

Review on Preformulation Studies and Preparation of Preformulation Data Sheet

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Abstract: *Preformulation data is necessary to comprehend possible medication pharmacokinetics in man and livestock, as well as the opportunities and difficulties for process adjustment when the product is ramped up in production. In order to ascertain the shelf life of the marketed product, optimized formulation studies are also carried out to anticipate the stability of the formulations throughout production, shipping, and storage. This paper discusses measures for solubility and dissolution rate, molecule dissociation, pka, diffusion, partition, and permeability, as well as how these may be included into a categorization scheme for biopharmaceuticals, are all discussed in this review. Absorption of the moisture Differential scanning calorimetric, thermo gravimetric analysis, and powder X-ray diffraction are used to classify hygroscopicity and evaluate polymorphism and crystallinity. Stress testing is used to evaluate the stability of active components and excipients in isolation and in pH, temperature, humidity, light, and oxidizing substances should all be taken into account. The evaluation of the essential and derived properties of powders and particle systems is described in the final section.*

Keywords: Preformulation

I. INTRODUCTION

Preformulation was first developed in the industry pharmaceutical product development in the late 1950s and early 1960s as a result of a shift in emphasis. Advances in analytical approaches served as inspiration for the initial preformulation programmes. The primary objective of preformulation testing is to generate information that the developer may utilise to formulate stable, bioavailable active components.

During the early phases of producing a novel medical product, synthetic chemists may obtain information that may be properly classified as preformulation data, either alone or in cooperation with specialists in the other field, including preformulation.

We should be knowledgeable of the drug's qualities, the content in comparison to comparable products, dose form, stability, and decay data before commencing the preformulation investigations. based on literature searches, the suggested method of drug administration, formulation strategies mentioned in the literature, and the bioavailability and pharmacokinetics of medications with comparable chemical make-ups. Additionally, it comprises preliminary investigation and molecular optimization by the drug should be tested to estimate the size of each potential problem area (Step I), and if a shortfall is discovered, a chemical modification should be implemented (Step II). To fill this gap, molecular modification is applied to salts, prodrugs, solvates, polymorphs, or new analogues. The salt version of a medicine dissolves much more slowly than its parent substance. It is much simpler to dissolve weak organic bases like sodium and potassium's hydrochloride salts than the comparable free acids or bases. The basis of ephedrine, for instance, is a weakly water-soluble compound with slow solubility and dissolution rates. So, it has been altered to take the form of the ionised salt Ephedrine HCL, which has a greater water solubility and dissolving rate. Prodrug production is the process of creating artificial drug derivatives (such as esters or amides) that release the actual drug in vivo.

Prodrug could or might not have pharmacological effects.

Sr. No.	Parameters	Evaluation Parameters
1.	Stability Solids state Solution	Temperature, light, humidity solvent, pH

2.	Solid state compatibility	TLC & DRS analysis
3.	Physico chemical properties colour, odour, partical size, shape crystallinity	Molecular structure & weight, melting point
4.	Thermal Analysis Profile solubility	DTA, DSC, TGA
5.	Absorbance Spectra	UV, IR
6.	Other properties Hygroscopicity	Potential bulk characterization volatility, optical activity, solvent
7.	Physico mechanical properties	Tapped density, compressibility photomicrographs
8.	In Vitro Availability Properties	Dissolution & analysis of Drug crystal, pallets
9.	Other Studies Plasma protein binding, ionization constant	Effect of compatible Excipient on dissolution, kinetic studies of solution Degradation, Use of Radio-labeled drug

Table 1: Evaluation parameter Used in Preformulation of Drug Development

1.1 Goals

Goals of preformulation's are:

- To establish a novel drug substance's physicochemical characteristic.
- To determine a novel drug substance's physicochemical property.
- To determine a novel pharmacological substance's kinetic rate profile,
- To determine if the novel drug material is compatible with the widely used excipients, and
- Choosing the appropriate dosage of a pharmacological substance

