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REVIEW ARTICLE

Preformulation: strengthen the foundation for formulation and development

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Abstract: The preformulation is the first step in the rational development of a dosage form of a drug substance alone and when combined with excipients. The main objective of this study to generate useful information to the formulator to design an optimum drug delivery system. Preformulation studies strengthen the scientific foundation of the guidance, provide regulatory relief and conserve resources in the drug development and evaluation process, improve public safety standards, enhance product quality, facilitate the implementation of new technologies, and facilitate policy development and regulatory decision making. Preformulation studies give directions for development of formulation in choice of drug form, excipients, composition, physical structure, helps in adjustment of pharmacokinetic and biopharmaceutical properties, support for process development of drug substance support and useful data for development of analytical methods.

Keywords: Process, Preformulation, Development, Properties, Analytical

Introduction:

Preformulation evolved in the late 1950s and early 1960s as a result of a shift in emphasis in industrial pharmaceutical product development. Up until the mid 1950s, the general emphasis in product development was to develop elegant dosage forms and organoleptic considerations far outweighed such consideration as whether a dye used in a preparation might interfere with stability or with bioavailability.[1]

Almost all drugs are marketed as tablets, capsules or both. Prior to the development of these major dosage forms, it is essential that pertain fundamental physical and chemical properties of the drug molecule and other divided properties of the drug powder are determined. This information decides many of the subsequent events and approaches in formulation development. This first learning phase is known as pre-formulation. Preformulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system[2].Two fundamental properties are mandatory for a new compound

1. Intrinsic Solubility (CO)
2. Dissociation constant (pKa) [3]

Sustained release, sustained action, controlled release, extended action, timed release, depot and repository dosage forms are the terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after the administration of single dose. The term "controlled release" has become associated with those systems from which therapeutic agents may be automatically delivered at predefined rates over a long period of time. The rate controlled drug delivery systems are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity, and or targeting the delivery of drug to a tissue[3].The term "sustained release" has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration (i.e. not necessarily at a predetermined rate). The onset of the pharmacologic action is often delayed, and the duration of its therapeutic agent is sustained. The term "controlled release" on the other hand, has a meaning that goes beyond the scope of sustained drug action. It also implies a predictability in the drug release kinetics, which means that the release of drug ingredient from a controlled-release drug delivery system proceeds at a rate profile that is not only predictable kinetically but also reproducible from one unit to another[4] .Preformulation investigation may merely confirm that there are no significant barriers to the compound's development. Prior to starting preformulation studies, the physical pharmacists should meet with the principal investigator involved in the drug's development to obtain information on the known properties of the compound and the proposed development schedule as listed.

Definition of preformulation: [2]

Prior to the development of major dosage forms such as tablets, capsules, injections, liquid oral, etc, 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.

The following events take place between the birth of a new drug substance and its eventual marketing. The drug is synthesized and tested in a pharmacological screen

- The drug is found sufficiently interesting to warrant further studies.
- Sufficient quantity is synthesized to
- Perform initial toxicity studies to do initial analytical work and do initial preformulation
- Once pass initial toxicity, phase 1 (clinical pharmacology) begins and there is a need of actual formulation
- Phase 1 and 2 clinical testing then begins, and during this phase an order of magnitude formula is finalized
- After completion of the above, an NDA is submitted
- After approval of the NDA, production can start (product launch) [3]

Table: 1 Shows Preformulation Drug Characterization in a Structured Program [3]

S.No	Test	Method/Function Characterization
	Fundamental	
1	Spectroscopy	UV Simple assay
2	Solubility	Phase solubility/ purity
	a) Aqueous	Intrinsic & pH effect
	b) pKa	solubility control , salt formation
	c) Salt	Solubility, hygroscopicity & stability
	d)Solvents	Vehicles & Extraction
	e) Ko/ w	Lipophillicity, structure activity
	f) Dissolution	Bio pharmacy
3	Melting point	DSC-polymorphism, hydrate & solvent
4	Assay development	UV, HPLC, TLC
5	Stability	
	In Solution	Thermal, hydrolysis, pH
	In solid state	Oxidation, proteolysis metal ion
	Derived	
6	Microscopy	Particle size and morphology
7	Bulk density	Tablet and capsule formation
8	Flow properties	Tablet and capsule formation
9	Compression properties	Acid / excipient choice
10	Excipient compatibility	Preliminary screen by DSC, Conformation by TLC

TABLE: 2 Shows the program of Analytical Preformulation[3] .

