dissolution method developed by Higuchi et al. According to this method the drug is first dissolved in a water-immiscible solvent and then partitioned into water. The aqueous phase is then analyzed to determine the solubility.

The drugs which degrade in their solution state present difficulty in solubility determinations. A kinetic method has been proposed by Ohnishi and Tanabe[4]. According to their proposal, the rate constants and orders of the reactions for degradation of the drugs (solutes) in the solutions or suspensions are determined. The rate of overall degradation of the drug in the suspension can be expressed as:

$$V_s = \Sigma K_n [S]^n$$

Where, V_s is the overall rate of degradation of the drug, n is the order of reaction, k_n is the rate constant of the nth order reaction, and [S] is the concentration of the saturated solution of the drug. Among these V_s , K_n and n are measurable quantities, and hence, [S] can be calculated.

Further, there are certain drugs whose metastable forms transform into more stable forms when come in contact with solvent. For determination of solubility of these drugs, determination of intrinsic dissolution rates should be used[5]. According to Noyes-Nernst equation, the initial dissolution rates for both metastable and stable forms are proportional to the respective solubilities of the polymorphic forms and the proportionality constants for both the forms of a drug will be same. Hence, by determining the intrinsic dissolution rates of metastable and stable forms, and solubility of the stable form, the solubility of the metastable form of the drug can be calculated.

pH and Solubility

If the drug substances are classified on the basis of their ionic character, less than 5% of the drugs are nonionic or amphoteric. While one fifth (20%) are weak acids and three-forth (75%) are weak bases. Hence, ionization and dissolution of about 95% of the drugs take place simultaneously. The degree of ionization as well as solubility of these drugs

depends on the pH of the medium. At a particular pH the saturation solubility will be the sum of the maximum solubility of ionized and unionized form of the drug. *This pH is called as* pH_{max}*, the pH of maximum solubility*. The effect of pH on the solubility and stability of drugs is very much important for liquid dosage forms, which may be intended for oral, topical, parenteral or ophthalmic administration.

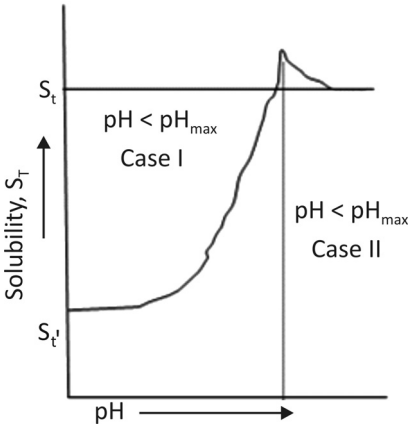


Fig. 1.3 pH-Solubility profile

Thus, the total amount of a monoprotic weak acidic drug (HA) in solution at a particular pH will be the sum of HA (unionized form) and salt form (A^-).

$$HA + H_2O \overset{K_a}{\longleftrightarrow} [H_3O]^+ + A^-$$

If the drug (HA) is present in excess amount, the amount of the unionized drug will be the maximum and constant. With increase of pH the amount of HA will increase, because the extent of salt formation will be less as shown in the Fig. 1.3. The total amount of drug, ionized and unionized, present in solution at a particular pH can be determined by use of one of the two equations given below depending on whether the pH is less than pH_{max} or more than pH_{max}.

In case of an acidic drug the total solubility, S_T, at a pH less than pH_{max}, = $(HA)_S \left(1 + \frac{K_a}{[H_3O^+]}\right)$ and at a pH more than pH_{max}, $S_T = (A^-)_S \left(1 + \frac{[H_3O^+]}{K_a}\right)$

Where

S_T = total saturation solubility with respect to the drug (HA) and its salt form (A^-),

$(HA)_S$ = saturation solubility of the unionized form of the drug,

$(A^-)_S$ = saturation solubility of the ionized form, and

K_a = apparent dissociation constant.

Similarly, for a basic drug substance, BH that ionizes as

$$BH + H_2O \overset{K_a}{\longleftrightarrow} + [H_3O]^+ + B^-$$

The total solubility at a particular pH can be calculated as follows:

When pH is less than pH_{max}, $S_T = (BH^+)_S \left(1 + \frac{K_a}{[H_3O^+]}\right)$ and

When pH is more than pH_{max}, $S_T = (B)_S \left(1 + \frac{[H_3O^+]}{K_a}\right)$

Where $(BH^+)_S$ represents the solubility of ionized(protonated) form of the drug and $(B)_s$ represents the solubility of unionized form.

Particle Size and Solubility

Generally the solubility is considered as a physicochemical constant, the solubility can be increased by reducing the particle size of a drug. Even in case of reaction also the rate of reaction increases with decrease in particle size[6].

The relation between solubility and particle size and surface area can be expressed as;

$$\log \frac{S_m}{S_1} = \frac{2\gamma V}{2.303RTr}$$

where, S_m is the solubility of smaller particles,
S_l is the solubility of larger particles,
γ is the surface tension,
V is the molar volume
R is the gas constant,
T is the experimental temperature in absolute scale, and
r is the radius of the smaller particles.

pK_a and Solubility

It has been mentioned earlier that most of the drugs are either weak acids or weak bases. Their dissolutions are very much dependent on pH. Hence, Henderson-Hasselbalch equation may be considered here:

For weak acid, HA: $pH = pK_a + \log_{10} \frac{[A^-]}{[HA]}$

For weak base, B: $pH = pK_a + \log_{10} \frac{[B]}{[BH^+]}$

The above two equations can be utilized;

- To find out the solubility at a particular pH, if the intrinsic solubility and pK_a are known,
- To select a salt-forming compound with desired solubility – pH profile.

Salt Formation

Since most of the drugs are either weakly acidic or basic, solubility of the drugs can be greatly improved by forming salts. Certain salts of strong acids or strong bases are freely soluble in water but these may be very hygroscopic. Such salts are difficult to be formulated as tablets or capsules due to their instability. For this reason it is better and preferred to form salts of weakly acidic or basic drugs to improve their solubilities. Usually *a less soluble salt is less hygroscopic and its solution will also be less acidic or basic*. Injections having pH within 3 to 9 cause less damage to the glass containers and cause less pain at the site of injection. Too acidic or too alkaline solutions are neither compatible to the containers nor suitable for oral administration as they are not palatable. Even hydrochloride salts are not suitable for aerosol preparations as they can react with propellant and corrode the aerosol container.

Although a weak base having intrinsic solubility more than 1 mg/mL is freely soluble in stomach, it is better to form a salt to control the pH of the diffusion layer. Further a weakly basic drug exhibits higher rate of dissolution in the stomach. When it moves down towards intestine the pH increases and dissolution rate decreases. Conversely a weakly acidic drug will show less dissolution in the stomach due to less solubility. As it goes down towards the intestine its dissociation as well as solubility will increase. Such solubility vis-à-vis dissolution adversely affects the absorption of the drug as the unionized fraction of a drug is absorbed and effective pharmacologically.

The physicochemical properties of a drug can be modified by forming different salts. For example, the solubility and dissolution rate can be modified. Such change in dissolution rate may alter the rate and extent of absorption, i.e. bioavailability of the drug.

Hence, every new drug substance should be examined for formation of suitable salt, since each salt behaves differently and is officially treated as different chemical entity.

