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Pre-Formulation stuilieso‘A novel drug candidate’or £Tral dosage From Development

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Abstract

Pre-formulation studies are a critical and foundational component of the pharmaceutical product development process. These studies involve the comprehensive evaluation of the physicochemical, mechanical, and biopharmaceutical properties of a novel drug candidate prior to the formulation of a suitable dosage form. In the development of oral drug delivery systems, such characterization is particularly important due to the complexities associated with solubility, stability, bioavailability, and drug-excipient compatibility.The present work focuses on conducting pre-formulation studies for a novel drug candidate intended for oral administration. Key parameters investigated include solubility profile, pKa, partition coefficient (log P), polymorphism, hygroscopicity, melting point, and thermal behavior. These attributes were assessed using a range of analytical tools such as differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), potentiometric titration, and high-performance liquid chromatography (HPLC). Furthermore, drug-excipient compatibility was evaluated under stress conditions to identify any potential chemical or physical interactions that may impact formulation stability.The findings from these studies provide vital insights into the drug’s behavior under physiological and storage conditions, guiding the selection of appropriate excipients and formulation approaches. For instance, poor aqueous solubility identified in the candidate suggested the need for solubility enhancement strategies such as salt formation or solid dispersion. Likewise, stability testing under varying conditions helped determine optimal storage parameters and potential degradation pathways.In conclusion, the pre-formulation phase plays a pivotal role in de-risking the development process, optimizing formulation design, and ensuring regulatory compliance. The systematic understanding of a drug's physicochemical characteristics not only accelerates the development timeline but also enhances the

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Keywords:
Pre-formulation studies; Novel drug candidate; Oral dosage form; Solubility; Stability; Drug-excipient compatibility; Physicochemical characterization; Bioavailability; Partition coefficient; Polymorphism.

I. INTRODUCTION

Before beginning preformulation studies, it's important to understand the drug's properties, how effective it is compared to similar products, and the type of dosage form being considered. A literature search should provide infonnation about the drug's stability and how it breaks down. You also need to decide on the method of dnig administration and look into existing research about how sinular drugs are formulated, their absorption into the body, and how they are processed. '

Once a drug that shows promising pharmacological activity is found, a team made up of experts from different areas is responsible for making sure the drug is developed in its best molecular form. When the flrst good quality sample of the new drug is ready, experiments should be done to identify any potential issues. If a problem is found, the team should decide on the best way to modify the molecule to improve its properties. These changes could involve making salts, prodnigs, solvates, polyinorphs, or even creating ncw analogs. Thc main arcas of prcforinulation rcscarch arc as follows.

l.Bulk Charactcrization
4 Crystallinity and polymorphism
V Hygroscopicity
4 Particle size
V Bulk density
4 Powder flow properties

2. Solubility Analysis
V Ionization constant - pKa H pH solubility profile
F Common Ion Effect - Ksp
4 Thermal Effects P Solubilization
4 Partition Coefficient
k Dissolution

3. Stability Analysis
4 Stability in Formulations
4 Solution Stability
k pH Rate Profile
k Solid State Stability
4 Bulk Stability
k Compatibility

forms identified, and there is a high chance that new polymorphs could appear. The bulk properties of these solid forms, such as particle size, bulk density, and surfacc appearance, are also likely to change during the development process.

Crystallinity and polymorphism: Elcmcnts can cxist in two or more different forms, known as allotropes. For example, carbon can exist as diamond, which has a cubic (tetrahedral) lattice structure, or graphite, which has a hexagonal layered structure. Polymorphs have the same properties when they are in liquid or gaseous states, but they behave differently when they are in solid fonn. Different polymorphs of a compound arc gcncrally diffcrcnt in structure and propcrtics, similar to how diffcrcnt compounds can form different crystal structures.

Furthermore, polymorphism is vcry common, cspccially among ccrtain structural groups. The phcnoincnon of polymorphism is quite common in organic molecules, and many drugs can crystallize into different polymorphic forms

Molecules Different forms of the same drug, known as polyinorphic forms, can be interesting for drug developers because their physical and chemical properties, like melting point, density, stability, and especially solubility, might offer improvements over the original form.