S.No	Attribute	Test
1	Identity	Nuclear Magnetic Resonance(NMR) Infrared spectroscopy(IR) Ultraviolet spectroscopy(UV) Differential scanning calorimetry(DSC) Optical rotation
2	Purity	Moisture (water and solvent) Inorganic elements Heavy metals Organic impurities and DSC
3	Assay	Titration UV,HPLC
4	Quality	Appearance , odour Solution colour pH of the slurry (Saturated solution) melting point

Goals of preformulation [1]

1) To establish the necessary physicochemical parameter of a new drug substance
2) To determine its kinetic rate profile
3) To establish its physical characteristics
4) To establish its compatibility with common excipients

Approach of Spectroscopy:

The first step in preformulation is to establish a simple analytical method. Spectroscopy is the branch of science dealing with the study of interaction of electro-Magnetic radiation of with matter. The most important consequence of such interaction is that energy is absorbed or emitted by the matter in discrete amounts is called quanta. The absorption or emission processes are known throughout the electromagnetic spectrum ranging from the gamma region to the radio region. When the measurement of radiation frequency is done experimentally, it gives the value for change of energy involved and from this one may draw the conclusion about the set of possible discreet energy level of the matter. Spectroscopy is one of the most powerful tools available for the study for atomic and molecular structure and is used in the analysis of a wide range of sample. The study of spectroscopy can be carried out under the following heads.[3]

Atomic spectroscopy deals with the interaction of electromagnetic radiations with atoms which are most commonly in their lowest energy state called the ground state. Molecular spectroscopy deals with the interaction of electromagnetic radiations with molecules. This result in transitions between rotational and vibrational energy levels in addition to electronic transitions. As a result, the spectra of molecule are much more complicated than those of atoms.

Definition:

Spectroscopy is the branch of science dealing with the study of interaction of electro-magnetic radiation of with matter.

Purpose:

The acidic or basic nature of the molecule can be predicted from functional Groups.

Using the UV spectrum of the drug, it is possible to choose an analytical wavelength suitable to quantify the amount of drug in a particular solution.

UV Spectroscopy

The first requirement of any pre-formulation study is the development of a simple analytical method for quantitative estimation in subsequent steps. Most of drugs have aromatic rings and/or double bonds as part of their structure and absorb light in UV range, UV spectroscopy being a fairly accurate and simple method is a performed estimation technique at early pre-formulation stages. The absorption Co-efficient of the drug can be determined by the formula:

$$E = AF / X$$

A=Absorbance
F = dilution factor
X = weight of drug (mg)

It is now possible to determine concentration of drug in any solution by measuring absorbance[1]

$$C = AF / E \text{ mg/ ml}$$

Characterization of drug molecules is very important step at the pre-formulation phase of product development.

Following studies are conducted as basic pre-formulation studies, special studies are conducted depending on

The type of dosage form and the type of drug molecules:

1. Solubility determination
2. pKa determination
3. Partition co-efficient
4. Crystal properties and polymorphism
5. Practical size, shape and surface area
6. Chemical stability profile

Solubility analysis[2]

The numbers of parts of solvent required to completely dissolve one part of the solute is called as its solubility. The solubility of drug is an important physicochemical property because it effects the bioavailability of the drug, the rate of drug release into dissolution medium and consequently, the therapeutic efficiency of the pharmaceutical product. The solubility of the molecules in various solvents is determined as a first step. This information is valuable is developing a formulation. Solubility is usually determined in variety of commonly used solvents and some oils if the molecule is lipophillic. The solubility of material is usually determined by the equilibrium solubility method, which employs a saturated solution of the material, obtained by stirring an excess of material in the solvent for a prolonged until equilibrium achieved[5]. The approximate solubilities of pharmacopeial and national formulary substances are indicated by the descriptive terms in accompanying Table:3.

