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# IMPORTANCE OF PHARMACEUTICAL PREFORMULATION IN PHARMACEUTICAL TECHNOLOGY

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## ABSTRACT

In recent years, there has been a significant increase in pressure on pharmaceutical companies to discover and develop new medicines ever faster to replace those coming off patent and to counter generic manufacturer competition. It is important that the reader is aware of the nature of pharmaceutical research and development (R&D) to appreciate the importance of preformulation and formulation in the overall process. After first-time-in-human (FTIH) studies in early development, if the compound progresses into full development, a more complete physicochemical characterization of the chosen compound, with particular emphasis on the dosage form, should be carried out, thus allowing a rational, stable, and bioavailable formulation to be progressed through to launch. Generally, drug absorption from the GI tract requires that the drug is brought into solution in the GI fluids and that it is capable of crossing the intestinal membrane into the systemic circulation. It has therefore been suggested that the drug must be in its molecular form before it can be absorbed. Approaches to lead generation during exploratory research often depend on how much is already known about the therapeutic target under consideration. The objective of the review is prior to the development of tablets, capsules and injectables dosage forms, it is essential that certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined. This information dictates many of the subsequent events and approaches in formulation development. This first learning phase is known as preformulation.

**KEYWORDS:** Solubility, Dissolution rate, melting point, flow properties, stability studies.

## INTRODUCTION

Almost all new drugs are marketed as tablets, capsules. Although only a few are marketed as an injection (25% of those marketed as tablets) the intravenous route is always required during early toxicity, metabolic, bioavailability and clinical studies to provide a precise drug and dose deposition. Prior to the development of these three major dosage forms, it is essential that certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined. This information dictates many of the subsequent events and approaches in formulation development. This first learning phase is known as preformutation.[19]

### Objective of Preformulation

1. To establish the necessary physico chemical properties of newdrug substances
2. To determine its kinetic rate profiles
3. To establish its physical charactersrics
4. To establish its compatibility with common excipients

A recommended list of the information required in preformulation is shown in Table.1.

**Table.1**

| **Preformulation drug characterization** | |
|---|---|
| **Test** | **Method/function/characterization** |
| **Spectroscopy** | Simple UV assay |
| **Solubility** | Phase solubility, purity |
| aqueous | Intrinsic solubility, pH effects |
| pKa | Solubility control, salt formation |
| salts | Solubility, hygroscopicity, stability |
| solvents | Vehicles, extraction |
| partition coefficient | Lipophilicity, structure activity |
| dissolution | Biopharmaceutics |
| **Melting point** | DSC - polymorphism, hydrates, solvates |
| **Assay development** | UV, TLC, HPLC |
| **Stability (in solution and solid state)** | Thermal, hydrolysis, oxidation, photolysis, metal ions, pH. |
| **Microscopy** | Morphology, particle size |
| **Powder flow**<br>bulk density angle of repose | Tablet and capsule formulation |
| **Compression properties** | Tablet and capsule formation |
| **Excipient compatibility** | Excipient choice |

## 1. SPECTROSCOPY

- The first step in preformulation is to establish a simple analytical method. Most drugs absorb light in the ultraviolet wavelengths (190-390 run) as they are generally aromatic and contain double bonds. The acidic or basic nature of the molecule can be predicted from functional groups.[1]
- Using the UV spectrum of the drug, it is possible to choose an analytical wavelength (λ max) suitable to quantify the amount of drug in a particular solution.
- Excitation of the molecule in solution causes a loss in light energy, and the net change from the intensity of the incident light ($I_O$) and the transmitted light (I) can be measured.
- Their greater training and knowledge in analysis will assist in the identification of suitable stability-indicating assays by high-performance liquid chromatography (HPLC). Independent of this pharmaceutical profiling analysts will generate data to confirm structure and purity, and this should be used to complement and confirm pharmaceuticals.

| Attribute | Test |
|---|---|
| 1.Identity | Nuclear magnetic resonance (NMR)<br>Infra red spectroscopy (IR)<br>Ultraviolet spectroscopy (UV)<br>Thin-layer chromatography (TLC)<br>Differential scanning calorimetry (DSC)<br>Optical rotation, where applicable |
| 2. Purity | Moisture (water and solvents)<br>Inorganic elements<br>Heavy metals<br>Organic impurities<br>Differential scanning calorimetry (DSC) |
| 3. Assay | Titration<br>Ultraviolet spectroscopy (UV)<br>High-performance liquid chromatography (HPLC) |
| 4. Quality | Appearance<br>Odour<br>Solution colour<br>pH of slurry (saturated solution)<br>Melting point |