1.2 Objective

The objectives of pre-formulation studies are:

- To create beautiful, reliable, potent, and secure dosage forms.
- Before creating any dose form, it is necessary to comprehend a medication substance's physical description.
- Pre-formulation is the initial stage in the logical development of a pharmacological substance's dosage form before the production of the dosage form. (2)

1.3 Physicochemical Parameters

Following are the major physicochemical characteristics of drug substances evaluated in the pre-formulation studies:

A. Physical Characters

- Organoleptic properties
 - Bulk characteristics
1. Solid state characteristics
 2. Flow property
 3. Densities
 4. Compressibility
 5. Crystalline
 6. Polymorphism
 7. Hygroscopicity

Solubility Analysis

- Ionization constant
- Partition co-efficient
- Solubilization

- Thermal effect
- Common ion effect
- Dissolution

B. Characteristics of Chemicals

- Hydrolysis
- Oxidation
- Photolysis
- Recemization
- Polymerization
- Isomerization (3)

A. Physical Characteristic

1. Organoleptic Properties

Color:

It should be the unsightly and only discernible by instrumental techniques or a distinctive visual trait that fluctuates from each batch. Regular monitoring of early sets and creating requirements is very useful for further manufacture. The body may be covered with the varying colour if it is deemed unpleasant.

Odor and Taste:

Using a chemical form that is less soluble or masking the drug's disagreeable flavour using inert ingredients, coatings, flavours, etc. Drug substances that cause skin irritation must be handled cautiously. Stability and bioavailability will be affected by the excipients, odors, and colours used. Possible colours include off-white, creamy yellow, brown, or glossy. The four types of smells are offensive, sulphurous, fragrant, and odorless. It is possible to have flavours that are acidic, bitter, bland, powerful, sweet, and tasteless.(3)

Bulk Characteristics

Solid State Characteristics

The bulk properties of the powder are significantly influenced by the mixture of the solid and fluid. The fluid's volume can change substantially, making it potentially the most difficult feature. Given the many factors that may change their rheological properties, materials' capacity to flow is perhaps the least expected of all. The physical characteristics of the particles, such as their height, structure, contours, size variability, and hardness, have an impact on the flow properties. Humidity, the transporting environment, and most notably aeration are external factors that will make the problem worse.

Particle Size Distribution

The particle size distribution and forms of pharmacological compounds have an impact on a variety of their chemical and physical characteristics. In some cases, the impact also affects the biopharmaceutical behavior of solid medications, in addition to their physical features. For instance, the particle size distributions of griseofulvin and phenacetin directly affect their bioavailability. It is now well accepted that administering poorly soluble medications in a finely split condition as opposed to a coarse substance will increase their bioavailability and bypass the solubility rate-limiting phase in the absorption process. The finished tablet's homogeneity is also influenced by its size. When there are significant size differences between the active ingredients and the excipients, mutual sieving (de-mixing) effects might happen, which can make thorough mixing challenging or difficult to sustain during the next processing processes. (3)

b) Flow Properties

The most crucial characteristic of powder is cohesiveness, which is measured in terms of Carr, S index, Hausers ratio, and angle of repose. Carr, s

$$\frac{(\text{Tape density} - \text{Bulk density})}{(\text{Tape density} - \text{Bulk density})} 100,$$



where Tap density /bulk density is the Hausers ratio.

Angle of Repose () measures the highest amount of resistance to particle movement.

angle formed between the powder's surface and the horizontal plane

Tan α = 2h/D

where h is the height of the surface pile and D is the diameter of the circle

Measurement of Angle of Repose

- Static angle of repose-Fixed funnel method and fixed cone method
• Kinetic or Dynamic angle of repose Rotating cylinder method and Tilting box method. (4)

Table with 4 columns: Carr's Index, Hausner's ratio, Angle of repose, Flowability. Rows show ranges for Carr's Index (5-15 to >40) and corresponding Hausner's ratio and Angle of repose values, along with flowability ratings (Excellent, Good, Fair possible, Poor, Very poor, Very, very poor).