Common solvents used for solubility determination are

Water, Polyethylene Glycols, Propylene Glycol, Glycerin, Sorbitol, Ethyl Alcohol, Methanol, Benzyl Alcohol, Isopropyl Alcohol, Tweens, Polysorbates, Castor Oil, Peanut Oil, Sesame Oil, Buffer at various pHs[5]

Table-3: Approximate Solubility's of Pharmacopeial and National Formulary Substances.[5]

Descriptive Terms	Part of Solvents Required for 1 Part of Solute
Very Soluble	Less than 1
Freely Soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly Soluble	From 32 to 100
Slightly Soluble	From 100 to 1000
Very slightly Soluble	From 1000 to 10000
Insoluble	From 10000 to over

Intrinsic solubility:

An increase in solubility in acid compared to aqueous solubility suggests a weak base and an increase in alkali, a weak acid. An increase in acidic and alkaline solubility suggest either impotence or zwitter ion behavior. In this case there will be two pKa's, one acidic & one basic. When the purity of the drug sample can be assured the solubility obtained in acid for a weak acid or alkali for a weak base can be assured to be the intrinsic solubility (Co.) i.e. the fundamental solubility when completely unionized. The solubility should ideally be measured at two temperature:

1) 4 ^{o}C to ensure physical stability and entered short term storage and chemical stability unit more definitive data are available. The minimum density of water occurs at 4 ^{o}C. This leads to a minimum aqueous solubility.

2) 37 oC to support biopharmaceutical evaluation.

Intrinsic Solubility:

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 (C_0), i.e. the fundamental solubility when completely unionized

pKa Determination

Determination of the dissociation content for a drug capable of ionization within a pH range of 1 to 10 is important since solubility and consequently absorption, can be altered by orders of magnitude with changing pH. The Henderson -Hasselbach equation provides an estimate of the ionized and un ionized durg concentration at a particular pH.

For acidic compounds,

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

For basic compounds,

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

Partition Coefficient

Partition Coefficient (oil/ water) is a measure of a drug's lipophilicity and an indication of its ability to cross cell membranes. It is defined as the ratio of unionized drug distributed between the organic and aqueous phases at equilibrium.

P o/w = (C oil / C water) equilibrium

For series of compounds, the partition coefficient can provide an empiric handle in screening for some biologic properties. For drug delivery, the lipophilic/ hydrophilic balance has been shown to be a contributing factor for the rate and extent of drug absorption. Although partition coefficient data alone does not provide understanding of in vivo absorption, it does provide a means of characterizing the lipophilic/ hydrophilic nature of the drug. Since biological membranes are lipoidal in nature. The rate of drug transfer for passively absorbed drugs is directly related to the lipophilicity of the molecule. The partition coefficient is commonly determined using an oil phase of octanol or chloroform and water. Drugs having values if P much greater than 1 are classified as lipophilic, whereas those with partition coefficient much less than 1 are indicative of a hydrophilic drug. Although it appears that the partition coefficient may be the best predictor of absorption rate, the effect id dissolution rate, pKa and solubility on absorption must not be neglected[7]

Dissolution[8]

The dissolution rate of the a drug is only important where it is the rate limiting step in the absorption process. The solubility of a drug exceeded to 1mg/ ml at pH 7, no bioavailability or distinction related problems were to be expected. Below 1mg/ 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. The dissolution rate of a drug substance in which surface area is constant during dissolution is described by the modified Noyes-Whitney equation.

$$dc/dt = DA/hv (Cs-C)$$

Where,

D - Diffusion coefficient

h - Thickness of the diffusion layer at the solid liquid interface

A- surface area of the drug exposed to dissolution medium

V- volume of medium

Cs- Concentration of a saturated solution of the solute in the dissolution medium at the experimental temperature

C - Concentration of drug in solution at time t.

t - Time

Intrinsic Dissolution Rate

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 K1 is defined by

$$K1 = 0.62\ D^{2/3}\ v^{1/6}\ w^{1/2}$$

Where, V is the kinematic viscosity
W is the angular velocity of a rotating disc of drug[9]

Common Ion Effect

A common ion significantly reduces, the solubility of a slightly soluble electrolyte. The 'salting out' results from the removal of water molecules as solvent owing to the completing hydration of other ions. The reverse process 'salting in' qries with large anions e.g. benzoate, salivate which open the water structure. These hydrotopics increase the solubility of properly water soluble compounds such as diazepam.

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

Capillary melting gives information about the melting range but it is different to assign an accurate melting point.

Hot Stage Microscopy

This the issued observation of melting under a microscope equipped with a heated and lagged sample stage.
The heating rate is controllable.