Ionization Constant

Since majority of the drugs are either weakly acidic or basic, their solutions in water contain ionized and unionized species. In other words, these drugs undergo dissociation in their aqueous solutions. The extent of ionization depends on the pH of the solution. For example, a weak acid will ionize mostly at alkaline pH and a weak base in acidic pH. The unionized drug is more lipid soluble and thus, readily absorbed.

Hence, the gastrointestinal absorption of a drug can be improved if the extent of absorption is reduced. The absorption of weakly acidic or basic drugs can be influenced by the factors:

- pH at the site of absorption,

- Ionization constant, and
- Lipid solubility of the unionized drug.

These factors togetherly considered as pH partition theory[7,8]. At a particular pH the relative concentration of unionized and ionized species in a drug solution can be estimated with the help of Henderson-Hasselbalch equation;

For acidic drugs $$pH = pK_a + \log \frac{[\text{ionized drug}]}{[\text{unionized drug}]}$$

For basic drugs $$pH = pK_a + \log \frac{[\text{unionized drug}]}{[\text{ionized drug}]}$$

The above equations are valid within pH range from 4-10. There are various methods to determine the ionization constant, K_a. Acid-base potentiometric titration can be used for the drugs having solubility about 0.01 molarity.

From the Henderson-Hasselbalch equations it is understood that the relative concentration of unionized acidic drug would increase as the pH of the solution will decrease. Similarly, in case of basic drugs, the concentration of the unionized drug will increase as the pH of the solution will increase. The contents of the stomach have pH ranging from 1-3, while pH of the intestinal fluids vary from 5-8. Thus, acidic drugs are preferentially absorbed from the stomach and basic drugs from the intestine. Schanker[9] observed that weakly acidic compounds having pK_a value less than 4.3 were absorbed relatively faster than those having pK_a value within 2-4.3, strongly acidic compounds were almost not absorbed. In case of basic compounds, the absorption is faster for the compounds having pK_a values less than 8.5 and the compounds having pK_a values within 9-12 were slowly absorbed.

Thus, for prediction of the site of absorption of weakly acidic or basic drugs, knowledge of pK_a value is necessary. The Table 1.4 presents briefly the relation between pK_a value of drug and its site of absorption.

Table 1.4 Relation between pK_a value and absorption characteristics of drugs

Drugs	pK_a value	Ionization and Site of absorption
Very weak acids e.g., pentobarbital, hexobarbital	> 8	Unionized at all pH values. Can be absorbed throughout any region of GIT.
Moderately weak acids e.g., aspirin, ibuprofen, phenylbutazone, indomethacin,	2.5-7.5	Unionized in gastric pH and ionized at intestinal pH. Mostly absorbed from stomach.
Stronger acids e.g., disodium chromoglycate	< 2	Ionized at all pH values. Poorly absorbed from GIT.

Table 1.4 *Contd…*

Drugs	pK_a value	Ionization and Site of absorption
Stronger bases e.g., guanethidine	> 11	Ionized at all pH values. Poorly absorbed from GIT.
Moderately weak bases e.g., codeine,	5-11	Ionized at gastric pH and unionized at intestinal pH. Mostly absorbed from intestine.
Very weak bases e.g., caffeine, theophylline	< 5	Unionized at all pH values. Can be absorbed throughout any region of GIT.

Partition Coefficient

As such absorption of drug through biological membrane is a complex process. A solid drug when administered orally the drug must dissolve in gastrointestinal fluid first, then cross the biological membrane for its absorption. In case of relatively insoluble drugs the overall absorption is dissolution rate-limited. While for soluble drugs the overall absorption depends on the permeation through gastrointestinal membrane. It is therefore necessary to study both dissolution and permeation characteristics of the drug during preformulation. The rate of permeation of a drug or any substance mainly depends on; molecular size, relative solubilities in water and lipid, and ionic charge of the molecule. Thus, assessment of permeation behavior of a new chemical entity (NCE) should be done even before studying dissolution characteristics.

The biological membranes are made of protein and lipid. To cross the membrane a drug must have some lipophilicity, that is, the solubility in lipids. Lipids present in biological membrane are complex and it is very difficult to obtain them in pure form. However, relative lipid solubility can be assessed by measuring partition coefficient of a drug which is the measure of its distribution between a polar solvent (water) and a nonpolar solvent. In other words, *partition coefficient is an index of the hydrophilicity and lipophilicity of the drugs.* Many organic solvents, like chloroform, ether, carbon tetrachloride, isopropyl myristate, amyl acetate, benzene, n-hexane, n-octanol, etc. have been tried for determining partition coefficient of drugs. Out of which n-octanol has been found to produce satisfactory results.

If a definite amount of the drug is added to a mixture of two immiscible liquids, usually n-octanol and water, the drug will distribute itself between the two solvents until equilibrium is reached at a particular temperature. The ratio of concentrations is termed as the partition or distribution coefficient of the drug. The ratio is independent of the concentrations of the dilute solutions. Actually, lipids show some solubility in aqueous phase and vice versa. Hence, before determining the partition coefficient the solvents are to be saturated with respect to each other.

The n-octanol-water (oil-water) partition coefficient is commonly used as a measure of lipophilic character of the drug. The distribution/partition coefficient, K_w^o is expressed as

$$K_w^o = \frac{C_o}{C_w} = P$$

Where C_o and C_w are the concentration of the drug in oil (n-octanol) and water phase respectively. The value of P depends on whether the drug molecules associate or dissociate in the solution. The above equation stands true when the drug molecules associate in solution. When the drug molecules dissociate in solution, the equation may be modified as,

$$P = \frac{C_o}{(1-\alpha)C_w}$$ where α is the degree of ionization.

The test is performed during preformulation studies for the selection of a solvent for,

- Extraction of drug,
- Crystallization of a drug,
- Extraction of a drug from its crude extract,
- Extraction and estimation of a drug from its formulation.

The relative polarities of the solvents can be expressed in terms of dielectric constant (ξ), solubility parameters (δ), interfacial tension (γ), or hydrophilic-lipophilic balance (HLB). The best solvent for any solute is one whose polarity matches with that of the solute; i.e., $\delta_{solute} = \delta_{solvent}$.

The most useful and easy method to know the polarity of drug is partition coefficient. The solvent solubility can be related to partition coefficient for majority of the drugs. Octanol is a partially polar solvent and it exhibits following properties similar to biological systems.

- Hydrogen bonding acceptor and donor, similar to many biological macromolecules.
- Inclusion of water, similar to biological lipid membranes.

For these reasons octanol has been widely used solvent for partition coefficient determination and the partition coefficient data has been used to correlate structure activity of the drug molecules also.

