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PREFORMULATION

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ABSTRACT

Preformulation may be a cluster of studies that specialise in the physicochemical properties of a drug candidate that would have an effect on the drug performance and also the development of an indefinite quantity kind. This could offer necessary data for formulation style or support the need for molecular modification. Each drug has own intrinsic chemical and physical properties that has been take into account before development of pharmaceutical formulation. This property provides the framework for medication combination with pharmaceutical ingredients within the fabrication of indefinite quantity kind. Objective of preformulation study is to develop the elegant, stable, effective and safe indefinite quantity kind by establishing kinetic rate profile, compatibility with the opposite ingredients and establish Physico-chemical parameter of drug substances. Among these properties, drug solubility, partition coefficient, dissolution rate, polymorphic forms and stability are plays important role in preformulation study.

Introduction

What is preformulation?

Preformulation studies focus on those physicochemical properties of the new compounds that could affect drug performance and development of efficious dosage form.

When a new drug molecule shows considerable pharmacological activity in animal trials it is then to be subjected to evolution in humans.
Preformulation commences when all parameters are to be evaluated for a drug molecule after it has shown promising pharmacological activity in animal trials. Preformulation encompasses activities ranging from supporting the discoveries identification of a new chemical ingredient to characterization of physical properties required for designing the dosage form. It's apparent that a significant chance of income is generated from these blockbuster products, and the fiscal health and prospects of the originator company are largely dependent upon the extent of patent protection and new medicine products in the development channel.

Almost all new drugs that are active orally are marketed as tablets, capsules or both only a few compounds are marketed as injections. Some other dosage homes may be required but they are usually specific.

Prior to development of a new drug in to any of these 3dosage forms it is essential to study certain physiochemical properties and other derived properties of drug molecule. The preformulation studies often proceed in following order.

Goals/scope of preformation studies:

- It is essential to scale back issues in later stage of the drug development.
- It will scale back the drug development price.
- Goals is to decide on the right variety of the drug substance, measure its physical properties, Associate in Nursing degenerate a radical beneath standing of the materials stability under the conditions that may cause development of an optimum drug delivery system.
- To gauge physical-chemistry properties of the drug substance on the performance of the drug product.

Objectives:

- To develop the elegant, stable, effective and safe dosage form by establishing kinetic rate profile compatibility with the other ingredients and establish physiochemical parameter of new drug substances.
- To study drug solubility, partition coefficient, dissolution rate, polymorphic forms and stability plays important role in formulation study.
- To generate information useful to formulate to increase drug stability.
- To reduce excipient incompatibility.
- To improve drug bioavailability.

Physicochemical properties:

1. Organoleptic properties:

Colour: It ought to be Unappealing to the attention and determined by either instrumental strategies or visible methodology that varies from batch to batch.

Record of early batches and establishing "specification" is very helpful for later production. Coating of body in variable colour is done if found undesirable.

Odour and taste: Use a less soluble chemical version of associate unappealing medication or mask it with flavours, excipients, coatings, etc

Odours may well be sturdy, weak, fruity, fragrant, sulphurous, pungent, or odourless . Acidic, bitter, bland, strong, sweet, and tasteless flavours area unit all attainable.

2. Bulk characterization of studies:

A. Crystallinity and polymorphism:

Crystal habit and also the internal structure of a drug will have an effect on bulk and chemical science properties. Changes with the inner structure typically alter the crystal habit, with such chemical amendments as conversion of a metallic element salt to its free acid type manufacture each a change in internal structure and crystal habit.

Crystals are characterized by repetition spacing of constituent atoms or molecules in a 3 dimensional array whereas amorphous forms having atoms or molecules randomly placed as in a liquid, MRPS forms are typically prepared by rapid precipitation, lyophilisation, a rapid cooling of liquid melts.

Identification of possible hydrate compounds is important since they acquire solubilities can be significantly less than their anhydrous forms, conversion of an anhydrous compound within the dosage form may reduce the dissolution rate and extent of drug absorption.

B. Hydrates and solvates:

Polymorphism is the ability of a compound to crystallise as over one distinct crystalline species with totally different internal latices.

Chemical stability and solubility changes will have an effect on a drug bioavailability and its development program.

Various chemical properties vary depending on the inner structure of a solid drug, as well as the temperature, density, hardness, crystal form and other optical properties.

C. flow property of powders:

Pharmaceutical powders could also be generally classified as free flowing or cohesive.