Differential Scanning Calorimetry and thermal analysis

Differential 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 differential scanning calorimetry (DSC) is similar to DTA except that the instrument measures the amount of energy required to keep the sample at the same temperature as the reference i.e. it measures the enthalpy of transition[9]

Crystal Properties and Polymorphism

Many drug substances can exit in more than one crystalline from with different space lattice arrangements. This property is known as polymorphism. Polymorphs generally have different melting points, x-ray diffraction patterns and solubility even though they are chemically identical. Differences in the dissolution rates and solubilities of different polymorphic forms of a given drug are very commonly observed. When the absorption of a drug is dissolution rate limited, a more soluble and faster-dissolving from may be utilized to improve the rate and extent of bioavailability. For drugs pane to degradation in the solid state, physical form of the drug influences degradation. Selection of a polymorph that is chemically more stable is a solution in many cases. Different Polymorph also leads to different morphology, tensile strength and density of powder bed which all contribute of compression characteristics of materials. Some investigation of polymorphism and crystal habit of a drug substance as it relates to pharmaceutical processing is desirable during its Preformulation evaluation especially when the active ingredient is expected to constitute the bulk of the tablet mass. Although a drug substance may exist in two or more polymorphic forms, only one form is thermodynamically stable at a given temperature and pressure. The other forms would convert to the stable form with time. In general, the stable polymorph exhibits the highest melting point, the lowest solubility, and the maximum chemical stability. Various techniques are available for the investigation of the solid state. These include microscopy (including hot stage microscopy), infrared spectrophotometry, single-crystal x-ray and x-ray power diffraction, thermal analysis, and dilalometry.

Particle Size, Shape and Surface Area

Bulk flow, formulation homogeneity, and surface-area controlled processes such as dissolution and Surface morphology of the drug particles. In general, each new drug candidate should be tested during Preformulation with the smallest particle size as is practical to facilitate preparation of homogeneous samples and maximize the drug' s surface area for interactions. Various chemical and physical properties of drug substances are affected by their particle size distribution and shapes. The effect is not only on the physical properties of solid drugs but also, in some instances, on their biopharmaceutical behavior. It is generally recognized that poorly soluble drugs showing a dissolution- rate limiting step in the absorption process will be more readily bio available when administered in a finely subdivided state rather than as a coarse material. In case of tablets, size and shape influence the flow and the mixing efficiency of powders and granules. Size can also be a factor in stability: fine materials are relatively more open to attack from atmospheric oxygen, the humidity, and interacting excipients than are coarse materials[10]

- Determination of particle size
- Determination of surface area

Particle size Determination

Though microscopy is the simplest technique of estimating size ranges and shapes, it is to slow for quantitative determination the material is best observed as a suspension in non-dissolving fluid. Sieving is less useful technique at pre-formulation storage due to lack of bulk material. And reason pipette is based on the rate difference of sedimentation of different particles, but techniques like this are seldom used due to their tedious nature instruments based on light scattering, (Royco), light blockage (HIAC) and blockage of electrical conductivity path (coulter counter) are available.

Surface Area Determination

Surface area is most commonly determined based on brunaver emette teller (BET) theory of adsorption. Most substances adsorb a mono molecular layer of gas under certain conditions of partial pressure of gas and temperature. Knowing the monolayer capacity of adsorbent and the area of absorbable molecule, the surface area can be calculated the adsorption process is carried out with nitrogen at-195 degree Celsius at a partial pressure attainable when nitrogen is in a 30% temperature with an inert gas (helium). The adsorption takes place by virtue of vander wall's forces.

Power Flow Properties

When limited amounts of drugs are available Power flow properties can be evaluated by measurements of bulk density and angle of repose. Changes in particles size, and shape are generally very important an increase in crystal size or a more uniform shape will lead to a small angle or repose and a smaller Carr's index.

Bulk Density

Knowledge of absolute and bulk density of the drug substance is Very useful in Having some idea as to the size of final dosage form the density of solids also of affects their flow Properties Carr's compressibility index can be used to predict the flow properties based on density measurement.

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

A similar index has been developed by Hausner:

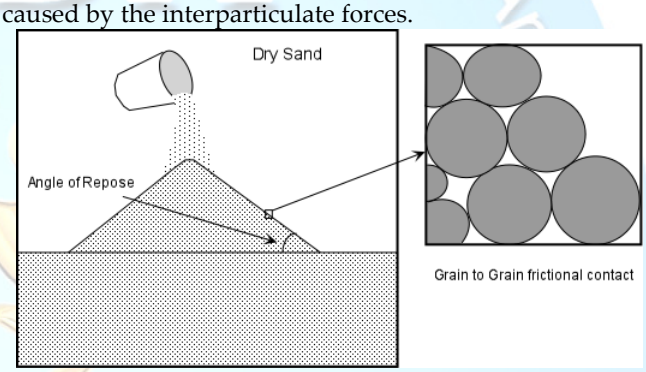
$$\text{Hausner ratio} = \frac{\text{Tapped Density}}{\text{Poured Density}} \times 100$$

Angle of repose: A static heap of powder, with only gravity acting upon it, will tend to form a conical mound. One limitation exists: The angle to the horizontal cannot exceed a certain value; this is known as angle of repose (θ).