Generally, the solubility of less stable polymorphs is higher than that of a more stable form, which could, at least in theory, help solve problems with how well a drug is absorbed by the body

However, it has been shown that dif'ferences in solubility between different

polymorphs are usually not more than a factor of two, or sometimes up to five ^ [7] So, while a polyinorph might offer a small increase in solubility compared to the original compound, this benefit might be canceled out by the fact that it is less stable. Therefore, there may not be any real advantage in using this polymorph instead of the original. In fact, lcss stablc and morc soluble forms often changc into thc morc stable form relatively quickly.

The prcscncc of certain excipients or specific chemical and production processes can speed up this change to the solid form. This transition usually follows the relative stability of the less stable forms Solvates, which are sometimes incorrectly called pseudopolymoiphs, are crystalline solids that include a certain amount of solvent within their structure [I'] . When the solvent is water, it is called a hydrate"

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'Using solvates in drugs is generally not preferred because the presence of organic solvents can be harmful. Regulations set limits on how much of these solvents can be present
A and E college of Pharmacy, Samastipur cry e c es e so u ty a ow qu a g sso es ca ary s g ca y between different solvates, especially between hydrates and the anhydrous form. Hydrates may dissolve faster or slower than the anhydrous form, though more often they dissolve more slowly [12]

Objectives
k To understand the physical and chemical features of a new drug candidate
V To check how well it works with typical ingredients used in medicines
4 To see how stable it remains under different enviromnental situations
4 To create a solid base of information for developing an oral medicine form

Pre-fomiulation studies arc essential to cnsurc the safcty, efficacy, and manufacturability of pharmaceutical dosage forms. They serve as a foundation for rational drug design and selection of suitable excipients and processing methods.
Aulton and Taylor [' 3 emphasized that understanding a drug's physicochcmical profile allows for the prediction of its behavior during formulation and storage.
Martin ['[4] highlighted that solubility, stability, and permeability are key attributes that influence oral bioavailability. Moreover, the Indian Phannacopoeia

l I provides
standard methodologies for assessing these characteristics.
Studies on poorly soluble drugs, such as BCS Class II compounds, have shown that enhancing solubility through solid dispersions, complexation, and particle size reduction can significantly improve oral absorption [' " Cyclodextrin inclusion complexes are another strategy explored by Loftsson and Brewster to improve the aqueous solubility of hydrophobic drugs.
Additionally, compatibility studies are crucial to avoid adverse interactions between the drug and excipients, which could lead to instability or reduced efficacy ['[7] Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared Spectroscopy (FTIR) arc commonly uscd techniques for this purpose.

In summary, thc litcraturc undcrscorcs thc multifacctcd rolc of prc-formulation in pharmaccutical dcvclopmcnt, offcring insights into drug behavior that arc instrumental for successful formulation design.

II. PHYSICOCHEMICAL PARAMETERS

'• '•

i. Organolcptic propcrtics:
ii. Bulk characterization studies:
.• Crystallinity and polymorphism
â• Hygroscopicity
•t• Fine particle characterization
suens ty
edl
ntr
•• Powder flow properties ü• Compression properties t• Physical description

iii. Solubility analysis:
ü• Intrinsic solubility determination ü• pka determination
ü• Partition coefficient ü• Dissolution studies ü• Common ion effect
iv Stability analysis:
ü• In toxicology formulations
.• Solution stability ü• Solid state stability
i Organoleptic properties Color:

The product should look unattractive to the eye, and this can bc dctcrmincd cithcr through special equipment or by visual methods that vary between batches. It is useful to keep records of early batches and create specifications for future production. If the color is considered undesirable, the product can be coated with different colors.
Odor and taste:
Use a less soluble version of' an unpleasant medicine or mask it with flavors, excipients, coatings, and so on. Medicînes that irritate the skin should be handled with care. Excipients such as flavors, colors, and dyes can affect the product's stability and how well it is absorbed by the body. Possible colors include off-white, cream yellow, brown, or glossy. Odors may bc strong, wcak, fmity, fragrant, sulphurous, pungcnt, or odorlcss. Possible tastcs includc acidic, bittcr, bland, strong, swcct, or tastclcss.

ii. **Bulk Characterization studies**
All solid forms that could occur from the synthetic process, such as the presence of polymorphs, must bc