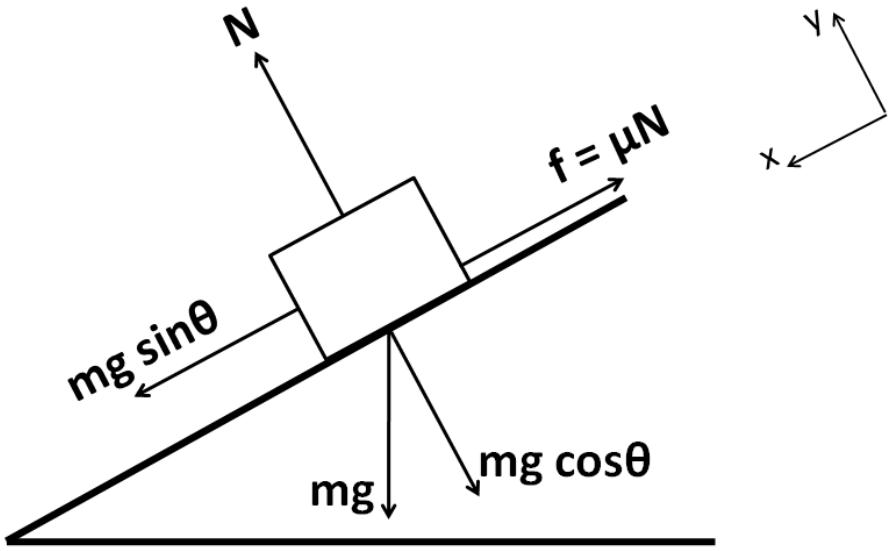
As a result, a free flowing drug candidate could become cohesive throughout development, so necessitating on entirely new formulation strategy.

Preformulation powder flow investigations ought to quantitatively assess the pharmaceutical consequences of every method improvement and supply direction for the formulation development project team. This direction could incorporates a formulation

recommendation like granulation or concretion via slugging, the necessity for special auger feed instrumentation or a check system for evaluating the advance in flow led to by formation.

Angle of repose:

It is usually used for determination of flow property of powder offers their lack of precision, observation of powder flow in a glass funnel and then a grounded metal funnel provides insight into the drug's flow properties, electrostatic properties and tendency to bring in a cone shaped hopper. Cohesive powders may be characterised by tensile testing or evaluated in shear cell. Since both methods require large samples of material for testing these methods are not discussed in this section rather, the reader is referred to the works of York, or experiment.



D. Hygroscopicity :

Hygroscopicity is the substance that has the ability to absorb and adsorb moisture or water from the surroundings environment. The substance that absorbs enough witness from the atmosphere to dissolve itself is hydrophilic. A substance that loses water to create a lower hydrate or becomes anhydrous is termed flowering. These are extreme cases, and most pharmaceutical compounds are typically either impassive to the water out there in the surrounding atmosphere or lose or gain water from the atmosphere, betting on the relative humidity. Materials unaffected by relative humidity square measure termed non hygroscopic. Whereas those in dynamic equilibrium with water within the atmosphere square measure absorbent.

These square measure classified as:

- Hydrophilic (a substance which absorb adequate weight from the atmosphere to dissolve itself at higher extreme)
- Efflorescent (a substance that loses water to make a lower hydrate or become anhydrous at lower level)
- Absorptive (a substance that exist during a dynamic equilibrium with water)

E. Fine particle characterization:

Certain physical and chemical properties of drug molecules are affected by the particle size, distribution, including drug dissolution rate, bioavailability, content uniformity, taste, texture, colour and stability. In addition properties such as flow characteristics and sedimentation rates are also important factors related to the particle size. Particle size, shape and surface morphology may be determined by following methods:

•Optical microscopy: light microscope fitted with calibrated grid may be used to find out size and shape.

•Stream counting devices: stream counting devices such as Coulter counter provider convenient method for characterizing particle size distribution.

•Gas adsorption: dissolution and degradation of the drug may be more directly related to the surface area rather than particle size.

Particle size can be characterized by some of the methods which are as follows:

1.Density & Porosity:

Density is that the magnitude relation of mass of powder to its volume. It is the derived property of powder which will be derived from particle size distribution, particle form, and extent.

2.Bulk density:

It is calculated when solid is non porous i.e. true & granular density are identical so measured by Mercury displacement or Helium densitometer. It is ratio of bulk weight to bulk volume Bulkiness is reciprocal of bulk density.

3.Hausnerr's ratio: $\frac{Tap\ density}{Bulk\ density}$

The Hausner quantitative relation is employed in a very wide selection of industries as a sign of the flowability of a powder. The Hausner quantitative relation (H) is said to the Carr index (C), another indication of flowability, by the formula.