Table 2: Powder Flow Properties

c) Densities

The mass to volume ratio is measured by density.

various densities

- Bulk density is calculated by measuring the volume of powder that has gone through a screen with a given mass.
• To determine the density, a measuring cylinder filled with powder is mechanically tapped (b).
• A solid's genuine density is referred to as its true density.
• The density of the granules may affect the porosity, compressibility, dissolution, and disintegration of tablets. (3)

d) Compressibility

Compressibility is the ability of a powder to shrink under pressure, while compactability is the ability to form a tablet with a particular tensile strength. It may be used to predict flow characteristics based on density readings.

Pored density less than Tapped frequency equals 100 according to Carr's indices.

e) Crystallinity

Drugs and excipients can exist in a range of crystalline or amorphous forms depending on their chemical composition and technique of separation or crystallisation. Molecules may organise themselves in different geometric configurations during crystallisation, leading to unique packing arrangements or orientations in the crystal structure..Based on symmetry, the diverse crystal forms are divided into the six different crystal systems.

- Cubic (Nacl)
• Tetragonal (urea)
• Three. Hexagon
• Rhombic
• Monoclinic
• Triclinic (boric acid)
• Trigonal (5)



f) Polymorphism

All these different states are referred to as polymorphism. Each polymorphic form may have incredibly unique physicochemical characteristics (such as solubility and melting point) that can significantly affect the bioavailability and stability of a medication. Moreover, polymorphism can affect how well medicines compress. (For instance, paracetamol is available in both monoclinic and orthorhombic forms, with the latter having better compaction characteristics.

The following categories apply to polymorphisms:

1. Enantiotropy describes how one form can change into another when the temperature or pressure are altered.
2. When it is monotropic, the polymorphic form is unstable at all pressures and temperatures.

Atoms or molecules are randomly arranged (without a clear structure) in amorphous drugs. In comparison to the comparable crystalline form, the amorphous form has a larger thermodynamic energy, greater solubility, and a higher rate of dissolution. (5)