Permeation through Biological Membrane

In-vitro measurement of the rate of permeation of drugs in solution through the biological membrane (intestine of rat or mouse) has been gaining importance in preformulation studies. The absorption characteristics of the drugs can be understood

from the results of these experiments. Bates and Gibaldi have reviewed the techniques for such experiments. The modified method[10] of Crane and Wilson[11] is simple and reproducible. According to this method a rat or mouse is fasted overnight with free access to drinking water. The animal is then anesthetized with ether or chloroform. By midline incision of the abdomen the small intestine is removed and rinsed with cold normal saline solution. From the pyloric end a section of about 15 cm is removed. The rest portion of the intestine is everted using a blunt glass or steel rod. The everted gut is stretched under a weight (about 10 g) and a segment of 10 cm is cut for use. At the distal end the gut segment is ligated using a nylon thread and the proximal end is connected to the canulated end of the tube A as shown in the Fig. 1.4. To keep the sac vertical a weight of 10 g is attached to ligated end of the sac. The assembly is introduced into a test tube B containing 80 mL of drug solution prepared in Krebs bicarbonate buffer solution. The test tube B is also attached to two needles C and D. A polyethylene tube is connected to the needle D for bubbling the solution with a mixture of oxygen and carbon dioxide gas (95:5). The temperature of the drug solution in tube B is maintained at 37 ^{o}C and is called as *mucosal solution*. Once the sac is maintained at 37 ^{o}C, 2 mL of Krebs solution (buffer) preheated to 37 ^{o}C is introduced into the sac through the tube B. thus the solution in the sac is called *serosal solution*. Through the needle D the gas mixture is introduced into the mucosal solution slowly and continuously. At predetermined time intervals aliquots of serosal solution are withdrawn for analysis. After each withdrawal same volume of fresh buffer solution, preheated to 37 ^{o}C, is introduced into the sac to maintain the volume same.

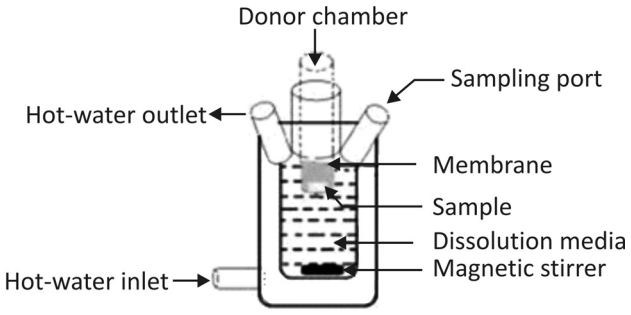


Fig. 1.4 Schematic diagram of Franz diffusion cell

The experiment is repeated with different mucosal concentrations of drugs. When the rates of transfer of drug per unit concentration are found constant, the transfer is considered as passive transfer of drug. That is passive diffusion of the drug across the membrane. No other process like active or electrochemical is involved for transfer of the drug. The driving force for drug diffusion is concentration gradient. The results can be satisfactorily compared with those obtained through *in-vivo* experiments.

Polymorphism and Crystal Properties

When a drug substance is prepared either by precipitation or crystallization, the precipitated molecules may either be arranged in regular pattern or in irregular way.

The orderly arranged molecules are called *crystals* having specific crystal lattice structure and irregularly or randomly arranged molecules are called as *amorphous.* The crystalline solids may exist in more than one crystalline form with different spatial arrangement in the crystal lattice, these crystal forms are called as *polymorphs* of the drug. The property of having polymorphs is called as *polymorphism*. Sometimes, during crystallization, solvent molecules are entrapped into the crystals with specific lattice position and in a specific stoichiometry. Such crystals are called as *solvates or pseudo polymorphs*. By controlling the parameters of crystallization, like solvent, temperature, rate of cooling, etc. the number of polymorphs can be controlled. In many cases crystals of single lattice structure can also be obtained. Generally sudden change of cooling temperature or sudden change in the composition of solvent of crystallization or freeze drying (lyophillization) can produce amorphous solids.

The polymorphs of a particular drug mainly differ from each other in physical properties and therapeutic effect also. The physical properties include crystal shape, solubility and dissolution (hence, bioavailability), true density, compressibility, flow property, solid-state stability, etc.

Hence, it is necessary to screen the polymorphs and to find out the suitable form for the formulation. This has been extensively reviewed also[12,13].

Crystal Characteristics and Bioavailability

Bioavailability of a drug administered as a dosage form can be defined as the extent to which the drug is absorbed from the dosage form and is available in the systemic circulation.

Absolute bioavailability can be expressed as;

$$\text{Absolute bioavailability} = \frac{AUC_{oral}}{AUC_{IV}} \times \frac{Dose_{IV}}{Dose_{oral}}$$

Powder drug consists of particles of different size. A molecule in powder form (crystal or amorphous) cannot directly be bioavailable, as the particle will not be absorbed as such into the body. To be absorbed the particles need to be dissolved in the body fluid.

In a crystalline solid the atoms or molecules are uniquely arranged. Thus the crystalline structure plays a great role for the physical properties of a compound such as melting point, solubility, dissolution, stability, etc. Compared to crystals, amorphous material contains molecules randomly arranged. Most of the drugs have different crystalline structures called polymorphs and one of the polymorphs is found stable at a particular set of conditions, other polymorphs are metastable. According to the laws of thermodynamics a metastable form can transform into a stable form. Thus, it is necessary to find out the most stable crystalline structure to avoid or reduce the risk of transformation.

Different polymorph of a drug will have different solubility characteristics and hence, different dissolution rate. If the absorption of the drug is dissolution rate-limited, the faster dissolving polymorph will show greater dissolution rate and greater extent of bioavailability. This has been experimentally observed by many researchers[14,15].

Crystal Characteristics and Chemical Stability

When a drug is susceptible to degradation in its solid state, the rate of degradation may be influenced by its physical form. For example, between two crystalline forms, needle-like and spherical, the former may degrade faster than the later under the same storage conditions, particularly in the presence of high humidity. Similarly, between crystalline solvate and anhydrous crystals, the former is more stable than the later under the same storage conditions. Nimodipine (1, 4-Dihydro-2, 6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine dicarboxylic acid 2-methoxyethyl 1-methylethyl ester) is usually administered to patients suffering from cerebral ischemia and subarachnoid haemorrhage. It is a racemate with two crystalline polymorphs, one metastable and one stable. In racemates, the solid structure of the crystals can be defined as being either a conglomerate or a racemic compound. In a conglomerate the solid consists of crystals of each enantiomer in a molar ratio of 1:1. The metastable polymorph crystallizes as a racemic compound with monoclinic crystals arranged in rough plates. The stable polymorph can be considered as a conglomerate with circular aggregates of orthorhombic crystals. Nimodipine (Fig. 1.5) is photosensitive, producing a pyridine degradant during radiation exposure. The pyridine degradant can be formed through aromatization.

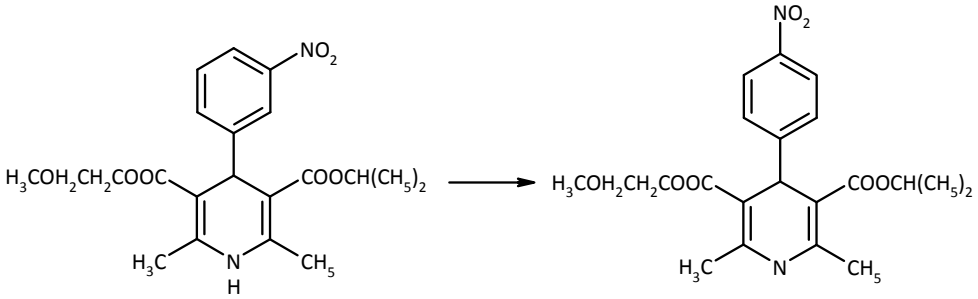


Fig. 1.5 Transformation (nitro-pyridine degradation) of Nimodipine

Crystal Property and Physical Stability

All the polymorphs of a drug are not physically stable. Only one polymorph is thermodynamically stable at a particular temperature and pressure. An unstable polymorph transforms to a stable form. This process is called as *polymorphic transformation*. The rate of transformation may be slow or fast. When a polymorph transforms slowly it is called metastable polymorph. A metastable polymorph does not have adequate chemical stability. Thus, the processing conditions for stable and

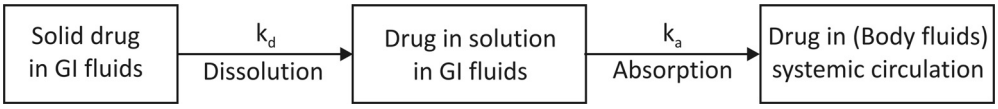
metastable polymorph should be decided. Usually a stable form is chosen for development of a formulation. If a metastable form is selected, the conditions for formulation processing need to be standardized accordingly. During formulation processing the polymorphic transformation may take place. For example, during grinding and compression of tablets phenylbutazone undergoes polymorphic transformation[16]. The solvent used for granulation can change amorphous form of calcium pantothenate to its crystalline form.