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idcntificd. During dcvclopmcnt, bulk properties like particlc sizc, bulk dcnsity, and surfacc shapc can bc changcd to prescrit incorrcct prcdictions about solubility and stability, which depend on a specific crystalline structure.

iü .Crystallinity and polymorphism

Crystallinity refers to the structure of a conipound in liquid or vapor form, which disappears. lt falls into the categoiy of internal structures like cubic, tetragonal, A and E college of Pharmacy, Samastipur**ed I nts** exago a r o c e c an a so st ong a ts e p a y nee e a u a p s a c bladed, and so on. Changing the chemical form, such as making a salt, affects both internal structure and crystal habit. Changing internal structures also affects crystal habits. Diffcrcnt polymorphs can be formcd through melting and solidifying after crystallization using various solvents. Whcn water is used as the solvent, it is called "hydrates. " [20]

Crystalline materials have atoms arranged in three dimensions in predictable, repeating patterns. Amorphous materials, on the other hand, contain metal, mineral, or molecules arranged randomly without a regular atomic stnicture. These materials diffcr in thcir physical and chcmical propcrtics, such as mclting point, dcnsity, vapor pressure, X-ray diffraction, color, crystal shape, hardness, solubility, dissolution rate, and bioavailability. It is important to idcntify the polyinorph that rcinains stablc at room temperature during preformulation. For example, there are three different forms Chlorainphenicol exists in three forms: A, B, and C. Among these, form B is the most stable and preferred. Riboflavin also has three forms: I, II, and III. Form III is significantly more soluble in water than form I. When the temperature is below the melting point of either polymorph, different forms can change into each other, and this transformation can be reversed at a specific temperature, similar to how sulfur behaves.

In pharmaceutical use, polymorphism can affect the properties of a drug. For example, during the suspension phase, changes in crystal size or caking can happen when an unstable form transforms into a more stable one. An example is oxyclozanide, an anthelinintic.

In creams, a gritty texture may develop due to crystal growth caused by a phase change. In suppositories, changes in the polymorphic form can lead to problems like the product not melting properly after use or melting too early during storage. This is similar to thc issuc seen with thc "basc" used in Thcorcm oil suppositorics. Charactcrizing solids involves confirming that thc solid is thc **cxpcctcd** chemical compound, describing its intcmal structure and crystal shape, dctcrmining how many polymorphic forms might exist and their stability, and checking for the presence of an amorphous form, among other things.

a. Hygroscopicity: Many medicine ingredients can absorb moisture from the air. This is the amount of water that a certain weight of dry material can take in when it's in balance with the air at a specific temperature. These are categorized into three types: Efflorescent, which is a substance that loses water to form a less hydrated form or become completely diy, Deliquescent, which absorbs so much moisture that it dissolves in the air, and Hygroscopic, which stays in a balance with water. The humidity level in the environment plays a big role in this process. Methods like Karl Fisher, gravimetric, TGA, or gas chromatography can bc uscd to mcasurc it. Any changes in moisturc content can affcct the stability, flow, coinpatibility, and othcr qualities of the medicine.

b. Cliaracterization of fine particles: The size of particles influences how well a medicine works, how evenly it mixes, its taste, texture, color, and how stable it is. It also affects how quickly it dissolves in the body. Particle size can be influenced by things likc how well the powdcr flows and how fast it settlcs. It's important to undcrstand how the sizc of the drug's particlcs might affcct the final product carly on. Techniques like using a light microscopc with a grid, sedimentation, scanning, a Coulter counter, and calculating thc surfacc arca using thc BET nitrogcn adsorption method can be used to measure particle size and distribution.

c. Bulk density: Knowing the true and bulk density of the drug helps in determining the final size of the dosage form. This is especially important for medicines with low potency, as they can make up most of the granulation or tablet. When there are density issues, they are often fixed quickly through processes like milling or reformulation. The bulk density can vary depending on how the drug is crystallized, milled, or formulated. This can also impact how the powder flows. It's important for the size of high-dose capsules and for ensuring even mixing in low-dose formulations where the drug and other ingredients have different densities.

d. Powder flow characteristics: Good powder flow is important for tablet inaking. So, duràig the

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preformulation stage, especially if a large dose is expected, it's important to assess how well the powder flows. Powders can either clump together or flow freely. Factors like particle size, density, shape, static electricity, and inoisture levels can affcct how wcll thc powdcr flows. Characteristics like Carr's index, Hausner ratio, angle of rcposc, rhcology, and thixotropy arc uscd to mcasurc this.

