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SYSTEMATIC REVIEW ON PREFORMULATION STUDIES AND RECENT TRENDS

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ABSTRACT

Preformulation studies carried out by various research scientists are reviewed. Preformulation begins after literature search of similar type of compounds to provide and understand (i) the degradation process, (ii) any adverse conditions relevant to the drug, (iii) bioavailability, (iv) pharmacokinetics and formulation of similar compound and (v) toxicity. Preformulation influences (a) selection of the drug candidate itself, (b) selection of formulation components, (c) API & drug product manufacturing processes, (d) determination of the most appropriate container closure system, (e) development of analytical methods, (f) assignment of API retest periods (g) the synthetic route of the API, (h) toxicological strategy. 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 for PAT (Process Analytical Technology) (critical process parameters),produce necessary and useful data for development of analytical methods.

KEYWORDS: *Preformulation, partition coefficient, dissolution rate, polymorphic*

I. INTRODUCTION [1,2]

After drug discovery, with a background of physical, chemical and derived powered properties of the drug molecule, the drug has to be formulated in the form that can suitably be administered. The first phase of physic-chemical data collection on drug substances, evaluating potential salts the and excipient suitability, prior to formulation, is known as preformulation. Preformulation is the interface between new drug entity and formulation development. It also provides road map for formulation development. Preformulation involves the application of bio pharmaceutical principles to the physic chemical parameters of the drug with the goal of designing an optimum drug delivery system. Preformulation studies are an important tool early in the development of both API and drug products. Preformulation testing is the first step in the rational development of dosage forms of a drug substance. Preformulation investigations are designed to deliver all necessary data especially physicochemical, physico- mechanical and bio pharmaceutical properties of drug substances, excipients and packaging materials.

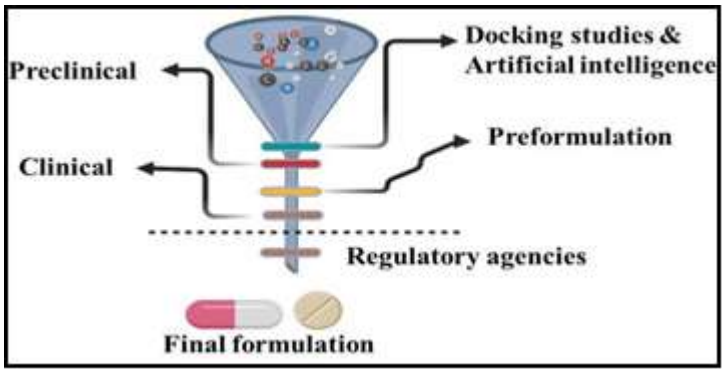


Figure No 01: Stages of Preformulation studies.

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Objectives

1. To develop the elegant dosage forms (stable, effective & safe}
2. It is important to have an understanding of the physical description of a drug substance before dosage form development.
3. It is 1st step in rational development of a dosage form of a drug subt before dosage form development.
4. It generates useful information to the formulator to design an optimum drug delivery system.

Goals

1. To establish the physico-chemical parameters of new drug substance.
2. To establish the physical characteristics
3. To establish the kinetic rate profile.
4. To establish the compatibility with the common excipient.
5. To choose the correct form of a drug substance.

Advantage

1. Preformulation studies help the drug development and evaluation process save resources while bolstering the scientific basis of the guidelines
2. Raise the bar for public safety.
3. Improve the caliber of the product
4. Assist in the adoption of new technology

Disadvantage:

1. Ionosphere is incorrect because resistance results from a spherical particle.
2. Crystals with needle-like shapes have a tendency to obstruct the aperture hole.
3. Compound dissolution in an aqueous conducting media.
4. Particle stratification within the suspension

II. PREFORMULATION PARAMETERS[3,4]

A. Physical characteristics

1. Organoleptic properties
2. Bulk characteristics
   - Solid state characteristics
   - Flow properties
   - Densities
   - Compressibility
   - Crystalline
   - Polymorphism
   - Hygroscopicity
3. Solubility analysis
   - Ionization constant(Pka)
   - Partition co-efficient
   - Solubilization
   - Thermal effect
   - Common ion effect(Ksp)
   - Dissolution
4. Stability studies
   - Solution-state stability
   - Solid-state stability
   - Drug-excipients compatibility

B. Chemical characteristics

- Hydrolysis
- Oxidation
- Photolysis
- Racemization
- Polymerization
- Isomerization

1. **Organoleptic properties:** A typical preformulation program should begin with the description of the drug substance. The color, odour and taste of the new drug must be recorded using descriptive terminology. It is important to establish a standard terminology to describe these properties in order to avoid confusion among scientists using different terms to describe the same property. A list of some descriptive terms to describe the most commonly encountered colors, tastes and odours of pharmaceutical powders is provided in table.