Thus, the processing solvent, temperature, grinding, etc. can result polymorphic transformation and can influence the physical stability of drug in the formulation.

There are many techniques to examine the solid-state structure of a drug. Among these microscopy, IR spectrophotometry, thermal analysis, powder x-ray diffraction are common.

Dissolution

In general absorption of poorly soluble drugs is dissolution rate-limited. The process of absorption of drug from its oral solid dosage form is shown schematically below.



Since the process of absorption depends on dissolution, the rate of dissolution can greatly influence the rate of absorption. When the rate of dissolution is very slower than that of absorption, i.e. $k_a >> k_d$, the absorption is called as dissolution rate-limited. In vivo dissolution depends on both the physicochemical properties of the substance and the physiological conditions prevailing in the GI tract. The physiological condition varies from fasted-to fed-states as well as within and among subjects. The most important in vivo parameters influencing dissolution of a dosage form are presented below[17,18].

Thus, it is necessary to know the dissolution characteristics of the drug, particularly poorly soluble drug, and its salt form.

Physicochemical and physiological parameters important to drug dissolution in the GI Tract		
Factor	**Physicochemical properties**	**Physiological properties**
Surface area of drug	Particle size, wettability	Surfactants in gastric juice and bile
Diffusivity of drugs	Molecular size	Viscosity of luminal contents
Boundary layer thickness	Concentration of the drug	Motility patterns and flow rate
Solubility	Hydrophilicity, crystal structure, solubilization	pH, buffer capacity, bile and food composition
Amount of drug	Hydrophilic, lipophilic nature of the drug	Permeability
Volume of solvent available	Depends upon type of body fluid	Secretion, co-administered fluids

Factors Affecting Dissolution

By repeating the dissolution test if reasonably consistent results are obtained, then the dissolution rate data may be of useful. To achieve reproducible results, the factors that influence the dissolution rate should be known and controlled. The factors that can influence the dissolution rate of a drug are listed below;

1. Factors relating to physicochemical properties of the drug
    - Solubility,
    - Particle size,
    - Solid state characteristics,
    - Polymorphism.
2. Factors relating to formulation of dosage form, like tablets
    - Granulating agents and binders,
    - Lubricant,
    - Disintegrating agents and diluents,
    - Method of granulation,
    - Compression force.
3. Factors relating to dosage form
    - Interaction between drug and excipient,
    - Deaggregation.
4. Factors relating to dissolution test
    - Eccentricity of the stirring device,
    - Guiding the shaft,
    - Vibration,
    - Alignment of the stirring device
    - Stirring speed,
    - Temperature,
    - pH of the dissolution medium,
    - Surface tension of the dissolution medium,
    - Viscosity of the dissolution medium.
5. Miscellaneous
    - Adsorbent present in the formulation,
    - Absorption of water by the drug/ formulation,
    - Humidity maintained during storage of the drug/formulation,
    - Laboratory error,

- Error due to personnel,
- Variation in the method used.

Dissolution is of two types: intrinsic dissolution and particulate dissolution.

Intrinsic Dissolution

Intrinsic dissolution rate may be defined as the rate of dissolution of a pure solid pharmaceutically active ingredient keeping the following conditions unchanged.

- surface area of the solid,
- temperature of the dissolution medium ,
- rate of agitation(stirring speed),
- pH and ionic strength of the dissolution medium

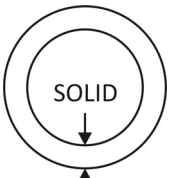


Fig. 1.6 Dissolution of solid particle

If m is the amount of solid remaining undissolved, C_s is the concentration of saturated solution, C is the concentration of the bulk solution at time t, A is the surface area of the solid and k is the intrinsic dissolution rate constant, then

$$\frac{dm}{dt} = kA\left(C_s - C\right)$$

When c is very small in comparison to C_s the above equation can be reduced to $\frac{dm}{dt} = kAC_s$

This condition is referred to as sink condition. Under this sink condition the stagnant film of dissolution medium is adsorbed onto the solid surface and the film is a saturated solution of the substance under test. The thickness of the film depends on the rate of agitation of the medium. The concentration of the test substance at the side of the film adjacent to solid as shown in the Fig. 1.6 Surface will be the maximum(C_s, concentration of the saturated solution) and that at the side of the film adjacent to the bulk solution will be minimum(C_b). The movement of the substance from the film to bulk (diffusion) will be driven by the concentration gradient. Thus, according to the Fick's first law of diffusion the rate of transfer movement of the substance will be directly proportional to concentration gradient per unit area. There are two methods, Rotating Disk method (USP Wood Apparatus) and Stationary Disk methods prescribed by the USP for determination of intrinsic dissolution rate of a pharmaceutical substance.

The dissolution rate of a substance from a constant surface area can be determined by using a tablet of the solid compressed under hydraulic press. Each apparatus has the provision for compression and holding the tablet within the assembly. In the Rotating Disk apparatus the assembly is mounted on the stirring shaft, while in the Stationary

Disk apparatus the assembly is kept at the bottom of the dissolution vessel. Both the apparatuses are shown in Fig. 1.7 a and 1.7 b.

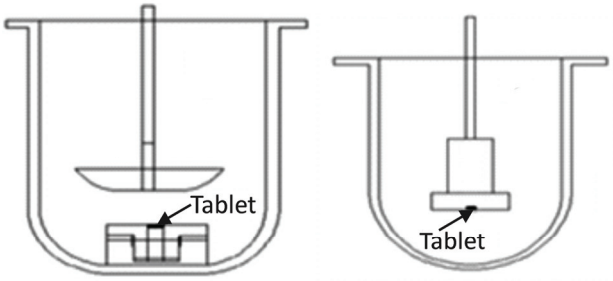


Fig. 1.7 (a) Static disc dissolution apparatus **(b)** Rotating disc apparatus

In recent years intrinsic dissolution test has been used as an alternative to solubility test. The solubility class of drug is determined by the value of the intrinsic dissolution rate (IDR). Compared to solubility test this test requires lesser amount of material and the results are not influenced by factors such as transition from crystalline structure or the formation of salts[19-23]. Traditionally during formulation development, *in vitro* dissolution test is conducted for several times to measure bioequivalence of the formulation.

Biopharmaceutics Classification System (BCS)

Amidon, et al in 1995 proposed this method that has effectively replaced the repeated in vitro dissolution tests and reduce the time and cost. Based on three parameters – solubility, permeability, and dissolution the drugs are classified into four categories.