Table- :4 Relationship between flows, angle of repose, Carr's index free powder flow[2]

Flow	Angle of Repose	Carr's Index
Excellent	<25	5-15
Good	25-30	12-16
Fair to passable	30-40	18-21
Poor	>40	23-35
Very poor	-	33-38
Extremely poor	-	>40

If any particle temporarily lies outside this limiting angle, it slides down the adjacent surface under the influence of gravity until the gravitational pull is balanced the friction caused by the interparticulate forces.



Accordingly, there is an empirical relationship between θ and the ability of powder powder to flow. However, the exact value for angle of repose does depend upon the method of measurement. A simple relationship between angle of repose, Carr's index and the expected powder flow is shown in fig.

Chemical stability profile

Preformulation stability studies are usually the first quantitative assessment of chemical stability of a new drug. Factor effecting chemical stability critical in rational dosage form design include temperature, pH and dosage form diluents. The method of sterilization of potential product will be largely dependent on the temperature stability of the drug. Drugs having decreased stability at elevated temperatures cannot be sterilized by autoclaving but must be sterilized by another means, e.g., filtration. The effect of pH on drug stability is important in the development of both oral administration must be protected from the highly acidic environment of the stomach. Buffer selection for potential dosage forms will be largely based on the stability characteristic of the drug.Typical stress conditions are shown in table 7. These

studies also include both solution and solid state experiments under condition typical for the handing, formulation, storage, and administration of a drug candidate as well as stability in presence of other excipients as follows :

- Solid state stability
- Solution phase stability
- Compatibility studies: stability in the Presence of excipients
- Typical stability protocol for new Chemical Entity.

Solid state stability

Chemical instability normally results from hydrolysis, oxidation, photolysis and /or pyrolysis of the drug. Esters and lactase and to lesser extent, amides are to prone to solvolysis Instauration or electron rich centre in the structure make the molecule vulnerable for free radical mediated or photo-catalysed oxidation. physical properties of drugs. Amorphous materials are less stable than their crystalline forms. Denser materials are more stable to ambient stress.

Elevated temperature studies

The elevated temperatures commonly used are 40, 50, and 60 degree centigrade with ambient humidity. The samples stored at highest temperature are observed weekly for physical and chemical changes and compared to an appropriate control. If a substantial change is seen, samples stored at lower temperature are examined. If no changes is seen after 30 days at 60 oc , the stability prognosis is excellent.

Stability under high humidity conditions

Solid drug samples can be exposed to different relative humidity conditions by keeping them in laboratory desiccators containing saturated solutions of various salts. The closed desiccators in turn are kept in oven to provide constant temperature. The preformulation data of this nature are useful in determining if the material should be protected and stored in controlled low humidity environment or if non aqueous solvent be used during formulation.

Photolytic stability

Many drugs fade or darken on exposure to light. Though the extent of degradations small and limited to the exposed surface area, it presents anaesthetic problem. Exposure of drug 400 and 900 foot-candles of illumination for 4 and 2 week periods respectively is adequate to provide some idea of photosensitivity. Resulting data may be useful in determining if an amber colored container is required or if color masking dye should be used in the formulation. The energy associated with the radiation increases as wave length decreases, so that the energy of UV visible is greater than that of IR and is independent of temperature (Table 10). When molecules are exposed to electromagnetic radiation they absorb light (protons) at characteristic wave lengths which causes an increase in energy,which can;

- Causes decomposition
- Be retained or transferred
- Be converted to heat
- Result in light emission at a new wave length (fluorescence, phosphorescence).

Natural sunlight lies in the wavelength range 290-780 nm, of which only the higher (UV) range (290-320 nm) causes photo degradation of drugs and sunburn [2]

Table-6: Shows Relationship between wavelength and associated energy of various forms of light.