Table No 1: Terminology to Describe Organoleptic Properties of Pharmaceutical Powders.

Colour	Odour	Taste
Off-white	Pungent	Acidic
Cream yellow	Sulfurous	Bitter
Tan	Fruity	Bland
Shiny	Aromatic	Intense

2. **Bulk characteristics:** It is needed to identify all the solid forms that may exist as a consequence of the synthetic stage such as the presence of polymorphs. Bulks properties such as particle size, bulk density, surface morphology may be changed during the development process and to avoid mislead predictions of solubility and stability which depends on a particular crystalline form.

- **Solid state characteristics:** Powders are masses of solid particles or granules surrounded by air (or other fluid) and it is the solid plus fluid combination that significantly affects the bulk properties of the powder.

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It is perhaps the most complicating characteristic because the amount of fluid can be highly variable. Physical characteristics of the particles, such as size, shape, angularity, size variability and hardness will all affect flow properties. External factors such as humidity, conveying environment, vibration and perhaps most importantly aeration will compound the problem.

- **Flow properties:** The flow properties of powders are critical for an efficient tableting operation. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. If a drug is identified at the preformulation stage to be "poorly flowable," the problem can be solved by selecting appropriate excipients. In some cases, drug powders may have to be precompressed or granulated to improve their flow properties.
- **Angle of Repose**: The maximum angle which is formed between the surface of pile of powder and horizontal surface is called the angle of repose. For most pharmaceutical powders, the angle-of repose values range from 25 to 45°, with lower values indicating better flow characteristics.

a) Densities

The ratio of mass to volume is known as density

Types of density:

- Bulk density: It is obtained by measuring the volume of known mass of powder that passed through the screen.
- Tapped density: It is obtained by mechanically tapping the measuring cylinder containing powder.
- True density: It actual density of the solid material.
- Granule density: may affect compressibility, tablet porosity, disintegration, dissolution

b) Compressibility: "Compressibility" of a powder can be defined as the ability to decrease in volume under pressure and "compactability as the ability of the powdered material to be compressed into a tablet of specified tensile strength.

c) Crystallinity: Generally most of drugs exist in solid state. Very few are in liquid state like valproic acid and even less in gaseous form like some general anesthetics. A crystal structure is a unique arrangement of atoms in a crystal. Physical properties affected by the solid-state properties can influence both the choice of the delivery system and the activity of the drug, as determined by the rate of delivery. Chemical stability, as affected by the physical properties, can be significant. A crystalline particle is characterized by definite external and internal structures

The various crystal forms are categorized into six distinct crystal systems based on symmetry.

- cubic (sodium chloride)
- tetragonal (urea)
- hexagonal (iodoform)
- rhombic (iodine)
- monoclinic (sucrose)
- triclinic (boric acid)
- Trigonella (crystal meth

d) Polymorphism: Many drug substances can exist in more than one crystalline form with different space lattice arrangements. This property is known as polymorphism. The different crystal forms are called polymorphs. When polymorphism occurs, the molecules arrange themselves in two or more different ways in the crystal; either they may be packed differently in the crystal lattice or there may be differences in the orientation or conformation of the molecule at the lattice sites.

Methods to Identify Polymorphism

- Optical crystallography
- Hot 0stage microscopy
- X- Ray Diffraction method
- NMR technique
- FTIR technique.
- Microcalorimetry
- Thermal methods
- Melting point determination

e) Hygroscopicity: Many compounds and salts are sensitive to the presence of water vapour or moisture. When compounds interact with moisture, they retain the water by bulk or surface adsorption, capillary condensation, chemical reaction and, in extreme cases, a solution (deliquescence). Deliquescence is where a solid dissolves and saturates a thin film of water on its surface. It has been shown that when moisture is absorbed to the extent that deliquescence takes place at a certain critical relative humidity, the liquid film surrounding the solid is saturated. This process is dictated by vapor diffusion and heat transport rates.

Hygroscopicity can be classified as:

- Deliquescent
- Very hygroscopic
- Hygroscopic
- Non-hygroscopic

Class I: Non-Hygroscopic At relative humidity below 90%, there are almost no moisture increases. Furthermore, after a week of storage at above 90% relative humidity (RH), the rise in moisture content is less than 20%.

Class II: Mildly Hygroscopic At relative humidity below 80%, virtually little moisture increases. The increase in

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moisture content after a week of storage at above 80% RH is less than 40%.