Class	Solubility	Permeability	Example
I	High	High	Metoprolol, Diltiazem
II	Low	High	Glibenclimide, Phenytoin
III	High	Low	Cimetidine, Neomycin
IV	Low	Low	Taxol, Hydrochlorothiazide

The absorption characteristics of a drug through gastrointestinal tract are correlated with three factors-**Absorption Number A_n,** Dose Number D_o, and Dissolution Number D_n. These are dimensionless numbers.

Dose Number D_o: is the ratio of dose concentration to solubility. That is, $D_o = \frac{M / V_o}{C_s}$

Where M is the dose, V_o is the volume of water ingested during swallowing of the medicament (250 mL), C_s is the solubility of the drug.

Dissolution Number D_n: is the ratio of mean gastric residence time, T_{si} to mean dissolution time, T_{diss}. Mathematically it can be expressed as;

$$D_n = \left(\frac{3D}{r^2}\right)\left(\frac{C_s}{p}\right)T_{si} = \frac{T_{si}}{T_{diss}}$$

where D is the diffusion coefficient, r is the initial radius of the drug particle, ρ is the density.

Absorption Number A_n: is the ratio of mean gastric residence time, T_{si} to mean dissolution time, T_{diss}.

A_n can be expressed as; $A_n = \frac{P_{eff}}{R} T_{si} = \frac{T_{si}}{T_{abs}}$ where p_{eff} is permeability, R is the mean radius of the intestine, and T_{abs} is the absorption time.

Thus for complete absorption of a drug, $D_o < 1$, $D_n > 1$, and $A_n > 1$.

Determination of Solubility (Limits of Solubility Term)

For biopharmaceutical classification equilibrium solubility of a substance is determined under the conditions of physiological pH and temperature. As per FDA, the test is to be conducted at 37 ± 1 ^{o}C in aqueous media within pH range of 1-7.5[24-26].

The bioequivalence test protocol prescribes one glass of water for oral administration of a dosage form to a human being. For this reason a drug is considered as the *highest soluble*, when its highest dose strength is completely soluble in 250 mL or less amount of aqueous media.

Determination of Permeability (Limits of Permeability Term)

Measuring the rate of absorption of a drug substance in humans (indirect method) and measuring the rate of transfer across human intestinal membrane (direct method) are used to determine permeability. Other method used is in-vitro culture method[27,28] that can predict drug absorption in humans. When 90% or more of the administered dose of a drug is absorbed, calculated on the basis of either measuring the mass-balance or comparing with an intravenous dose, the drug is said to have the *highest permeability*.

Particulate Dissolution

This method is used to assess the effect of particle size, surface area and excipients on the dissolution of a drug. Maintaining a constant surface area of the dissolving surface is not required in this method. A weighed quantity of powder sample of a particular size range is put into the dissolution medium. The medium is stirred by a propeller at a constant speed. The rate of dissolution increases with the particle size.

Sometimes, an opposite relationship between particle size and rate of dissolution may be observed. This may be due to the poor wetting of the powder. In such cases a suitable surfactant is mixed with the dissolution medium to improve dissolution and normal relationship can be achieved. The solubility of acidic or basic drugs depends on the pH of the medium.

For a slowly dissolving powder, particle size is reduced to increase dissolution. In some cases, techniques of comelting, coprecipitation or trituration with a suitable excipient improves the dissolution of a poorly soluble drug[29,30].

Stability

The knowledge about the inherent stability of a drug is very much essential for designing the suitable dosage form. Because, it helps,

- to select the type of dosage form,
- to select the suitable and compatible excipients,
- to decide how best the excipients can be used,
- to ensure that no toxic substance is formed due to interaction between the components,
- to determine the limits of acceptability or standards with respect to excipients, drug and the formulation,
- to determine the shelf-life of the product, and
- to recommend the best possible storage conditions for maximum stability of the product.

Thus, the preformulation stability studies are conducted to assess the solid-state stability and solution-state stability of a drug. The physical stability includes appearance, polymorphic transformation, hygroscopicity and others. Usually the drug substances degrade due to oxidation, solvolysis, photolysis, and pyrolysis. For example, esters and lactams undergo solvolytic degradation.

Solid-State Stability

The stability of a drug may be influenced by certain physical properties, like solubility, pK_a, melting point, crystal form, etc. Usually the crystalline form of a drug is more stable than its amorphous form.

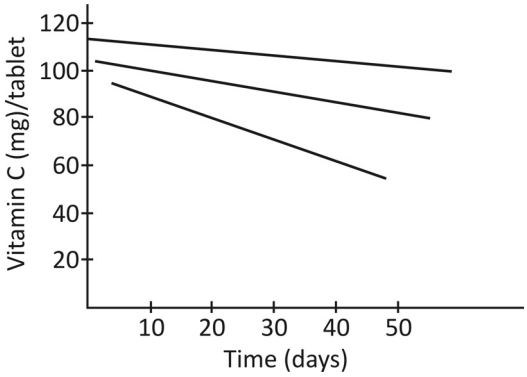


Fig. 1.8 Degradation of vitamin C in a tablet formulation

Sometimes, melting point can also indicate relative stabilities of structurally similar compounds. Generally, the mechanism of degradation of asolid substance is complex and it is difficult to ascertain. However, through stability studies the causative factors can be known. The most common factors are moisture, heat, light and oxygen (air). Moisture can make a substance heat sensitive. Moisture and heat can accelerate degradation of a solid also. When a drug is sensitive to more than

one factors, during studies the effect of one factor should be studied at one time keeping other factors unchanged **Fig. 1.8** Usually the solids undergo slow degradation. To measure the rate of degradation a solid is put under stress conditions. The data obtained are extrapolated to normal storage conditions (temperature, moisture, relative humidity) to predict the stability.

The actual rate of degradation at higher temperatures sometimes may not match with the extrapolated data. For example, few ergot alkaloids when stored at 45 °C degrades completely, but when stored at temperature less than 35 °C less than 1% of alkaloids degrade[31].

β-chlortetracycline hydrochloride trans-forms to its α-form. The rate of transformation increases with the relative humidity particularly when RH is more than 65%. If the humidity is maintained at 65% or below, no polymorphic transformation takes place[32].

Even then, the accelerated stability studies are useful and conducted to understand degradation reaction kinetics, and to isolate and characterize degradation products.

Effect of Temperature on Stability

Usually the studies are conducted at temperature ranging from 30 °C to 60 °C, sometimes to 70 °C. When the effect of temperature is examined humidity is maintained ambient. The physical and chemical properties of the samples exposed to elevated temperatures should be examined at short intervals of time and compared with a control sample kept at lower temperature, 5 °C or below. A sample should also be kept at room temperature. The results obtained at elevated temperatures may be extrapolated using Arrhenius equation. The Fig. 1.9 shows how vitamin C degrades at 50 °C, 60 °C and 70 °C. The Fig. 1.9 shows the Arrhenius plot and extrapolation of degradation data to lower temperature.

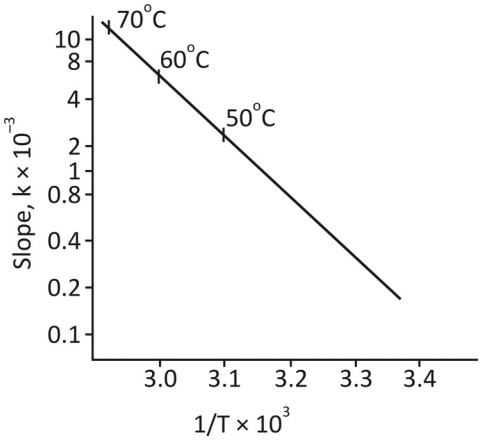


Fig. 1.9 Arrhenius plot of the data on degradation of vitamin C (Ref Fig. 1.8)

If no sign of degradation is found at 60 °C after a month's study, the sample may be considered as stable. Then samples should be kept at lower temperature for longer period, usually for 6 months and the results should be compared to establish the

stability. Woolfe and Worthington[31] recommended conducting the stability studies at 33 °C with three sets for a period of 3-6 months.