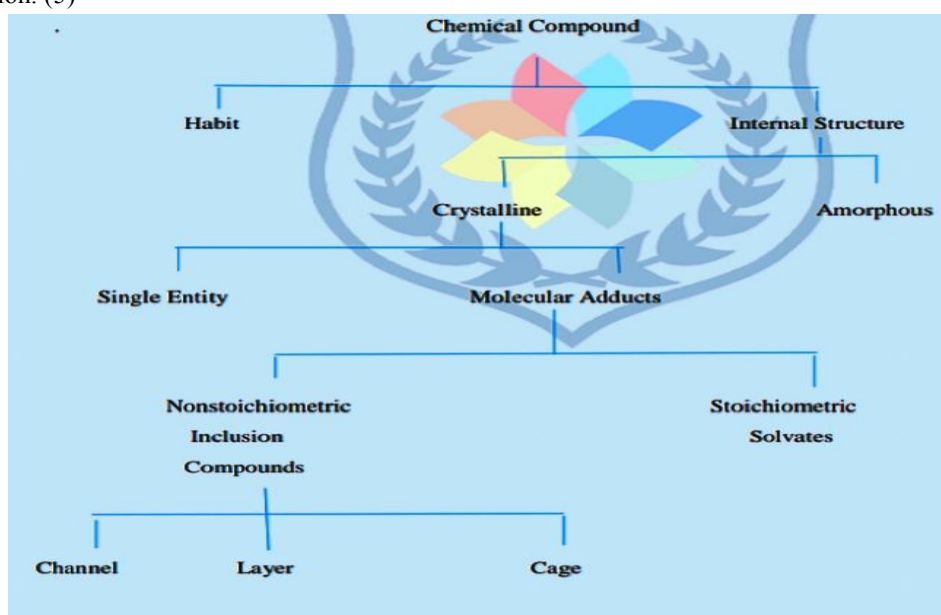


Figure 1: Outline of differentiating habit and crystal chemistry

g) Hygroscopicity

The word "hygroscopicity" is used to characterize a substance's capacity to absorb moisture from its surroundings. The process might take a number of different shapes. A condensed layer will occur when water vapour physically adsorbed on the surface and within the pores of a porous substance like activated carbon. A process might begin at "active locations" and then expand from there. Other materials, like silica gel, may have surface interactions that are not entirely physical and may also involve loose chemical interactions. Many cellulosic materials are hygroscopic, which means they absorb water and alter their physical characteristics. Examples of these materials include hair, cotton, and wool. This kind of material is usable.

Hygroscopicity can be classified as:

- Deliquescent
- Very water-soluble
- Hydrophilic
- Not hydrophilic

Class I: Non-Hygroscopic,

There are essentially no moisture increases at relative humidity levels below 90%. Furthermore, the increase in moisture content is less than 20% after a week of storage at relative humidity levels exceeding 90%.

Class II: Mildly Hygroscopic,

Nearly no moisture increases at relative humidity levels below 80%. After a week of storage at a relative humidity of above 80%, the rise in moisture content is less than 40%.

Moderately Hygroscopic, Class III

The moisture content does not increase by more than 5% after storage at relative humidity levels below 60%. After a week of storage at a RH of above 80%, the increase in moisture content is less than 50%.

Class IV: Extremely Hydrophobic

Moisture might grow at relative humidity levels as low as 40 to 50 percent. The product's moisture content rises after some time in storage. (5)

3) Solubility Analysis

Solvency, in particular fluid solvency, is an important physical chemical attribute of a drug ingredient. For remedial sufficiency in the physiological P H range of 1 to 8, a drug should have some fluid solubility. A drug must be the first item in the arrangement structure in order to enter fundamental course and provide remedial influence. If a medicine substance's solvency isn't quite attractive, consideration should be taken to increasing its solvency. Unlucky solvency (10mg/ml) may arise due to insufficient or irrational retention across the pH range of 1 to 7 at 37°C. However, the disclosure of two crucial features is required for a different molecule.

- Internal solubility (a) (Co)
- Consistent dissociation (Pka).

A. Intrinsic Solubility

It is recommended to assess the inborn dissolvability at two different temperatures: 37° C for biopharmaceutical evaluation and 4–5° C for good real solidity, increasing transient stockpiling and synthetic stability, and providing great real solidity until more definitive data is available. As a function of PH capacity, the equation may be used to estimate how easily pitifully required and feebly acidic medications will dissolve.

B. Dissociation Constant (PKA):

Numerous drugs are either pitifully basic or acidic compounds, and depending on the pH value, they can exist as ionised or unionised species. The unionised species are more quickly lipid-dissolvable and retained as a result. In this way, the minimal portion of the medicine in the arrangement that is un-ionized is related to the gastrointestinal retention of pitifully acidic or basic drugs. The conditions that smother ionization favor retention. Retention is favoured by smothering circumstances. The pH at the retention site, the ionisation steady, and the lipid solvency of the un-ionized species are the factors that are crucial in the retention of pitifully acidic and fundamental chemicals. Together, these components support the widely accepted pH segment theory. The Henderson-Hasselbalch equation may be used to quickly calculate the overall centralizations of unionised and ionised kinds of a pitifully acidic or basic drug in a system at a certain pH

Feebly acidic mixes with pKa values below 4.3 were quickly absorbed, while those with pKa values between 2.0 and 4.3 were absorbed more gradually. Solid acids with pKa values over 2.4 were hardly ever absorbed. For bases, those with pka values less than 8.5 were absorbed more quickly than those with pka values between 9 and 12, while completely ionised quaternary ammonium compounds were not digested. The degree of ionisation in the pharmacokinetic zone, together with its impact on retention, dispersion, and end, is the devil. The PH of the medium containing the medication is frequently a very important factor in determining the degree of Pka. (6)

B. Partition Coefficient:

The fraction of the unionised compound that is centralised at harmonisation between the organic and fluid phases is commonly represented as a parcel coefficient, or log P, when describing the lipophilicity of an organic molecule.