## 2. SOLUBILITY

### a. Aqueous solubility

- The availability of a drug is always limited and the preformulation scientist may only have 50 mg.
- Kaplan suggested that unless a compound has an aqueous solubility in excess of 1% (10 mg/mL) over the pH range 1-7 at 37°C, potential bioabsorption problems may occur.[2]

- If the intrinsic dissolution rate was greater than 1 mg cnr2 mkr1 then absorption was unimpeded. Dissolution rates less than 0.1 mg /cm$^2$ /min were likely to give dissolution rate-limited absorption. This tenfold difference in dissolution rate translates to a lower limit for solubility of 1 mg /mL.
- A solubility of less than 1 mg/ mL indicates the need for a salt, particularly if the drug will be formulated as a tablet or capsule. In the range 1-10 mg/ *mL* serious consideration should be given to salt formation.
- When the solubility of the drug cannot be manipulated in this way (neutral molecules, glycosides, steroids, alcohols, or where the *pKa* is less than 3 for acid or greater than 10 for an base) then liquid filling in soft or hard gelatin capsules may be necessary.

### b. Intrinsic solubility ($C_0$)

- When the purity of the drug sample can be assured, the solubility value obtained in acid for a weak acid or alkali for a weak base can be assumed to be the intrinsic solubility (C0), ie. the fundamental solubility when completely unionized.
- The solubility should ideally be measured at two temperatures:

1. 4°C to ensure physical stability and extend short-term storage and chemical stability until more definitive data are available. The maximum density of water occurs at 4°C.This leads to a minimum aqueous solubility.
2. 37°C to support biopharmaceutical evaluation

### c. pKa from solubility data[3]

- 75% of all drugs are weak bases; 20% are weak acids and only 5% are non-ionic, amphoteric or alcohols
- It is therefore appropriate to consider the Henderson-Hasselbalch equations for weak bases and acids.
- For weak bases: pH = pKa+ log (unionized/ionized)
- For weak acids pH = pKa+ log (ionized/unionized)
- Equations can be used:

1. to determine pKa by following changes in solubility

2. to predict solubility at any pH, provided that the intrinsic solubility ($C_0$) and pKa are known

3. to facilitate the selection of suitable salt-forming compounds and predict the solubility and pH properties of the salts

- To obtain precise pKa values by potentiometry, spectroscopy and conductivity.

### d. Salts

- In some cases, salts prepared from strong acids or bases are freely soluble but very hygroscopic. This does lead to instability in tablet or capsule formulations, as some drug will dissolve in its own adsorbed films of moisture.[4]
- Salts require for Basic drugs such as Hydrochloride, Sulphate, Mesylate, Maleate, Phosphate, Salicylate, Tartrate, Lactate, Citrate. Succinate, Acetate.
- Salts require for acidic drugs such as Potassium, Sodium, Lithium, Calcium, Magnesium, Diethanolamine, Zinc, Choline, Aluminium.
- It is often better to use a weaker acid or base to form the salt, provided any solubility requirements are met. A less soluble salt will generally be less hygroscopic and form less acidic or basic solutions.
- Injections should ideally lie in the pH range 3-9 to prevent vessel or tissue damage and pain at the injection site. Oral syrups should not be too acidic, to enhance palatability.
- Packaging may also be susceptible: undue alkalinity will attack glass, and hydrochloride salts should not be used in aerosol cans as a propellant-acid reaction will corrode the canister.
- A weak base with an intrinsic solubility greater than 1 mg/ mL will be freely soluble in the gastrointestinal tract, especially in the stomach. However, it is usually better to formulate with a salt, as it will control the pH of the diffusion layer.
- A weak base will have a high dissolution rate in the stomach, but as it moves down the gastrointestinal tract the pH rises and dissolution rate falls.
- Conversely, a weak acid has minimal dissolution in the stomach but becomes more soluble and dissolution rate increases down the gut.
- Paradoxically, as dissolution rate increases so absorption falls because the drug is ionized.
- The dissolution rate of a particular salt is usually much greater than that of the parent drug. Sodium and potassium salts of weak acids dissolve much more rapidly than do the parent acids.[8,17,18]
- However, the pH of the diffusion layer is higher than that of gastric fluid because of its buffering action.
- Different salts of a drug rarely change pharmacology, but only physical properties. This statement has been qualified to acknowledge that salts do affect the intensity of response.