Effect of Humidity on Stability

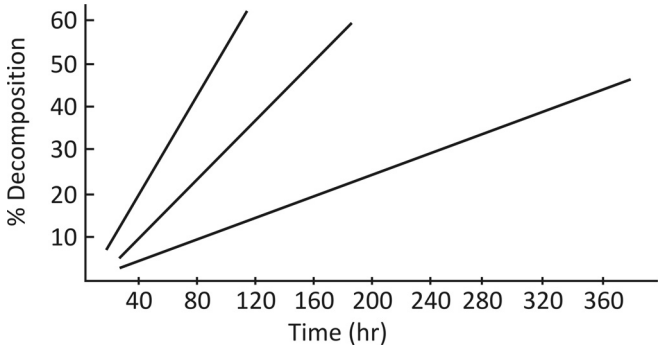


Fig. 1.10 Percent decomposition-time curves for decarboxylation of p-aminosalicyclic acid at 70°C under high humidity

Many water-soluble salts of drug may hydrolyze or react with other excipients in the presence of moisture. These salts can adsorb moisture (water) from the moist atmosphere. The extent of adsorption and equilibrium moisture content depends on atmospheric moisture content (relative humidity), temperature, exposed surface area and the mechanism of adsorption of moisture[33]. Some substances, e.g. sodium chloride, adsorb water sufficient to dissolve (deliquescent) under a suitable atmospheric condition (e.g., in rainy season). Others adsorb water to form hydrates. Hygroscopy can greatly affect flowability, compressibility and chemical stability of solids. The Fig. 1.10 shows the effect of humidity on degradation of p-aminosalicylic acid at 70 °C under different humidity. This may be examined by exposing the solid drugs to different relative humidity conditions. Particular relative humidity can be generated in laboratory desiccators using saturated solutions of different salts. These closed desiccators are kept inside a hot-air oven, maintained at a particular temperature. As a result different humidity at a particular temperature can be maintained. Powder samples are taken in open containers and placed in the desiccators. The sample is spreaded as a thin layer for maximum exposure. Duration of exposure may range from 24 hrs to 12 weeks. Water adsorbed by the sample can be estimated by Karl Fischer titration, gravimetry, thermal gravimetric analysis (TGA) or by gas chromatography depending on the accuracy of result desired and on the amount of water adsorbed. The result is expressed as mg H_2O/g sample.

Effect of Light

When exposed to light the color of many drugs changes, i.e., Fades or darkens. This is due to photolytic degradation of drugs. The molecules at the surface exposed to light decompose. Thus, the extent of degradation depends on area of the surface exposed to light and duration of exposure. Such photolytic degradation can be controlled by packing the drug in an amber glass, opaque plastic or in any other light resistant container.

However, the discoloration, if takes place even to a small extent, the aesthetic value of the drug would be lost. Sometimes a suitable dye is mixed with the drug to cover up the discoloration. The photosensitivity of drug should be evaluated during preformulation stability testing. To measure the photosensitivity the drug is exposed to illumination of 400 fc (foot-candle) for 4 weeks or 900 fc for 2 weeks. During this period the samples are examined at regular intervals for their physical change (change in color) and chemical purity. Similarly a set of sample is kept under same conditions of temperature, pressure and humidity, but in a light resistant container (control sample) and are evaluated at the same interval. Both results are regularly compared. The change in color may be determined visually or by diffuse reflectance spectroscopy.

Effect of Air (Oxygen)

Some drugs are oxidized by atmospheric oxygen. Thus, each new drug should be evaluated for its sensitivity to oxygen. So that preventive measures like,

1. packing under inert gas,
2. addition of a suitable antioxidant,
3. controlling of the trace element present in the drug, can be taken to ensure better stability.

For rapid evaluation the drug substance can be exposed to air containing oxygen at a pressure of 20 mmHg. The extent of degradation depends on the exposed surface area and period of exposure. The drug under test is taken in a wide, low height glass tube (test). The drug is spreaded as a thin layer. The tube is placed in vacuum desiccators. The air inside the desiccators is replaced by the air containing oxygen exerting 20 mmHg pressures. The humidity, temperature and pressure are maintained normal. At regular intervals aliquots are drawn for evaluation. Similarly, the same amount of the drug (control) is kept in desiccators under inert gas and at same time interval the drug is evaluated. After each withdrawal of sample the desiccators should be filled with same air. The results of both test and control are compared to assess the effect of oxygen on the stability of the drug.

To ascertain the effect of humidity and oxygen, the experiment is repeated in the same way under different relative humidity conditions.

Solution-State Stability

This test is applicable for all drugs, even for those which are intended to be formulated as solid dosage forms. The reasons are

- To ensure that the drug in solution in the gastrointestinal fluids is sufficiently stable, so that absorption of adequate amount of unchanged drug can take place.

- To prepare granules for formulation of a tablet dosage form (wet granulation method) a suitable solvent can be selected.
- To prepare a stable liquid dosage form an appropriate solvent system can be selected and a suitable stabilizing agent can be used.

Thus, the stability of a drug in its solution at pH ranging from 1 to 8 should be studied. If a drug is found to be extremely unstable in acidic pH, the tablets or granules of the drug can be enteric coated, or the drug can be modified to a stable salt which is stable in acidic pH.

Drug-Excipient Compatibility Studies

In most of the formulations drug and excipients remain in intimate contact. Hence, the information about interaction between drug and excipient is very much essential. Ideally there should be no interaction. For existing drugs these tests have already been conducted and information is available. For a new drug this test must be conducted for selection of compatible excipients. The proportion of drug-excipient in the mixture should match with the actual.

The drug-excipient compatibility is commonly analyzed using chromatography (TLC or HPLC), differential thermal analysis and diffuse reflectance spectroscopy.

Chromatographic Method

The mixtures of drug and excipient are prepared in the form of powders or granules (based on actual use) or in the form of solution. These are packed in ampoules or vials and sealed. The sealed containers are stored in ambient as well as at higher temperatures. If necessary the head space (the space above the sample in the container) of the containers should be filled with inert gas (e.g., nitrogen). The samples kept at normal temperature are called as control. All samples are tested periodically using TLC or HPLC to assess decomposition. If the chromatograph shows appearance of a new spot or change in R_f value or retention time of the components, it is considered that there is interaction between drug and excipient. At higher temperature, 50 ^{o}C or 60 ^{o}C or 70 ^{o}C, particularly in the presence of moisture and air, if there is no change in the chromatograph, it is considered that the excipient and drug are compatible to each other. If a sign of degradation is noticed, the spots may be isolated, identified and quantified to find out the rate of degradation and its kinetics.

Differential Thermal Analysis

This is useful for evaluating solid-state stability. The method is very quick. When there is no interaction, almost same pattern in the thermograms of the mixture and of pure components will be observed.

Occurrence of interaction will indicate considerable change in the pattern of the thermograms of the mixture, like appearance of one or more new peaks or disappearance of one or more original peaks. The interpretation needs expertise.