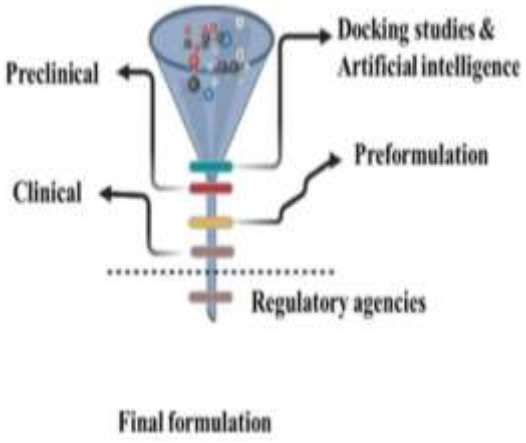
c) Compression propcrtics: lt's possible to test a ncw drug's compression propertics, such as elasticity, plasticity, how it breaks, and how it sticks to the machine parts, using small ainounts of the dnig. Thèse properties help in choosing the best ingredients for the fuial formulation.

f) Physical characteristics: Thèse can be observed or measured using tools or the naked eye, based on the size, shape, and appearance of the substance.

dissolve. The drug needs to be in solution for it to enter the bloodstream and have a therapeutic effect. Drugs that don't dissolve well are often not absorbed properly. For a substance to dissolve, the forces between its molecules and the solvcnt must bc stronger than the forces between its own molecules.

h)Pka Determination: The pH-partition theory is based on how the dissociation constant, lipid solubility, pH at the absorption site, and the properties of different medications interact during absorption. Potentioinetric titration is commonly used to find the dissociation constant or pKa. These days, most medications are either weak organic acids or bases. It's important to understand cach substance's unique ionization or dissociation behavior because the level of ionization a substance undergoes when it comes into contact with mcmbranc barricrs grcatly affccts how wcll it is absorbcd. The ionization level of a drug is determined by its pKa, or dissociation constant, as well as the pH of the solution in which it is delivered to the biological membrane, whether that solution is acidic or basic. The term "pKa" comes from this understanding.

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



Figur No. 01 Stagcs of prcformulation studies

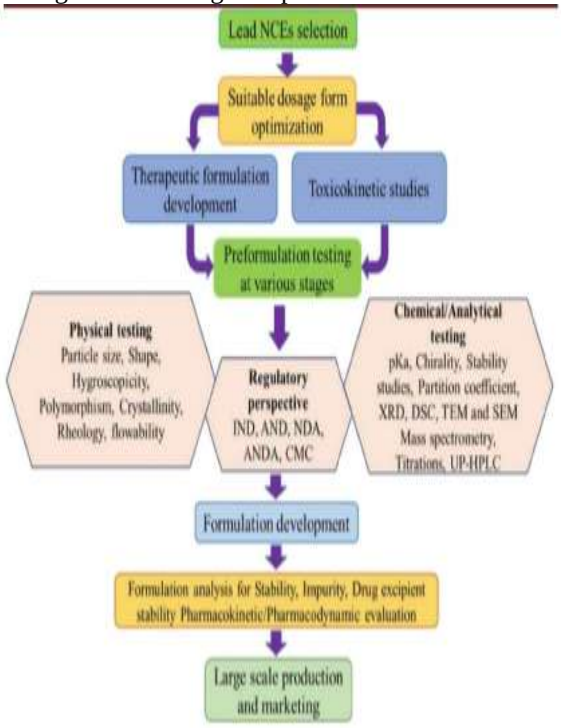


Figure No. 02 Preformulation study schematic representation.