Salt Formation:

Salt formation is that the most typically used approaches for molecular modification. Salt formation is one of the only chemical reactions involving either a nucleon transfer or a neutralization between an acid and a base.

Salt kind of a drug square measure usually ready to with chemicals stabilize the molecule, to convert it to a less absorbent compound. To boost stability, to retard solubility for sustaining unharness, to boost process of a drug, to boost softness and flow properties and improve bioavailability.

Salt selection process:

In the preformulation stages of drug development multiple salt forms are often ready for a drug that's to be developed. Those salts forms have to be compelled to be compared with relevance their physiochemical and biopharmaceutical properties. The most of the method is to settle on an optimum salt type which will make sure the most fascinating properties of process, storage, and products performance.

The first stage of salts election is crystallinity assessment. Crystalline structure is related to higher stability and thus the properties of crystalline salt is also expected to not vary extensively throughout transportation, handling, storage, and use. However, the amorphous salt from might have benefits i.e. improved solubility profile.

After that, the hygroscopicity profile of the salt type is evaluated to outline the degree of variability of the properties within the variable wetness conditions. The salt type with applicable hygroscopicity profile square measure after evaluated for solubility.

Finally, the chosen salt type is tested in relevance its medicine properties (onset and therefore the period of activity) and drug profile. These stages is also followed by safety studies. Upon satisfying completion of the check, optimum salt type can enter diagnosing and clinical testing phases.

Effects of salt formation:

Salt form of drugs have significant effects on physicochemical properties of a drug influencing its quality, safety and performance. Importantly, different salt forms rarely change drugs pharmacological properties.

One of the main effect is the drugs increase solubility and dissolution rate. If the drug is a weak base and formulated as a salt, it's solubility and dissolution rate will be increased in the intestine due to the buffering action of the salt.

3. Solubility analysis:

Aqueous solubility of the drug indicates at ease with which it can be formulated has an aqueous solution for oral use and intravenous injections are preclinical studies. Preformulation solubility that is the drug for oral administration should be checked for solubility in media having isotonic chloride ion concentration and acidic pH.

Preformulation solubility studies typically embody determination of pKa, temperature rely, hydrogen ion concentration solubility profile, solubility merchandise solubilization mechanism, and rate of dissolution.

Analytic strategies that square measure notably helpful for solubility activity embody HPLC, ultraviolet illumination chemical analysis, light chemical analysis, and gas natural action.

A. Partition coefficient

The partition coefficient is defined as the ratio of unionized drug distributed between the organic and aqueous phase at equilibrium.

Partition constant (the solvent: water quotient of drug distribution) includes a variety of applications which square measure relevant to preformulation:

1. Solubility: each liquid and in mixed solvents.

2. Drug absorption in vivo: applied to a homologous series for structure activity relationships (SAR).

3. Partition chromatography: selection of column (HPLC) or plate (TLC) and selection of mobile phase (eluant).

The oil/water partition coefficient could be a live of a molecule's oleophilic characters that's, its preference for the deliquescent or oleophilic section. The partition constant ought to be thought-about in developing a drug substance into a dosage type.

B. pKa determination :

Solubility largely depends on pH. Therefore, it is important to determine dissociation constant of a drug capable of ionizing in the pH range of 1 to 10. The concentration of ionized drug at a particular pH can be estimated by the use of Henderson - hasselbalch equation.

For weekly acid drugs having pKa values more than three, the unionized form is present in stomach in acidic pH. The drug is a nice predominantly in the neutral medium of the intestine.

pKa value can be most efficiently determined by detection of spectral shifts by UV or visible spectroscopy. Another method of potential metric titration is very sensitive for compounds having pKa values of 3 to 10. A suitable co-solvent such as methanol or dimethyl sulfoxide can be incorporated to avoid precipitation of an ionized species.

For acidic compounds pH= pKa + log (ionized drug/ unionized drug)

For basic compounds pH= pKw - pKb + log (unionized drug/ionized drug)

C. Effect of temperature on solubility:

Most solution processes are endothermic with positive heat of solution. Therefore, increasing the solution temperature increases the solubility.

D. Intrinsic Solubility :

Solid drug substances are command along in an exceedingly three-dimensional array as a result of building block bonds. The strength of the bonds (the bravais lattice energy) governs several of the physical attributes of the megascopic crystal (such as hardness, temperature and then on). Because the temperature of a solid increases therefore will the energy it contains. From everyday expertise, when the temperature reaches a particular vital level (the melting temperature range) the solid undergoes a phase change to make a liquid.