$Po/w = (C)$ equilibrium oil/water

You might also use $\log P = \frac{(\text{unionized compound})_{\text{org}}}{(\text{unionized compound})_{\text{aq}}}$.

The partition coefficient, sometimes referred to as the dissolving coefficient, is a ratio that is essentially devoid of grouping of weakly organised configurations of a specific solute animal species. It is implied by $\log P = 0$ that the substance is a comparable solvent in both water and the apportioning dissolvable. In the event that the compound has a $\log P = 5$, then, at that point, the compound is multiple times more dissolvable in the apportioning dissolvable. The compound is multiplicatively more dissolvable in the apportioning dissolvable if the compound has a $\log P = 5$ at that point. A $\log P = -2$ indicates that the substance is very hydrophilic and several times more solvent in water. Drugs classified as lipophilic have P upsides that are significantly greater than 1, while hydrophilic drugs have segment coefficients that are significantly lower than 1.

II. METHODS

1. The shake-flask technique
2. Chromatographic technique
3. The probe approach using countercurrent and filters.
4. The Tomlinsons filter probe approach.
5. There are now automated instruments accessible.
6. The micro-electron titration technique

Applications of Partition Coefficient

percentage of particles that are lipophilic. recovery of anti-infection drugs from outdated inventory. medicine extraction from natural liquid for beneficial testing. medication absorption. distribution in emulsion research.

Thermal Effect:

A potential medicinal molecule's response to temperature can be assessed using the heat of the solution. Heat of solution, also known as enthalpy of dissolution or enthalpy of solution, is the heat produced or absorbed when a solute dissolves completely in a sufficient amount of solvent. This is important since a medicinal ingredient's solubility in a particular solvent depends on temperature. Whether the heat of the solution is positive (endothermic) or negative (exothermic) depends on the amount of energy required to break the bonds existing in the solutes as well as the amount of energy created through the creation of solid-solvent bonds (exothermic). The solubility of medications can be increased by raising the temperature of endothermic (positive heat of solution) solutions.

Solubilization:

Limited studies to discover potential solubilization mechanisms should be included in the preformulation research for drug candidates that have either low water solubility or inadequate solubility for the intended solution dosage form.

Techniques to Boost Solubility:

- Alteration of pH
- The Co-Solvency
- Diathermic Constant
- Surfactant-mediated Solubilization
- The complexity
- The hydrotropy
- Drug chemical modification (3)

Chemical Characteristics

Hydrolysis

The labile groups, such lactam ester amide imide, are attacked by nucleophiles. Solvolysis is the term for assault by a solvent other than water. Given that water and API are the two interacting species, it typically behaves according to 2nd order kinetics. Water is present in abundance in aqueous solution, making the reaction first order. The presence of the

hydroxyl ion, hydroxide ion, divalent ion, heat, light, ionic dissolution, solution polarity, and high concentration of the drug are conditions that catalyse the breakdown. (7)

Oxidation

It is the most typical route by which drugs in both liquid and solid forms degrade. Two processes lead to oxidation.

Initial auto-oxidation

Free radical chain reaction 2.