III. OVERVIEW OF PREFORMULATION STUDIES

1. Preformulation studies: an essential concept in formulation development Preformulation is a key concept in creating the final dosage form of a drug, aimed at targeting a specific disease. Therefore,

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preformulation studies are conducted to gather usable data and uncover important information that innovators and professionals in the industry can use to develop dosage forms that are stable, ef'1'ective, and saie tor patients. lt is the first major step in creating the final drug product. This process involves understanding the physical and chemical properties of the drug and how it mixes with appropriate additives to design an effective, safe, and stable drug delivery system [21]. It is also important to havc data on the basic properties of thc drug molecule, its stability, pharmacokinetic data for lead compounds or similar molecules already on the market, bioavailability, and the most suitable route of administration before starting prefonnulation studies [22]. Additionally, it includes optimizing the active pharmaceutical ingredient (API) to change its dissolution and solubility, for example, using salt production techniques to improve solubility (such as Diclofenac sodium salt) and prodrug approaches (like Levodopa and Enalapril). It also determines the relationship between physical and chemical properties and the kinetic behavior of a ncw drug and investigates various aspects such as the bulk properties, solubility, stability, and compatibility of thc drug with excipients [23,24]. Biotherapeutics, such as vaccines, proteins, and peptides, face many challenges when being developed into a drug candidate, depending on the unique physical, chemical, and biological characteristics of the biotherapeutic molecule, including stability, viscosity, manufacturability, bioavailability, and immunogenicity. To address these challenges, prefonnulation studies are perfonned on monoclonal antibodies, peptides, and proteins bcforc final dosage fonns arc dcvclopcd. Thcsc studics include analyzing thc primary, secondary, and tcrtiary structures of thc macromolcculcs and tcsting for types and concentrations of contaminants. Then, various screening procedures arc used to cvaluate thc functions of thc compounds, along with research on their solubility and stability [25]. As a result, it paves the way for creating dosage forms that are wellreceived by patients, stable, safe, effective, and affordable.

2. Pharmaceutical drug product life cycle In today's fast-paced world, driven by the internet and artificial intelligence, the pharmaceutical industry has seen rapid changes. Drug discovery and data mining tools have significantly sped up the industrial process. Scientists in various research and development teams in the pharmaceutical industry are working closely to generate new drug concepts and brand development for the industry z j. with the use of modem data science tools, technology such as discovery biology, medicine research and development, production, and validation is transforming the entire product life cycle. Industrial operations must ensure that the process meets the required specifications and validated limits, both for isolated process parameter controls and comprehensive production controls once the process is validated. **ICH** recommendations, specifically **ICH** -Q 12, cmphasizc the technological and legal aspects of pharmaceutical product lifecycle management [27].

Key funding from product life cycle management:

4• Provide in-depth and detailed knowledge about the product to the company's product pipeline.

4• Continuously detennine productspecifications within the regulatory framework and understand the product specifications.

maintenance and corrective actions.

4• Manage post-commercialization data covering regulatory approvals, change management, data from other sources, and sales.

3. Prcformulation:

Objectives

The preformulation tool plays a key role in helping make important decisions during the dnig discovery and development process. Having a deep understanding of the physical and chemical properties of a drug and how these affect its behavior in the body helps in choosing potential lead molecules and identifying possible challenges in drug delivery [28, 29]. 4• This tool helps generate the necessary information needed to develop drugs that are effective, safe, easy to use, stable, and can be made in large quantities. 4• It helps build a clear undcrstanding of thc physical and chcmical features of new drug substances before they are turned into the final form of medication. •t• The physical properties of a drug detennine the best way to present it, such as as a tablet, capsule, or liquid. 4• Choosing the right excipients and additives that work well with the drug substance is also an important part of preformulation.

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4. Preformulation:
Goals Understanding the physical and chemical properties helps determine if a drug candidate is suitable for development. It helps identify how the drug behaves in the body, including how it is absorbed, distributed, and removed. It also helps find out if the drug works well with commonly used excipients. Identifying these issues is crucial for creating successful pharmaceutical products.
5. Preformulation study challenges and mitigation There are many obstacles that can make it difficult to develop a successful drug product. This is why scientists in pharmaceutical development often ask questions like: Why do 90% of drug development projects fail during the clinical stage, and what can be done to prevent that? [30]. There are several basic challenges when evaluating a drug candidate during the research and development phase, such as the drug's market potential, poor planning for the project, difficulties before submitting for approval, long development timelines, high costs of drug product development, and the need for proper regulatory filing[31]. Drug development starts from discovery and is a long and expensivetoxicity (30%), lack good drug-like properties and strategic planning (10—15%), or have limited business opportunities (10%). Some of the challenges in drug discovery and development are listed in Table 1 [32].