- However, the salt form does change the physiochemical properties of the drug. Changes in dissolution rate and solubility affect the rate and extent of absorption (bioavailability), and changes on hygroscopicity and stability influence formulation.

### e. Solvents

- The first choice solvent is obviously water. However, although the drug may be freely soluble, it may be unstable in aqueous solution.[5]
- Accordingly, water-miscible solvents are used:1. in formulations to improve solubility or stability 2. in analysis to facilitate extraction and separation (e.g. chromatography).
- Oils are used in emulsions, topicals (creams and ointments), intramuscular injections and liquid-fill oral preparations (soft and hard gelatin capsules) when aqueous pH and solvent solubility and stability are unattainable.
- Aqueous methanol is widely used in HPLC and is the standard solvent in sample extraction during analysis and stability testing.
- The most acceptablenon-aqueous solvents pharmaceutically are glycerol, propylene glycol and ethanol. Generally for a lipophilic drug.
- Formulations rarely use pure non-aqueous solvent, particularly injections. For example, ethanol should only be used up to 10% in an injection to prevent haemolysis and pain at the injection site, and include isotonic salts.

### f. Partition coefficient

Partition coefficient has a number of applications which are relevant to preformulation[15,16]: 1. Solubility: both aqueous and in mixed solvents 2. Drug absorption in vivo: applied to a homologous series for structure activity relationships (SAR) *3.* Partition chromatography: choice of column (HPLC) or plate (TLC) and choice of mobile phase (eluant).

- **Solvent solubility:** The relative polarities of solvents can be scaled using dielectric constant (e), solubility parameter, interfacial tension and hydrophilic-lipophilic balance (HLB).

### Methodology and structure activity prediction

### Choice of non-aqueous solvent

- Many partition solvents have been used. The largest database has been generated using n-octanol. Thesolubility parameter of octanol *(8* = 10.24) lies midway in the range for drugs (8-12), although some non-polar *(8* < 7) and polar drugs (8 > 13) are encountered.

- In the ***shake flask method*** the drug, dissolved in one of the phases, is shaken with the other partitioning solvent for 30 minutes, allowed to stand for 5 minutes, and then the majority of the lower aqueous phase (density of octanol = 0.8258 g mL L) is run off and centrifuged for 60 minutes at 2000 rpm. The aqueous phase is assayed before $(\Sigma C)$ and after partitioning (Cw) [the aqueous concentration] to give $K\ o/w = \Sigma C - C_W)/(C_w)$.
- In general, polar solvents are advocated to correlate biological activity with physicochemical properties.
- Solvents less polar than octanol, measured by water solvency, have been termed hyper discriminating, whereas more polar solvents such as butanols and pentanols, are hypo discriminating. This concept refers to the discriminating power of a partitioning solvent within a homologous series.
- Octanol generally gives a range consistent with other physicochemical properties when compared to drug absorption in the GI tract.
- Hyper discriminating solvents reflect more closely the transport across the blood-brain barrier, whereas hypo discriminating solvents give values consistent with buccal absorption.

## g. DISSOLUTION

- solubility of a drug exceeded 10 mg mL"1 at pH <7, no bioavailability- or dissolution-related problems were to be expected.
- Below 1 mg mL such problems were quite possible, and salt formation could improve absorption and solubility by controlling the pH of the microenvironment independently of the drug and dosage forms' position within the GI tract.

### Intrinsic dissolution rate[20]

- When dissolution is controlled solely by diffusion the rate of diffusion is directly proportional to the saturated concentration of the drug in solution Under these conditions the rate constant $K$ is defined by: $\mathbf{k=0.62\ D^{2/3}\ V^{1/6}\ \omega^{1/2}}$
- where $v$ is the kinematic viscosity and $\omega$ is the angular velocity of a rotating disc of drug. By maintaining the dissolution fluid viscosity and rotational speed of the sample constant, the dissolution rate *(dc/dt)* from a constant surface area *(A)* will be constant and related solely to solubility $\mathbf{IDR= K_1Cs\ mg/cm^2/min}$

- This constant rate differs from the dissolution from conventional dosage forms, which is known as total dissolution (mg /mg), where the exposed surface area *(A)* is uncontrolled as disintegration, deaggregation and dissolution proceed.
- Accordingly, the IDR is independent of formulation effects and measures the intrinsic properties of the drug and salts as a function of dissolution media, e.g. pH, ionic strength and counter-ions.

### h. Common ion effect

- A common ion often significantly reduces the solubility of a slightly soluble electrolyte. The 'salting out' results from the removal of water molecules as solvent owing to the competing hydration of other ions.
- The reverse process, 'salting in', arises with larger anions, e.g. benzoate, salicylate, which open the water structure.
- These hydrotropes increase the solubility of poorly water-soluble compounds such as diazepam.