Type of radiation	Wavelength (nm)	Energy (kcal mole $^{-1}$)
UV	50-400	287-72
Visible	400-750	72-36
IR	750-10 000	36-1

Stability to Oxidation

Drug's sensitivity to oxidation can be examined by exposing it to atmosphere of high oxygen tension. Usually a 40% oxygen atmosphere allows for rapid evaluation. A shallow layer of drug exposed to a sufficient headspace volume ensures that the system is not oxygen limited. Samples are kept in desiccators equipped with three-way stop cocks, which are alternatively evacuated and flooded with desired atmosphere. The process is repeated 3 or 4 times to ensure 100% desired atmosphere. Results may be useful in predicting if an antioxidant is required in the formulation or if the final product should be packaged under inert atmospheric conditions.

Compatibility studies

The knowledge of drug excipients interaction is useful for the formulation to select appropriate excipients. The described preformulation screening of drug excipients interaction requires only 5mg of drug in a 50% mixture with the excipients to maximize the likelihood of obscuring an interaction. Mixtures should be examined under nitrogen to ultimate oxidation and paralytic effect at a standard heating rate on DSC, over a temperature range, which will encompass any thermal changes due to both the drug and appearance or disappearance one or more peaks in themograms of drug excipient mixtures are considered of indication of interaction.

Solution phase stability

As compared with the dry form, the degradation is much rapid in solution form. It is important ascertain that the drug doesn't degrade when exposed to GI fluid. The pH based stability study, using different stimulator GI condition can be designed. A poor solution stability of drug may urge the formulator to choose a less soluble salt form, provided the bioavailability is not compromised.

Absorption behavior

It is essential to test the in vivo behavior of the new drug for successful formulation of a dosage from good bioavailability. Partial in vivo and in vitro test are designed to study.

Excipient Compatibility [2, 14, 15]

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. Thermal analysis can be used to investigate and predict any physicochemical interactions between components in a formulation and can therefore be applied to the selection of suitable chemically compatible excipients. The following are Various ingredients used in tablet and capsule formulations

EXCIPIENT	FUNCTION
Lactose monohydrate	Filler/diluent
Dicalcium phosphate dehydrate	Filler/diluent
Dicalcium phosphate anhydrous	Filler/diluent
Microcrystalline cellulose	Filler/diluent
Maize starch	Disintregrant
Modified starch	Disintregrant
Sodium starch glycollate	Disintregrant
Sodium crosscarmellose	Disintregrant
Polyvinyl pyrrolidone	Binder
Magnesium stearate	Lubricant
Stearic acid	Lubricant
Colloidal silica	Glidant

Method

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 or10°C min-1) on the DSC apparatus, over a temperature range which will encompass any thermal changes due to both the drug and excipient. The melting range and any other transitions of the drug will be known from earlier investigations into purity, polymorphism and solvates. For all potential excipients it is sensible to retain representative thermo grams in a reference file for comparison.

Interpretation

Basically, the thermal properties of a physical mixture are the sum of the individual components, and this thermo gram can be compared with those of the drug and the excipient alone. An interaction on DSC will show as changes in melting point, peak shape and area and/or the appearance of a transition. However, there is invariably some change in transition temperature and peak shape and area by virtue of mixing two components, and this is not due to any detrimental interaction. In general, provided that no new thermal events occur, no interaction can be assigned. Chemical interactions are indicated by the appearance of new peaks, or where there is gross broadening or elongation of an exo- or endothermic change. Second-order transitions produce changes in the baseline. Such observations may be indicative of the production of eutectic or solid solution-type melts. The excipient is then probably chemically reaction. and incompatible with the drug, and should be avoided. Where an interaction is suspected but the thermal changes are small, the incompatibility should be confirmed by TLC.

Where confirmation is required by TLC, samples (50:50 mixtures of drug and excipient) should be sealed in small neutral glass test tubes and stored for either 7 days at 50°C or 14 days at 37°C.It is important to view the results of such incompatibility testing with caution. For example, magnesium stearate is notoriously incompatible with a wide range of compounds when tested, yet because it is only used at low levels - typically 0.5-1% - such apparent incompatibility rarely produces a problem in practice in long-term storage and use[13]. Other techniques such as Fourier transform infrared analysis (FTIR) spectroscopy, X-ray powder diffraction (XRD), and liquid chromatography–tandem mass spectrometry (LC–MS/MS) analysis have been also used to investigate drug/excipients compatibility[16, 17].This application of complementary techniques is useful in determining the extent. and nature of interactions between the drug substance and the excipients. Compatibility information provides a means to predict the potential challenges that may be faced as clinical development proceeds.