s. No.	Challenge	Description	Strategies to Overcome
1	Poor Aqueous Solubility	Limits drug dissolution and absorption	Use of solubilizers, solid dispersions, nanocrystals, salt formation, lipid-based systems
2	Low Permeabilit y	Reduces transport across biologiCal membranes	Use of permeation enhancers, prodrugs, carrier systems (e.g., liposomes)
	Chcmica1 Instability	Degradation due to pH, light, oxygcn, or temperature	Antioxidants, pH adjustment, protective packaging, refrigeration
4	Polymorphi SIH	Variable solubility, dissolution rate, and stability among different fonns	Polymorph scrccning, usc of the most stable or bioavailable form
5	Hygroscopi city	Moisture uptake leads to degradatioR or formulation failure	Use of desiccants, moisture-barrier packaging, dry granulation
6	Drug- Excipient lncompatibi lity	Chemical or physical interactions leading to instability or reduced efficacy	Compatibility tcsting, cxcipicnt optimization, usc of protective coatings

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7	Poor Flow Properties and Compressib ility	Affects tablct uniformity and manufacturability	Use of glidants, granulation (wet/dry), particle size optimization
		ineffectiveness	
9	First-Pass Metabolism	Drug degradation in liver before reaching systemic circulation	Use of prodrugs, alternative routes (e.g., sublingual, buccal), enzyme inhibitors
10	Patient Non- compliance	Poor adherence to complex regimens	Use of sustained/controlled release systems, fixed-dose combinations, taste masking

Table No 01. List of drug product development challenges and strategies to overcome the challenges.

IV. CHEMICAL PROPERTIES OPTIMIZATION

1. Hydrolysis Hydrolysis is a common chemical reaction that causes drugs to break down. This happens because water molecules, which have a strong charge, can attach to drug molecules and start breaking them apart. This process often involves a nucleophilic reaction with a labile group [33]. The pH level can be adjusted to stop this reaction. Since most dnigs are weak acids or bases, it's important to formulate the drug solution with a pH that keeps it stable. This can be done by using a water-soluble solvent, choosing the right buffer concentration to prevent ionisation, or adding a surfactant to protect against enzyme activity. Drug solubility can decrease if less soluble salts or esters are formed, which are more likely to break down through ester hydrolysis. Functional groups like carbonyls in esters, lactones, amides, lactams, carbamates, and imides are especially prone to hydrolysis. By adjusting the pH of a liquid dosage form, you can extend the shelf life of the drug, but you must cnsurc that stability and solubility arcn't affcctcd. To prcvcnt hydrolysis, diffcrcnt methods can bc used. One approach is to check for drug hydrolysis and stop it bcforc it starts. This can be done by adding bulky alkyl groups near the functional group through chemical changes, which can block the action of a nucleophile or enzyme and reduce hydrolysis. Similarly, replacing a labile ester group with a urethane or ainide can improve the chemical and metabolic stability of the drug [34].
2. Oxidation A high-oxygen environment is useful for testing how sensitive a drug is to oxidation. This can be done by placing samples in desiccators with a three-way stopcock, which can be alternately evacuated and filled with the desired oxygen level.

This process is usually repeated three or töur times to ensure the correct environment is created. Thèse results can help decide whether the drug formulation needs an antioxidant or whether the final product should be packaged in an inert environment [34].

3. Rcduction Rcduction is a common way drugs arc mctabolizcd in thc body. Nicotinamide

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adenine dinucleotide phosphate (NADPH) is needed by liver microsomes to carry out various reductive reactions. Cytochrome P450 enzymes help reduce azo and nitro coinpounds. Alcohol dehydrogenase helps convert chloral hydrate into its active form, trichloroethanol. Prednisolone and cortisone are also rcduccd to form the active mctabolitc hydrocortisonc. Azo dyes, which arc uscd as color additivcs in drugs and food, can bc brokcn down by bactcria in the livcr and intcstincs into amincs [35].