### 3. Melting point

- The melting point of a drug can be measured using three techniques:
  1. Capillary melting
  2. Hot stage microscopy
  3. Differential scanning calorimetry or thermal analysis
- ***Capillary melting*** (the observation of melting in a capillary tube in a heated metal block) gives information about the melting range but it is difficult to assign an accurate melting point.
- ***Hot stage microscopy***

  This is the visual observation of melting under a microscope equipped with a heated and lagged sample stage. It is more precise as the phase transitions (first melt, 50% melt and completion) can be registered on a recorder as the melting proceeds, and because of the high magnification the values are more accurate.

- ***Differential scanning calorimetry and thermal analysis***
- DTA measures the temperature difference between the sample and a reference as a function of temperature or time when heating at a constant rate.

- DSC is similar to DTA, except that the instrumentmeasures the amount of energy required to keep the sample at the same temperature as the reference, i.e. it measures the enthalpy of transition.

### a. Polymorphism

- A polymorph is a solid material with at least two different molecular arrangements that give distinct crystal species. The highest-melting species is generally stable; other polymorphs are metastable and convert to the stable form.
- Solubility (particularly important in suspensions and biopharmaceutically)[9,10], melting point, density, crystal shape, optical and electrical properties and vapour pressure are often very different for each polymorph.
- Polymorphism is remarkably common, particularly within certain structural groups: 63% of barbiturates, 67% of steroids and 40% of sulphonamides exhibit polymorphism.

#### *Pseudo polymorphism*

- It should be identified, as most polymorphs can be obtained by changing the recrystallizing solvent. Typical solvents inducing polymorphic change are water, methanol, ethanol, acetone, chloroform, n-propanol, isopropanol alcohol, butanol, n-pentanol, toluene and benzene.
- The distinction between these false forms and true polymorphs can be ascertained by observing the melting behaviour of the compound dispersed in silicone oil using hot-stage microscopy.
- Pseudopolymorphs will evolve a gas (steam or solvent vapour), causing the oil to bubble. True polymorphs merely melt, forming a second globular phase.[11,12]
- The temperature at which the solvent volatilizes will be close to the boiling point of the solvent.

### b. Crystal purity

- Thermal analysis has been widely used as a method of purity determination.

### c. Solubility

- Melting point and solubility are related via the latent heat of fusion, which is the amount of heat generated during melting or fusion.

- A crystal with weak bonds has a low melting point and low heat of fusion. Conversely, a strong crystal lattice leads to a high melting point and a high heat of fusion.

## 4. ASSAY DEVELOPMENT

- In order to follow drug stability, in both solution and solid phase, it is mandatory to have suitable stability indicating assays.[13,14]
- In some cases UV spectroscopy can be used, but in general chromatography is required to separate the drug from its degradation products and any excipients.

## 5. DRUG AND PRODUCT STABILITY

- commercial pharmaceutical products should have a shelf-life of 3 years.[7]
- The potency should not fall below 95% under the recommended storage conditions and the product should still look and perform as it did when first manufactured.

### a. Temperature

- Typically a 10°C increase in temperature can produce a 2-5-fold increase in decay. Often the increase in reaction rate with temperature follows an Arrhenius-type relationship: a plot of the log of the rate of reaction against the reciprocal of absolute temperature yields a straight line.
- The reaction rate can then be calculated at any temperature and allows a prediction of shelf-life at room temperature by extrapolation.
- This assumption forms the basis of accelerated stability tests.

### d. Order of reaction

- The most common is the ***half-life,*** the time at which the concentration has halved • The shelf-life of a product can be likewise expressed as $t_{95\%}$ (i.e. the time for 5% loss) etc.

### e. Hydrolysis

- Hydrolytic reactions involve nucleophilic attack of labile bonds, e.g. lactam > ester > amide > imide, by water on the drug in solution, and are first order.
- *A* number of conditions catalyse the breakdown: The presence of OH, presence of $H_3O$, presence of divalent metal ions, Ionic hydrolysis (protolysis) is quicker than molecular, Heat, Light,Solution polarity and ionic strength, High drug concentrations.