Diffuse Reflectance Spectroscopy

In this method the physical mixture of solids (drug and excipient) are exposed to a radiation. The incident radiation will be partly absorbed and partly reflected in a diffuse manner. The reflection of radiation depends on particle size, crystal form, packing density of the powders and other factors. By controlling these factors properly, the physical and chemical changes occurring at powder surface can be assessed by examining the diffuse reflectance spectrum.

Miscellaneous Properties

Under this category the important properties are density, flowability, compactibility, wettability of the drug.

Density

The information about true density and bulk density of a drug sometimes become very useful for developing a formulation. For example, while developing a suspension formulation, the true density of the dispersed solids helps to design the suspending medium to control the sedimentation. Similarly, to select the capsule size the knowledge about the bulk density of the powders is necessary. The bulk density of the granules helps to select punch size for compression as the dose of the drug is fixed and particularly when the dose size is high.

Bulk density of powders depends on the method of crystallization, milling or method of manufacture of the drug. As the bulk density can be changed either by compaction or by milling, this problem can be solved satisfactorily. Many active pharmaceutical ingredients are porous and hydrophobic. Determination of their density is not easy. It requires special instrument for accurate results. Alternatively it is determined by suspending the powders in an immiscible solvent of known densities. Each solvent should contain small amount of suitable surfactant, so that the powders are properly wetted. The suspension is shaken vigorously, then mildly centrifuged and kept undisturbed until the powders either float or settle. The medium in which the powders float or suspend freely will have the density equal to that of powders. The density of the medium should be determined using a standard pycnometer. It is better to determine the density of the medium after removal of dispersed phase by filtration, as the medium may contain some dissolved solid which can contribute to the density of the medium.

Bulk density, alternatively called as tapped density, can be measured by tapping a known amount of powder taken in a cylinder using a tap density apparatus. The number of tapping may be done up to about 1000. The volume of the powder after tapping is recorded. The ratio of weight to volume will give the density.

Flowability

For manufacture of solid dosage forms, like tablets, capsules, powders, the drug powder need to flow smoothly. Hence, flowability is an important property of the drug powder and should be evaluated during preformulation studies. Flow property of the powders depends on particle size, shape, density, electrostatic charge and adsorbed moisture. During processing or formulation these properties may change leading to change in flowability. If preformulation study indicates poor flowability of the drug, necessary excipients can be mixed with the drug to improve its flow property. The powders or granules should have good flowability to ensure efficient powder mixing and to compress the tablets with acceptable uniformity of weight.

Among various methods discussed by Amidon and Houghton[34], angle of repose, flow through an orifice, Carr's compressibility index is common. None of these can measure all the factors that influence flow of a powder.

Carr's compressibility index is a simple test to evaluate flowability of a powder. I this method the tapped density or bulk density, ρ_t and fluff (poured or initial bulk density) density, ρ_o are compared and expressed in percent. ρ_o is obtained by simple pouring a known amount of powder into a cylinder and the volume is noted. The tapped density or bulk density is determined by tapping a cylinder filled with the powder. The tapped volume and mass are noted and used to calculate the tapped density, ρ_t. With these two values the Carr's index (%) is calculated as below,

$$\text{Carr's index (\%)} = \frac{\rho_t - \rho_o}{\rho_t} \times 100$$

The Table 1.5 shows the relationship between Carr's index and flowability of powders with few examples.

Table 1.5 Carr's index (%) and flow property of pharmaceutical powders

Carr's index (%)	Flowability	Example
5 - 15	Excellent	Emcompress
12 - 16	Good	
18 - 21	Fair	Lactose monohydrate
23 - 35	Poor	Maize starch,
33 - 38	Very poor	Dicalcium phosphate, dihydrate
More than 40	Very, very poor	

When powders are poured over a flat, circular surface, the powders deposit in the form of a heap under the gravitational force as shown in the Fig. 1.11. The angle between the free surface of the heap and horizontal surface is called as static angle of repose. This angle of repose is most commonly used to express flow characteristic of a powder. Most of the pharmaceutical powders or granules show angle of repose between 25 °C and 45 °C. Lower is the angle of repose greater is the flowability.

Sometimes the angle of repose does not flow property correctly. For example, sodium chloride, spray dried lactose having lower angle of repose fail to flow suitably through 6 mm orifice. Hence, the flow property of powders should be evaluated using more than one method.

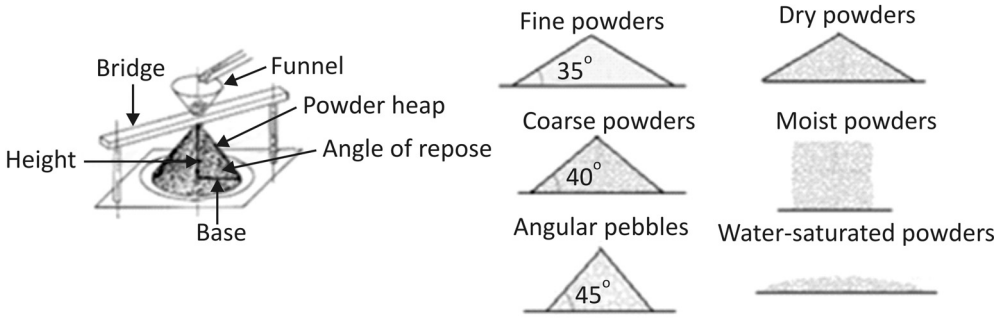


Fig. 1.11 Schematic diagram showing how the angle of repose varies with the nature of powder

Compactibility or Compressibility

This test is most required for formulation development of solid dosage form, particularly tablet. As the formulation contains many ingredients, the mixture should exhibit the required flow characteristics. According to Lueuenberger and Rohera[35] compressibility of a powder may be defined as the *ability to decrease in volume under pressure* and compactibility is defined as the *ability of a powder to be compressed in the form of a tablet of specified tensile strength*. For a new drug the compressibility and compactibility properties should be tested on the drug alone and on the drug-excipient mixture.

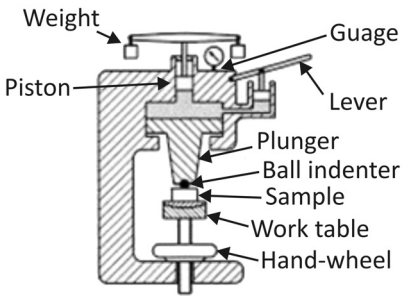


Fig. 1.12 Brinell hardness test apparatus

The simple method of testing compactibility is to compress a mass of powder by hydraulic press under pressure. If there is no sign of capping or chipping in the compressed mass, the powder is considered to be compactable. Another test for

compactibility is tensile strength. The tensile strength of a compact indicates the hardness. Hardness is the resistance to deformation. This can be measured by using Brinell test apparatus shown in Fig. 1.12.

According to this method the compact is placed over a smooth flat platform and is pressed with a hard, spherical indenter having diameter D, from the top. This will result an indentation on the compact. The diameter of the indentation, d can be measured or calculated using the depth, h. the Brinell hardness number (BHN) is calculated as follows;

$$BHN = \frac{2F}{\pi D\left[D - \sqrt{\left(D^2 - d^2\right)}\right]}$$

According to Heckel[36] compressibility of a powder can be expressed through density-compression pressure relationship as shown below,

$$\log \frac{1}{1-\rho_{rel}} = \frac{KP}{2.303} + A$$

Where P is the compression pressure, ρ_{rel} is the relative density, K and A are the constants. The Heckel plot provides the information about the extent of compression, yield value or minimum pressure required that results deformation of solid, and the nature of deformation (plastic or brittle deformation), etc.