4. Chirality During thc prcformulation stagc, determining the chirality of a drug is part of the drug development plan. The unwanted enantiomer should be removed from the drug formulation since, in most cases, one of the enantiomers doesn't have the necessary pharmacological effects. If a separation method is available, the inactive form should be removed to save costs. Evaluating optical activity for drug molecules is an essential step during the early discovery of new cheinical entities (NCEs). This helps identify the active enantiomeric form of the drug. The drug must be in an enantiopure form as it's a legal requirement for an Investigational New Drug (IND) filing. Therefore, the appropriate enantiomeric form for the market product should be selected before IND filing or a patent. As an example, Sirolimus, which is marketed as Rapamune by Pfizer and approved by the FDA in 1999 for immunosuppression, contains Phosal 50-PG as the active ingredient and polysorbate 80 as an inactive, nonaqueous ingredient. ln solid form, Sirolimus is a chiral compound, but in aqueous solutions, it exists in A, B, and C isomers. Hence, a nonaqueous fonnulation is chosen for drug dcvclopmcnt [36].

V. PREFORMU1ATION STUDIES FOR BIOPHARMACEUTICALS DEVELOPMENT: PROTEINS, PEPTIDES, AND VACCINES

The idea of tising recombinant DNA technology and CRISPR -associated protein 9 is becoming more popular in developing biopharmaceutical products. These technologies, along with artificial intelligence, help analyze large genome data, which is useful for designing peptide, protein, and vaccine products [37]. Proteins are pepes cturest area o n easy cane maeoesaessoey chemically changing the peptides to create stronger, longer-lasting prodrugs. These prodrugs are made through chemical changes and reactions such as replacing amino acids with dehydroamino acids, D-amino acids, or using thio-methylene modifications, carboxyl reduction, and joining with **PEG** -amino acids [38]. Preformulation studies help choose the best adjuvants and conditions needed during production. For example, the stability of a live Ty2la typhoid vaccine was studied using spectroscopic methods. This gave real-time data on how the vaccine behaves at different temperatures (10—85°C) and pH levels (4—8) over time. This information is hclpful for prcformulation studies of similar pcptidc drugs. An cinpirical phase diagram, made using data from circular dichroism and fluorescence tcchniqucs, shows that Ty2 la cells can exist in different physical states. The most stablc state is when the pH is between 6 and 7 and the temperature is below 30°C. Among other possible stabilizing agents, 10% sucrose and 0. 15 M glutamlc acid provide the best protection, raising the transition temperature of Ty2la cells by aboiit 10°C each. Foam-dried formulations have also been studied as a possible alternative method to help stabilize Ty2la cells further. In addition, using 10% sucrose and trehalose solutions can improve the stability during the production process [39,40].

VI. ROLE OF ARTIFICIAL INTELLIGENCE IN PREFORMULATION STUDIES

Artiticial intelligence is a broad, multi-disciplinary field that enables machines to think, learn, and make decisions. It has two main branches: machine learning and deep learning. Scientists often use computer-aided drug design tools combined with artificial intelligence to support decision-making at key stages of drug discovery programs [40,42] Currently, deep learning-based artificial neural networks and machine learningbased expert systems are widely used for predicting how drugs interact with their targets, as well as for assessing the physieocheirical properties, quality, stability, toxicity, safety, and biological activity of formulations. AI is also applied in healthcare for medical diagnoses, tracking outbreaks, and developing personalized treatments [43]. The healthcare sector is making significant progress with Al tools. For instance, the Adaptive neuro-fuzzy inference system (ANFIS) performs wc11 in sclccting cxcipicnts, making drug rcscarch casicr and rcducing thc time needed for drug discovery and development. In-silico models arc now recognized as

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effective tools for dctcrmining the aqucous solubility of drugs. These assessments consider factors like molecular size, shape, and the ability to form hydrogen bonds [44].