Initiation and Propagation are two steps in the free radical chain process. Oxidation is a natural occurrence that needs oxygen (or another oxidizer), light, and trace metals that can catalyse the reaction. When molecular oxygen is present, the process is often quick and is known as "autooxidation." Chemically, oxidation is defined as the loss of electrons, which necessitates the presence of an electron acceptor, also known as an oxidising agent, such as iron transitioning from ferric (Fe^{3+}) to ferrous (Fe^{2+}), hydroperoxide breakdown, or termination. Oxygen content, light, and heavy metals, especially those with two or more valence states, are factors that impact the oxidation process (iron, nickel, cobalt), temperature, hydroxyl ion, and hydrogen. Reduced oxygen concentration helps prevent oxidation. Since the medicine undergoes oxidative destruction in an aqueous solution, the oxygen concentration can be reduced by boiling the water, keeping the formulation cold and dark, or adding an antioxidant, reducing agent, or chain inhibitor of radical-induced breakdown.

Based on Solubility, there are two types of antioxidants.

- Oil soluble
- It is water soluble. (7)

Racemization

Various pharmacokinetic characteristics (ADME), as well as different pharmacological and toxicological effects, might result from interconversion from one isomer to another. For instance, racemic mixture only has half the activity of L-epinephrine. First order kinetics are used. Temperature, the catalyst, and the presence or absence of light all have a role. (7)

Reduction

It is a substantially more prevalent drug metabolism route. NADPH is necessary for the hepatic microsomes to conduct a variety of reductive chemical reactions. Cytochrome P-450 is the enzyme that catalyses the azo and nitro reduction. Alcohol dehydrogenase converts chloral hydrate to its active metabolite, trichloroethanol. The active metabolite hydrocortisone is produced when prednisolone and cortisone are reduced. Azo dyes are converted to amines in the liver and by the intestinal flora when they are utilised as colouring ingredients in medicinal items or food.

Photolysis

The drug's electrical structure matches the spectrum of natural or artificial light, leading the electron to absorb energy and become excited. This is photodecomposition in action. Being unsteady, they discharge the energy they've taken in and break down the drug to go back to where they started. In the phenomena of photosensitization, molecules or intermediates absorb energy without directly contributing to the process; instead, they pass the information to others who eventually damage cells by producing radicals. Photosensitizer By converting oxygen from its lowest energy to its singlet higher energy state, you may create the powerful oxidant superoxide, which is an anion radical.

Polymerization

It is a persistent chemical interaction between molecules.

In order to create a polymer, more than one monomer interacts.

For instance, the polymerization of breakdown is what causes the glucose solution to darken.

[5- (hydroxyl methyl)furfural] is the product.

For instance, HCHO may polymerize to form para-HCHO, which then crystallises from solution. (3)

Drug-excipient compatibility study using DSC, FTIR

For product stability, high quality, and to prevent incompatibilities during manufacture, the drug-excipient compatibility research is crucial. There are several approaches accessible for the study, including D, S.C., I.R., etc. Comparative Scanning It is common practise to employ calorimetry to monitor or anticipate any physio-chemical interaction between a medicine and an excipient. The study of infrared light absorption and how it changes states from the red end of the visible spectrum to the microwave area is known as infrared absorption spectroscopy. That investigation is entirely dependent on the thermal activity, chemical modifications, and structural alterations of substances. (8)

Methods for Determination DSC

- 1) Thermal Determination
 - a) DSC
 - b) DTA
- 2) Study of Accelerated Stability
- 3) IR Spectroscopy
- 4) Diffuse Reflectance Spectroscopy (DRS)
- 5) Chromatographic (3)

1) Differential Scanning Calorimetry (DSC)

Comparative Scanning Many different physio-chemical interactions between a medication and an excipient can be seen or predicted using calorimetry. It uses a thermal process. When exothermic and endothermic changes take place in a DSC sample, an inert reference is heated independently by a variable heater as the power supply to the sample, thus power is changed to keep $T = 0$.

Sample sizes in these range from 2 to 10 mg, and DSC allows for regulated heating and cooling. Liquids and solids in the form of powder, granules, or foil can be analysed using DSC. Alumina is utilised as the reference material since it is inert. In addition, a pan with a cover is utilised. DSC measurements are often made in a gaseous atmosphere. The DSC method is the most efficient, trustworthy, and requires relatively little sample.