### f. Influence of pH

- The degradation of most drugs is catalysed by extremes of pH, i.e. high [H3O+] and [OH], and many drugs are most stable between pH 4 and 8.
- Where maximum stability dictates wider values, it is important for injections that there is low buffer capacity to prevent unnecessary challenge to the homeostatic pH (7.4) of blood.
- In some cases, therefore, the inclusion of a water-miscible solvent in the formulation will increase stability by: Suppressing ionization, Reducing the extreme of pH required to achieve solubility, Reducing water activity by reducing the polarity of the solvent, e.g. 20% propylene glycol in chlordiazepoxide HC1 injection.

### g. Solvolysis

- Where the reacting solvent is not water, then breakdown is termed solvolysis.
- In general, if a compound produces degradation products which are more polar then the addition of a less polar solvent will stabilize the formulation.
- If the degradation products are less polar, then the vehicle should be more polar to improve stability.

### F. Oxidation

- Oxidation is controlled by the environment, i.e. light, trace metals, oxygen and oxidizing agents
- However, most antioxidants function by providing electrons or labile H+, which will be accepted by any free radical to terminate the chain reaction

### G. Chelating agents

- Chelating agents are capable of forming more than one bond. For example, ethylene diamine is bidentate, ethylene diamine tetra-acetic acid (EDTA) is hexadentate (six), which makes it particularly effective as a pharmaceutical chelating agent.

### h. Photolysis

- The energy associated with this radiation increases as wavelength decreases, so that the energy of UV visible is greater than that of IR and is independent of temperature which can cause decomposition, be retained or transferred, be converted to heat, result in light emission at a new wavelength (fluorescence, phosphorescence)[7]

- Thus photolysis is prevented by suitable packaging: low actinic amber glass bottles, cardboard outers and aluminium foil overwraps and blisters

### i. Solid-state stability

- In all solid dose formulations there will be some free moisture (contributed by excipients as well as the drug), and certainly in tablets a significant percentage, typically 2% w/w, is required to facilitate good compression

### j. Hygroscopicity

- A substance that absorbs sufficient moisture from the atmosphere to dissolve itself is deliquescent. A substance that loses water to form a lower hydrate or becomes anhydrous is termed efflorescent
- Good packaging will accommodate moisture challenge, e.g. glass bottles, foil blisters and dessicant.
- However, preformulation studies on the drug and potential excipient combinations should provide the basis for more robust formulations and a wider, more flexible and cheaper choice of pack, while still reducing significantly any hydrolytic instability due to absorbed free moisture.

## 6. MICROSCOPY

- Two major applications in pharmaceutical preformulation: Basic crystallography, to determine crystal morphology (structure and habit), polymorphism and solvates, Particle size analysis.
- Most pharmaceutical powders have crystals in the range 0.5-300 $\mu$. However, the distributions are often smaller, typically 0.5-50 µ, to ensure good blend homogeneity and rapid dissolution. These are
- The major reasons for particle size control. There are numerous methods of particle sizing.
- Sieving is usually unsuitable during preformulation owing to the lack of bulk material. The simplest method for small quantities is the microscope.
- The Coulter Counter and laser light scattering are widely used for routine bulk analysis and research.

## 7. POWDER FLOW PROPERTIES

- When limited amounts of drug are available this can be evaluated by measurements of bulk density and angle of repose.
- These are extremely useful derived parameters to assess the impact of changes in drug powder properties as new batches become available.

## 8. COMPRESSION PROPERTIES

- When the dose is less than 50 mg, tablets can usually be prepared by direct compression with the addition of modern direct compression bases. At higher doses the preferred method would be wet massing.
- Nonetheless, information on the compression properties of the pure drug is extremely useful
- Although it is true that the tableted material should be plastic, i.e. capable of permanent deformation, it should also exhibit a degree of brittleness (fragmentation).
- Thus if the drug dose is high and it behaves plastically, the chosen excipients should fragment, e.g. lactose, calcium phosphate.
- If the drug is brittle or elastic, the excipients should be plastic, i.e. microcrystalline cellulose, or plastic binders should be used in wet massing.
- The compression properties elasticity, plasticity, fragmentation and punch filming propensity

## 9. EXCIPIENT COMPATIBILITY

- The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients that are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation.
- The preformulation screening of drug-excipient interactions requires 5 mg of drug, in a 50% mixture with the excipient, to maximize the likelihood of observing an interaction.
- Mixtures should be examined under nitrogen to eliminate oxidative and pyrrolytic effects at a standard heating rate (2, 5 or 10°C /min) on the DSC apparatus, over a temperature range which will encompass any thermal changes due to both the drug and excipient.

## CONCLUSIONS

- Preformulation studies have a significant part to play in anticipating formulation problems and identifying logical paths in both liquid and solid dosage form technology.

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