Factors affecting Controlled Release Dosage Forms Dose Size

If an oral product has a dose size greater than 0.5gm it is a poor candidate for sustained release system, Since addition of sustaining dose and possibly the sustaining mechanism will, in most cases generates a substantial volume product that unacceptably large.

Aqueous Solubility Most of drugs are weak acids or bases, since the unchanged form of a drug preferentially permeates across lipid membranes drugs aqueous solubility will generally be decreased by conversion to an unchanged form for drugs with low water solubility will be difficult to incorporate into sustained release mechanism. The lower limit on solubility for such product has been reported 0.1mg/ml. drugs with great water solubility are equally difficult to incorporate in to sustained release system. pH dependent solubility, particularly in the physiological pH range, would be another problem because of the variation in pH throughout the GI tract and hence variation in dissolution rate.

Partition Coefficient

Partition coefficient is generally defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly compounds with relatively high partition coefficient are predominantly lipid soluble and consequently have very low aqueous solubility. Compounds with very low partition coefficients will have difficulty in penetrating membranes resulting poor bioavailability. Typical relationship between drug activity and partition Coefficient K, generally known as Hansh Correlation.

Pka:

It is the relationship between Pka of compound and absorptive environment. Presenting drug in an unchanged form is adventitious for drug permeation but solubility decrease as the drug is in unchanged form.

Drug Stability

Orally administered drugs can be subject to both acid base hydrolysis and enzymatic degradation. Degradation will proceed at the reduced rate for drugs in the solid state, for drugs that are unstable in stomach, systems that prolong delivery ever the entire course of transit in GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered form a sustaining
dosage from. This is because more drug is delivered in small intestine and hence subject to degradation.

Molecular size and diffusivity

The ability of drug to diffuse through membranes its so called diffusivity & diffusion coefficient is function of molecular size (or molecular weight).Generally, values of diffusion coefficient for intermediate molecular weight drugs, through cm2 / sec. with values on the order of 10-8 being most common for drugs with molecular weight greater than 500, the diffusion coefficient in many polymers frequently are so small that they are difficult to
quantify i.e. less than 16-12 cm2/sec.Thus high molecular weight drugs and / or polymeric drugs sustained release device using diffusion through polymer membrane.

Biological Half Life

The usual goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period. To action this, drug must enter in the circulation of approximately the same rate of which it is eliminated. The elimination rate is quantitatively described by half-life (t1/2). Therapeutic compounds with short half-lives are excellent candidates for sustained release preparations. Since this can reduce dosing frequency. In general drugs with half-lives shorter than 3hrs are poor candidates of sustained release dosage forms of dose size will increase as well as compounds with long half-lives, more than 8 hrs. are also not used in sustained release forms because their effect is already sustained.

Absorption

The rate, extent and uniformity of absorption of a drug are important factors when considered its formulation into a sustained release system. As the rate limiting step in drug delivery from a sustained-release system is its release from a dosage form, rather than absorption. Rapid rate of absorption of drug, relative to its release is
essential if the system is to be successful. It we assume that transit time of drug must in the absorptive areas of the GI tract is about 8-12 hrs. The maximum half life for absorption should be approximately 3-4 hrs. Otherwise device will pass out of potential absorption regions before drug release is complete.

Distribution

The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition. For design of sustained/ controlled release products, one must have information of disposition of drug.

Conclusion:

This review of concept of preformulation highlights various parameters which are tested in preformulation studies. Preformulation studies have a significant part to play in anticipating formulation problems and identifying logical paths in both liquid and solid dosage forms technology. The need for adequate drug solubility cannot be over emphasized. The availability of good solubility data should allow the selection of the most appropriate salt for development. Stability studies in solution will indicate the feasibility of parental or other liquids dosage forms, and can identify methods of stabilization. In parallel, solid-state stability by DSC, TLC and HPLC, and in the pres-

ence of tablet and capsule excipients, will indicate the most acceptable vehicles for solid dosage forms. By comparing the physicochemical properties of each drug candidate within a therapeutic group (using Cs, pKa, melting point) the preformulation scientist can assist the synthetic chemist to identify the optimum molecule, provide the biologist with suitable vehicles to elicit pharmacological response, and production of the best salt with appropriate particle size and morphology for subsequent processing. Importance of preformulation is sproved performing the case study explained earlier.

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