Class III: Moderately Hygroscopic At relative humidity below 60%, moisture content does not grow more than 5% after storage. The rise in moisture content after a week of storage at above 80% RH is less than 50%.

Class IV: Very Hygroscopic At relative humidity as low as 40–50 percent, moisture might increase. After a period of storage, the moisture content of the product increases.

3. Solubility Analysis: An important Physical-chemical property of a drug substance is solubility, especially aqueous solubility. A drug must possess some aqueous solubility for therapeutic efficacy in the physiological P H range of 1 to 8. For a drug to enter into systemic circulation, to exert therapeutic effect, it must be first in solution form. If solubility of drug substance is less than desirable, than consideration must be given to increase its solubility. Poor solubility (< 10mg/ml) may exist incomplete or erratic absorption over PH rang 1-7 at 37°C. However, knowledge of two fundamental properties is mandatory for a new compound

i) Intrinsic solubility (Co)
ii) Dissociation constant (Pka).

a) Ionization Constant(PKA)

Many drugs are either weakly acidic or basic compounds and, in solution, depending on the pH value, exist as ionized or un-ionized species. The un- ionized species are more lipid-soluble and hence more readily absorbed. The gastrointestinal absorption of weakly acidic or basic drugs is thus related to the fraction of the drug in solution that is un- ionized. The conditions that suppress ionization favor absorption. The factors that are important in the absorption of weakly acidic and basic compounds are the pH at the sit e of absorption, the ionization constant, and the lipid solubility of the un- ionized species.

Determination of Pka:

- Potentiometric Titration
- Spectrophotometric Determination
- Dissolution rate method
- Liquid-Liquid Partition method

b) Partition Coefficient:

The lipophilicity of an organic compound is usually described in terms of a partition coefficient; log P, which can be defined as the ratio of the concentration of the unionized compound, at equilibrium, between organic and aqueous phases:

Methods of finding Partition coefficient:

- Shake-flask method
- Chromatographic method.
- Counter current and filter probe method.
- Tomlinson's filter probe method.
- Microelectrometrictitratation method
- Automated instrument is now available.

c) Solubilization: For drug candidates, with either poor water solubility or insufficient solubility for projected solution dosage form, preformulation study should include limited experiments to identify possible mechanism for solubilization.

Methods for Increasing Solubility:

- Change in pH
- Co-Solvency
- Dielectric Constant
- Solubilization by Surfactant
- Complexation
- Hydrotropy
- Chemical Modification of drug

d) Common Ion Effect:

A common interaction with solvent, which often overlooked, is the common ion effect. The addition of common ion often reduces the solubility of slightly soluble electrolyte. This salting out results from the removal of the water molecule as the solvent due to competing hydration of other ions. So, weakly basic drug which are given as HCL salts have decreased solubility in acidic (HCL) solution.

e) Dissolution: In many instances, dissolution rate in the fluids at the absorption site, is the rate limiting steps in the absorption process. This is true for the drug administered orally in the solid dosage forms such as tablet, capsule, and suspension as well as drug administered I.M. in form of pellets or suspension

f) Stability studies

- **Solid State Stability Studies:** Solid state reactions are much slower and more difficult to interpret than solution state reactions, due to a reduced no. of molecular contacts between drug and excipient molecules and to the occurrence of multiple phase reactions.
- **Solution State Stability Studies:** It is easier to detect liquid state reactions as compared to solid state reactions. For detection of unknown liquid incompatibilities, the program set up is same as solid dosage forms. Following conditions be evaluated in studies on solutions or suspensions of bulk drug substances:
  - Acidic or alkaline pH.
  - Presence of added substances- chelating agents, stabilizers etc.
  - High Oxygen and Nitrogen atmospheres
  - Effect of stress testing conditions

g) Drug-Excipient Compatibility Studies: In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug-excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may already

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be in existence for known drugs. For new drugs or new excipents, the preformulation scientist must generate the needed information. A typical tablet contains binders, disintegrants, lubricants, and fillers. Compatibility screening for a new drug must consider two or more excipients from each class. The ratio of drug to excipient used in these tests is very much subject to the discretion of the preformulation scientist.