Wettability

Even for development of a suitable dosage form wettability of drug plays an important role. For granulation of powders, dissolution of tablets or granules and for adhering a coating solution over the surface of tablet, wetting of solids is necessary. Wettability of solids can be expressed in terms of contact angle. Contact angle can be measured by placing a drop of liquid, usually water, over a powder compact. If the angle is more than 90 ^{o}C, the solid is considered as hydrophobic. This problem can be solved either by using a surfactant or by mixing with hydrophilic excipients before granulation.

Model Questions

Questions carrying 1-2 marks

1. Define preformulation study?
2. Why development of a new drug product is said to be a multidisciplinary activity?
3. What is meant by organoleptic property?
4. How can particle size influence the solubility?
5. What is meant by dissolution?

6. Name the physicochemical properties of a drug and physiological properties that influence dissolution of a drug in GI tract?
7. What are reasons for which solution-state stability of a drug is measured?
8. Define the term wettability?

Questions carrying 3-5 marks

1. Enlist the preformulation tests to be conducted on new drug substance?
2. Explain the terms purity and impurity?
3. Explain the relation between pH and solubility?
4. Discuss the relation between absorption through biological membrane and partition coefficient of a drug?
5. Write note on polymorphism and crystal properties?
6. Explain how chemical stability of a drug is influenced by its crystal characteristics?
7. Explain intrinsic dissolution?
8. Write note on solid-state stability?
9. Discuss in brief the effect of temperature on stability of drug?
10. Explain the effect of humidity on stability of a solid drug substance?

Questions carrying 5-7 marks

1. Discuss how particle size distribution and shape can influence various physical as well as biopharmaceutical properties of a drug substance?
2. Define the term solubility. How can it be determined?
3. Describe how the rate of permeation of drugs in solution through the biological membrane is measured by *in-vitro* method?
4. Explain the factors that influence dissolution rate of a drug?
5. Discuss biopharmaceutical classification system?
6. Discuss how drug-excipient compatibility test is conducted?
7. Explain how the flow property of a drug substance is measured and mention its importance in formulation development?
8. How can compressibility of a solid drug substance be measured and why?
9. How does bioavailability of a drug depend on its crystal characteristics?

References

1. Prescott, L.F., Steel, R.F., and Ferrier, W.R.; Clin. Pharmacol. Ther.; 11, 496,1970.
2. Atkinson, R.M., Bedford, C., Child, K.J., and Tomich, E.G.; Nature; 193, 588, 1962.
3. Higuchi, T., Shih, F.L., Kimura, T., and Rytting, J.H.; J. Pharm. Sci.; 68, 1267, 1979.

4. Ohnishi, R., and Tanabe, K.; Bull. Chem. Soc. Jap.; 41, 2647, 1971.
5. Milosevic, G.; J. Pharm. Sci.; 53, 484, 1964.
6. Weng, H. and Parrot, E.L.; J. Pharm. Sci.; 73, 1059, 1984.
7. Schanker, L.S., Tocco, D.J., Brodie, B.B., and Hogben, C.A.M.; J. Pharmacol. Exp. Ther.; 123, 81, 1958.
8. Hogben, C.A.M., Tocco, D.J., Brodie, B.B., and Schanker, L.S.; J. Pharmacol. Exp. Ther.; 125, 275, 1959.
9. Schanker, L.S.; J. Pharmacol. Exp. Ther.; 126, 283, 1959.
10. Kaplan, S.A. and Cotler, S.; J. Pharm. Sci.; 61, 1361, 1972.
11. Crane, R.K. and Wilson, T.H.; J. Appl. Physiol.; 12, 145, 1958.
12. Haleblian, J.; J. Pharm. Sci.; 64, 1269, 1975.
13. Byrn, S.R.; Solid State Chemistry of Drugs, Academic Press, New York, 1982.
14. Wadke, D.A. and Reir, G.E.; J. Pharm. Sci.; 61, 868, 1972.
15. Aguiar, A.J. and Zelmer, J.E.; J. Pharm. Sci.; 69, 983, 1969.
16. Ibrahim, H.G., Pisano, F. and Bruno, A.J.; J. Pharm. Sci.; 66, 669, 1977.
17. Blume, H. H., Schug, B. S.; Eur. J. Pharm. Sci.; 9 (2), 117–121, 1999.
18. Dressman, J. B., Reppas, C.; Eur. J. Pharm. Sci.; 11 (Suppl. 2), S73–S80, 2000.
19. Yu, L. X., Carlin, A. S., Amidon, G. L., Hussain A. S.; Int. J. Pharm.; 270 (1–2), 221–227, 2004.
20. Sehic, S., Betz, G., Hadzidedic, S., El-Arini, S.K., Leuenberger, H.; Int. J. Pharm.; 386,(1–2), 77–90, 2010.
21. The United States Pharmacopeia and National Formulary USP 32–NF 27; The United States Pharmacopoeial Convention, Inc.: Rockville, MD, 2009.
22. Zakeri-Milani, P.; Barzegar-Jalali, M.; Azimi, M.; Valizadeh, H.; Eur. J. Pharm. Biopharm.; 73 (1), 102–106, 2009.
23. Yu, L. X.; Amidon, G. L.; Polli, J. E.; Zhao, H.; Mehta, M. U.; Conner, D. P.; Shah, V. P.; Lesko, L. J.; Chen, M.; Lee, V. H. L.; Hussain, A. S.; Pharm. Res. 2002, 19 (7), 921–925.
24. Verma, M.V.S., Khandavilli, S., Ashokraj, Y., Jain, A., Dhanikula, A., Sood, A.,Thomas, N.S., Pillai, O., Sharma, P., Gandhi, R., Agrawal, S., Nair, V., Panchagnula, R.; Curr. Drug Metab.; 5, 375 – 388, 2004.
25. Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J.R.; Pharm. Res.; 12 (3), 413 – 420, 1995.
26. Lipka, E.; Amidon, G. L.; J. Controlled Release; 62, 41–49, 1999.
27. Karlsson, J., and Artursson, P.; Int. J. Pharmaceutics; 71, 1-2, 1991.
28. Franke, H., Galla, H.J., Beuckmann, C.T.; Brain Research Protocols; 5, 3, 2000.
29. McGinity, J.W., Manes, D.D. and Yakatan, G.J.; Drug Dev. Commun.; 1, 396, 1975.
30. Shah, N., Pytelewski, R., Eisen, H. and Jorowski, C.; J. Pharm. Sci.; 63, 1339, 1974.
31. Woolfe, A.J. and Worthington, H.E.C.; Drug Dev. Commun.; 1, 185, 1974.

32. Miyazaki, S., Nakano, M. and Arita, T.; Chem. Pharm. Bull.; 24, 1832, 1976.
33. Van Campen, L., Amidon, G.l., and Zografi, G.; J. Pharm. Sci.; 72, 1381, 1983.
34. Amidon, G.E., and Houghton, M.E.; Pharm. Mfg.; July, 1985, p.21.
35. Leuenberger, H., and Rohera, B.D.; Pharm. Res.; 3, 12, 1986.
36. Heckel, R.W.; Trans. Metall. Soc. AIME; 221, 671, 1961.