VII. PREFORM A ON TU SA REGUAORY PESPEE

A preformulation report for a new molecule includes details on stability, compatibility with excipients, solid-state characteristics, physicochemical properties, biopharmaceutical features, thermal behavior, mechanical properties, and analytical profiling. In the IND (Investigational New Drug) process focused on CMC (Chemistry, Manufacturing,and Controls)/phannaceutical development, these features of the drug substance must be clearly outlined. For example, the drug must be in its enantiopure form, as this is a legal requirement for IND submissions. Therefore, the appropriate enantiomeric form of the drug should be selected and its activity documented before submitting an IND or a patent [45]. Nowadays, the characteristics of a specific drug material should be thoroughly examined early in the development process, and the results of these studies should be included in the CMC section of an IND. As part of robust regulatory guidelines, the CMC section covers drug excipient additivcs, manufacturing proccsscs, and storagc conditions used to producc thc drug substancc and drug product. This data is analyzed to cnsurc that the company can consistcntly manufacturc and supply thc drug. Today, rcgulatory agcncics havc cstablishcd a common format for submissions, as spccificd by ICH guidclincs, to standardize CMC requirements for global marketing. This common technical document is designed to harmonize CMC regulatory requirements for worldwide development and marketing. The creation of CMC sections based on European Union and American standards leads to two formally distinct NDAs. The CMC sections of EU Marketing Authorization Applications and US-FDA submissions are largely similar [46].

VIII. PREFORMULATION STUDIES FOR NANO-BASED THERAPEUTICS

Nano-based therapeutics are effective approaches for delivering active drug ingredients because of their well-designed structure and properties. These new drug dclivcry systcms arc [47]. Thc main goals of prcformulation studics for nano-bascd formulations arc to design and show the drug's rclcasc pattcrn, how well it mixcs with other substances, its physical and chemical properties, and its crystalline or amorphous form to create an effective dosage form [48]. During the preformulation stage, important characteristics like the shape, size, whether it's crystalline or not, and how consistent the size is are evaluated for nano-based delivery systems, meaning the creation of nano-based therapeutic systems is based on these physical and chemical features [49]. The use of diluents and solvents also influences the uniformity, size,

and shape in nanoprecipitation methods. Studying the active drug components is ed I nts essen a ocus g o t e so u ty ne g po nt e a p ope es anoey react with pH. In the preformulation phase, the physical and chemical properties of the drug and how it interacts with other ingredients in the formulation play a key role in choosing thc best nano-system for thc final drug design. Preformulation studics help develop a suitable dosage form by understanding the drug's absorption and effect patterns [50,51]. Also, important aspects like the drug's dissolution, different crystal forms, how it moves in the body, its availability, details on how it breaks down, unwanted side effects, and how it affects the body are all part of preformulation studies, and these are determined by the drug's physical and chemical features. Nano- based formulations can be uscd for various dclivcry mcthods such as topical, transdermal, injcctablc, and oral, and arc uscful for compound dcvclopmcnt, scrccning, thcrapy, imaging, and diagnosis, making thcin innovativc tools for targcting cancer, inflammatory diseases, and autoimmunc conditions [52,53]. For instance, considering these factors helps justify the preparation of nanoparticles, lipid - based naiioparticles, and polymeric nanoparticles, including the choice of polymer and adjuvant, important formulation evaluation, preparation techniques, optimization of process-related variables for better outcomes, nanoparticle analysis, stability testing, and improving the efficiency of drug entrapment [54].

IX. CONCLUSÎOLL

Pre-formulation studies are an essential phase in the pharmaceutical development process, particularly for oral dosage forms. Through systematic physicochemical and compatibility evaluations, thèse studies provide critical information

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about a drug candidatc's characteristics, including solubility, pKa, partition coefficient, thermal stability, polymorphism, and potential interactions with excipients.

The insights obtained from pre-fonnulation allow fonnulation scientists to identify challenges such as poor solubility, low permeability, cheinical instability, or unfavorable solid-state properties early in the development process. Addressing thèse challenges at the pre-formulation stage minimizes the risk of failure in later stages such as formulation, scalc-up, and clinical testing.

In this study, comprchcnsivc pro-formulation testing of a novcl drug candidatc enabled the selection of suitable formulation strategies and guided excipient selection. lt also supported the identit'ication ot' appropriate storage conditions and packaging requirements based on the drug's sensitivity to moisture, light, and temperature.

Overall, pre-formulation studies not only facilitate the rational design of oral drug delivery systeins but also enhance the overall efficiency, quality, and regulatory compliance of pharmaceutical product development. They serve as the scientific backbone for making informed decisions that contribute to the creation of safe, stable, and effective oral dosage forms. For any novel drug candidate, this step is indispensable in ensuring a successful transition from the laboratory to the clinic and eventually to the market.

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