Analytical techniques used to detect Drug Excipient Compatibility:

1) Thermal methods of analysis
   I. DSC- Differential Scanning Calorimetry
   II. DTA- Differential Thermal Analysis
2) Accelerated Stability Study
3) FT-IR Spectroscopy
4) DRS-Diffuse Reflectance Spectroscopy
5) Chromatography
   I. SIC-Self Interactive Chromatography
   II. TLC-Thin Layer Chromatography
   III. HPLC-High Pressure Liquid Chromatography
6) Miscellaneous
   I. Radiolabelled Techniques
   II. Vapour Pressure Osmometry
   III. Fluorescence Spectroscopy

B. Chemical characteristics

1. **Hydrolysis**: It involves nucleophilicattack of labile groups eg: lactam ester amide imide. When the attack is by the solvent other than water, then it is known as solvolysis. It generally follows 2nd order kinetics as there are two reacting species, water and API. In aqueous solution, water is in excess so the reaction is 1st order. Conditions that catalyze the breakdown are Presence of hydroxyl ion, hydride ion, divalent ion and heat, light, ionic hydrolysis, solution polarity and ionic strength, high drug concentration. Hydrolysis can be prevented by Adjusting the PH.As most of the potent drugs are weakly acidic or weakly basic in nature.
2. **Oxidation:** It is a very common pathway for drug degradation in liquid and solid formulations. Oxidation occurs in two ways
   1. Auto- oxidation
   2. Free radical chain process.

   Antioxidants are of two types based on Solubility. Oil soluble and Water soluble. Oil Soluble Antioxidants are Free radical acceptors and inhibit free radical chain process eg: hydroquinone, propylgallate, lecithin whereas Water soluble Antioxidants Oxidizes itself and prevents oxidation of drug Eg: sodium metabisulphate, sodium bisulfate, thioglycolic acid, thioglycerol.
3. **Reduction:** is a relatively more common pathway of drug metabolic process. Hepatic microsomescatalyze diverse reductive chemical reaction* and require NADPH for this purpose. Azo and nitro reduction is catalyzed by cytochrome P450.Chloral hydrate is reduced to its active metabolite trichloroethanol by alcohol dehydrogenase. Reduction of prednisolone and cortisone results in the formation of their active metabolites hydrocortisone. Azo dyes used as coloring agents in pharmaceutical products or food are reduced to form amines in the liver and by the intestinal flora.
4. **Photolysis:** Electronic configuration of drug overlaps with the spectrum of sunlight or any artificial light where energy is absorbed by the electron resulting in excitation. As they are unstable, they release the acquired energy and return to the ground state by decomposing the drug. The phenomenon where molecules or excipients which absorb energy but do not participate themselves directly in the reaction but transfer the energy to others which cause cellular damage by inducing radical formation is known as photosensitization.

III.PREFORMULATION CONSIDERATION IN DEVELOPMENT OF SOLID DOSAGE FORMS[4,5]

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 formsThe following parameters should be investigated:

Organoleptic characteristics

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

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IV. PREFORMULATION CONSIDERATION IN DEVELOPMENT OF PARENTERAL DOSAGE FORMS [6,7]

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

V. RECENT NEW INNOVATION IN PREFORMULATION STUDIES[8,9]

1. Advanced Imaging Technologies

These technologies, such as Nano tomography and tetrahertz spectroscopy, can help characterize amphorus solid dispersion (ASDs) at sub micro level. The two main aspects of preformulation assessment are saturation solubility and stability, which inherently depend on active pharmaceutical ingredient's (API's) properties and the added excipients used in the formulation. A tremendous amount of research has been conducted in the past few decades, which mainly emphasized the amorphous advantage of APIs, the selection of proper excipients, and the prediction of the physical stability of ASDs. In the past, traditional methods employed a large amount of API material to determine these properties. Considering recent advances, several material-sparing methods were developed for initial preformulation assessment. As specified in the available literature, the difference in free energy is one of the notable properties that helps to understand the advantage of solubility for the amorphous form over the crystalline form. The higher the free energy of the amorphous form, the better its solubility.

2.SUBA™ Technology (Via Spray Drying Process):

The oral bioavailability of poorly soluble active ingredients is enhanced by the patented SUBATM technology, with superior bioavailability. The main objective behind developing this technology relies on improving bioavailability, reduction in dose, mitigating inter and intra-patient variation, enabling more predictive clinical response based on dose, and obtaining clinical levels of activity in the blood stream. For the very first time, this process was used on the well-known, poorly soluble compound BCS class II compound Itraconazole. The FDA-approved prescription drug Itraconazole has a long history of safe and successful usage in treating severe fungal or yeast infections in people. The novel SUBATM process produces amorphous Itraconazole dispersed in a polymer matrix instead of a conventional crystalline form. This approach utilizes spray-drying with enteric polymer to increase active ingredient solubility in the gastrointestinal system to achieve "super bioavailability" in comparison to traditional formulations. In this technology, API was spray-dried using a novel amorphous pH-dependent enteric polymer HPMC Phthalate.