The concentration of drug dissolved at this time is understood because the equilibrium solubility (usually the term solubility is employed alone) and therefore the resolution is saturated. If the drug has associate ionisable cluster then the equilibrium solubility of the un-ionised kind is named the intrinsic solubility (So). This can be necessary, as a result of if the drug is ionisable it'll ionise to a larger or lesser extent with resolution pH and this may have an effect on the discovered solubility. If the structure of the compound is thought, then it ought to be clear whether solubility can exhibit a dependence upon pH. If the structure isn't known then measure solubility over a variety of pH can show whether or not an ionisable moiety is present (although care should be taken once choosing the buffer to make sure salts don't seem to be accidentally formed).

4. STABILITY ANALYSIS

Preformulation stability studies area unit typically the primary quantitative assessment of a chemical stability of a replacement drug. These studies embody each resolution and solid state experiments below condition typical for the handling formulation, storage and administration of a drug candidate. This section focuses on the analysis of a chemical stability throughout theory analysis. Wherever potential, business pharmaceutical products ought to have a shelf-life of three years. The potency mustn't fall below ninety fifth below the recommended storage conditions and therefore the product should still look and perform because it did once 1st manufactured. A drug for oral use may destabilize either during it's self life or in the GIT.

A. TOXICOLOGY FORMULATION :

It is often advisable to evaluate samples of the toxicology preparation for stability and potential homogenicity problems. Usually, a drug is administered to the animal in their feed or by oral gavage of a solution or suspension of the drug in an aqueous vehicle. Water, vitamins, minerals, enzymes are present in a feed, which can severely be reduce the shelf life of drug.

Enzymes activity and moisture levels typically decrease with time while feed composition varies with the "consumer", thus, a fresh sample of a feed to be used in the toxicology test provides the most releva nt stability data. Since enzymes activity and mobility of adsorbed water vary substantially with temperature, it is recommended that storage temperature typical of the toxicology laboratory be used for this stability study.

B. SOLUTION STABILITY :

The primary objective of this phase of preformulation research is identification of a condition necessary to form a stable solution. These studies should include the effect of pH, ionic strength, co-solvent, light, temperature and oxygen. As compared with the drug form, the degradation is much rapid in solution form.

In solution state decomposition occurs through Hydrolysis- Follows second order kinetic, order of hydrolysis is Lactum > Ester > Amide > Imide. The most probably reason for drug instability is reaction. Water plays a dominant role and in several cases it is involved passively as a solvent vector between 2 reacting species in answer. e.g. Anaesthetic, antibiotic, vitamins and barbiturate

Oxidation- loss of electron or addition of oxygen or removal of hydrogen or increase in valency is called oxidation. Oxidation is controlled by the environment i.e. light, trace metals. e.g. epinephrine, vitamins etc.

Photolysis- drugs like antibacterial, fluoroquinolones are sensitive to light & even such drugs shows daylight tanning as side effect.

Racemization- Follows initial order kinetics, optically active substances converted into optically inactive without any change in it's chemical composition.

C. pH rate profile :

The concentration of drug dissolved at this time is understood because the equilibrium solubility (usually the term solubility is employed alone) and therefore the resolution is saturated. If the drug has associate ionisable cluster then the equilibrium solubility of the un-ionised kind is named the intrinsic solubility (So).

This can be necessary, as a result of if the drug is ionisable it'll ionise to a larger or lesser extent with resolution pH and this may have an effect on the discovered solubility. If the structure of the compound is thought, then it ought to be clear whether solubility can exhibit a dependence upon pH. If the structure isn't known then measure solubility over a variety of pH can show whether or not an ionisable moiety is gift (although care should be taken once choosing the buffer to make sure salts don't seem to be accidentally formed) The drug sample in solution state are intentionally degraded at extreme pH and temperatures (0.1 N HCl / 0.1 N NaOH at 90° C).

This data gives idea on maximum rates of degradation. This study is followed by a generation of complete pH - degradation rate profile by using buffers of varying pH. The ionic strength, drug and co-solvent levels should be kept constant while studying the pH rate profile.

CONCLUSION:

After completion of preformulation analysis of latest drug candidates, it is counseled that a comprehensive report be prepared lightness the pharmaceutical issues associated with molecules. It helps in developing phase I formulations and in getting ready regulative documents and aid in developing future drug candidates. If, drug is found satisfactory ample quantity is synthesized to perform initial toxicity studies, initial analytical work and initial preformulation. Once past initial toxicity, phase I (clinical toxicology) begins for actual formulations. After that clinical test and III clinical testing begins, and during this part an order of magnitude formula is finalized. Once completion of all higher than, an NDA is submitted and once approval of NDA, production will begin.

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