Limitation

1. Very small thermal changes condition DSC cannot be used.
2. It is unable to detect the incompatibility which occur after long term storage.
3. It is important to new result of incompatibility testing with caution.
4. This method is not applicable if test material properties that make data interaction difficult.[8]

Applications

- ✓ We can study DSC of liquid crystals
- ✓ To study the oxidative stability of samples
- ✓ It is used in pharmaceutical and polymer industry as a way of determining melting point.
- ✓ To study drug polymer interaction.
- ✓ To study food dynamics by food science. (10)

2) Fourier Transform Infrared Spectroscopy (FT-IR)

Another useful analytical method for determining compatibility based on the same functional group shift that occurs during the interaction between a medicine and its excipients is FTIR (Joshi et al. 2002, Monajjemzadeh et al 2009). Comparative analysis is done on the placement and structure of functional groups in the spectra of pure drugs and drug-excipient combinations. There is an interaction between the active medication and excipients if there is a band shift and broadening in the spectra (Swathi et al. 2017). (9)

Application of preformulation in dosage form design

1) Preformulation Consideration in Development Of Solid Dosage Forms

The majority of medications today are sold and delivered in solid dosage forms. Nearly 70% of the medications that are delivered are in solid forms. Pharmaceutical businesses choose it because of its great safety and inexpensive price.

The pre-formulation phase of drug development is when the physicochemical characteristics of the drug substance are identified. It is crucial that a drug material be chemically and physically defined before being turned into a dosage form. Pre-formulation influences the selection of the drug candidate, the components of the formulation, and the manufacturing process of the drug product, as well as the creation of analytical methodologies and toxicological testing strategy. The physical and chemical stability of the investigated API has an impact on it. It affects the pharmacological action, delivery method, and route of administration. Studies often focus on amorphous forms, polymorphism, and crystal morphology.

Also evaluated are the API's solubility, salt form, melting point, and dissolution.

Research done before developing solid dosage forms

The following parameters should be investigated:

Organoleptic characteristics

- Clarity
- Surface area, shape, and size of the particles
- Liquidity
- Disintegration
- The membrane's permeability, ionisation constant, and partition coefficient
- Polymorphism and crystal characteristics
- Density, wettability, and so on.
- Studies on stability (11)

Preformulation Consideration in Development of Parenteral Dosage Forms

The word "parenteral" comes from the Greek word's "para" and "enteron," which both indicate intestine. The method of administration is injection.

Among the parenteral dosage form's pre-formulation investigations are

1. Bulk characterisation includes factors such as crystallinity, polymorphism, and particle size.
2. Solubility research, which takes into account the partition coefficient, common ion effect, and pka determination.
3. Solid-state stability and solution stability are both included in the stability analysis.
4. Spectroscopy: The material is characterised using UV, IR, and X-ray diffraction techniques as well as spectrophotometers.
5. Microscopy: In this approach, a sample is inspected under a microscope to learn more about a drug molecule's shape, thickness, particle size, etc.
6. Chromatography: Analytical data are obtained using TLC (11)

III. CONCLUSION

Impacts of Preformulation: Preformulation affects the choice of the drug candidate, formulation elements, manufacturing processes for API and drug products, choosing the best container closure system, development of analytical methods, API retest intervals, API synthetic route, and toxicological strategy. Preformulation studies help establish the scientific basis for the guidance, offer regulatory release, conserve resources during the drug development and evaluation process, raise public safety standards, raise product quality, make it easier to use new technologies, and aid in the development of regulatory and policy decisions. Preformulation studies offer guidelines for formulation development, including modifications to pharmacokinetic and biopharmaceutical characteristics, excipients, content,

and physical structure of the medication. A pharmaceutical preparation cannot be created without first undertaking pre-formulation studies, as this review article's findings from earlier investigations show.

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