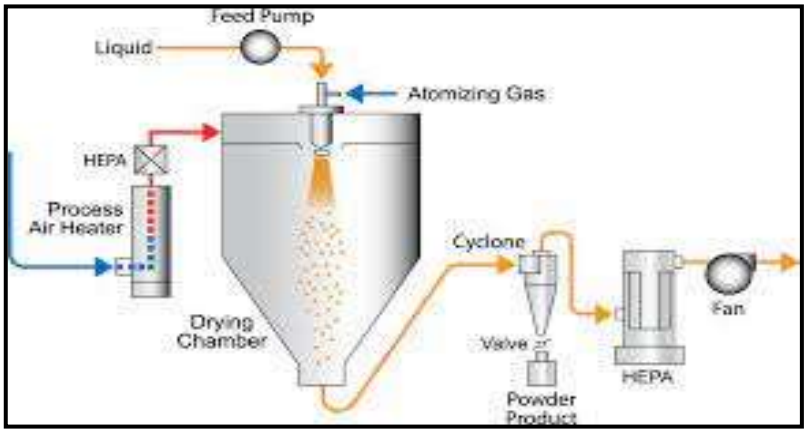


Figure No 2: SUBA™ Technology (Spray Drying Process)

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3.Deep Learning Algorithms: These algorithms can be used be to predict stroage stability tablet defects, particle flow ability, and drug dissolution profiles.

Applications

- Predicting material properties
- Optimizing formulation composition
- Identifying potential toxicities
- Designing controlled release systems
- Modeling pharmacokinetics and pharmacodynamics

Benefits

- Improved accuracy and efficiency
- Ability to handle complex data
- Enhanced decision-making
- Reduced experimental costs and time
- Better understanding of complex relationships

Materials

- Small Molecules (APIs, Excipients)
- Polymers (Natural, Synthetic)
- Proteins (Therapeutic Proteins)
- Peptides (Therapeutic Peptides)
- Organic Compounds (Intermediates, Impurities)
- Biomaterials (e.g., collagen, gelatin)
- Nanomaterials (e.g., nanoparticles, nanotubes)

4.In Silico Tools

These tools can be used to make molecular stimulation predictions and understand interaction between formulation components at a molecular level.

Benefits

- Reduced experimental costs and time
- Improved accuracy and reliability
- Enhanced decision-making
- Increased productivity
- Better understanding of complex relationships

Applications

- Predicting drug solubility and bioavailability
- Optimizing formulation composition
- Modeling pharmacokinetics and pharmacodynamics
- Identifying potential toxicities
- Predicting stability and shelf-life

5.3D Printing and Additive Manufacturing

3D printing and additive manufacturing are revolutionizing preformulation technology by enabling:

Benefits

- Personalized medicine: patient-specific dosing and formulation
- Complex geometries: creating intricate structures for controlled release
- Multi-material printing: combining different materials for optimized performance
- Rapid prototyping: accelerating formulation development and testing
- Increased precision: improving dosage accuracy and uniformity

Applications

- Tablets and capsules: printing customized dosage forms
- Implants: creating complex geometries for sustained release
- Transdermal patches: printing precise drug-loaded patches
- Ophthalmic inserts: creating customized inserts for eye care
- Inhalation devices: printing complex structures for pulmonary delivery

Materials

- Polymers (e.g., PLA, PVA)
- Pharmaceuticals (e.g., APIs, excipients)
- Ceramics
- Metals
- Biomaterials (e.g., collagen, gelatin)

VI.ROLE OF ARTIFICIAL INTELLIGENCE IN PREFORMULATION STUDIES [10]

A large, multidisciplinary discipline known as artificial intelligence gives machines the ability to think, learn, and reason. Artificial intelligence has two subsets: machine learning and deep learning. Scientists frequently integrate computer-added drug design tools with artificial intelligence, powered decision-making at crucial stages of drug discovery programs Deep learning-based artificial neural networks and machine learning-based expert systems are currently very well-liked for predicting interactions between drugs and their targets as well as physicochemical properties, quality, stability, toxicity, safety, and biological activity of formulations. Medical diagnostics, epidemic breakouts, and individualized treatments are all examples of how AI is used in the healthcare industry. The healthcare industry pursues exceptional advancements with the help of AI tools for example Adaptive neuro-fuzzy inference system (ANFIS) performance is satisfactory for excipients selection hence the AI-based algorithms made drug research simple and shorten the drug discovery and development timelines. In-silico models found their way as successful tools for determining drugs' aqueous solubility's. These factors include molecular size, molecular shape, and hydrogen bonding capacities.

VII.CONCLUSION[11]

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.

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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 preformulation studies, as this review article's findings from earlier investigations show.

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