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Review Article

Pharmaceutical Formulation and Development: A Comprehensive Review

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ABSTRACT

The abstract discusses the significance of preformulation studies, which analyze the physicochemical characteristics of potential new drug candidates and their impact on drug performance and dosage form development. These studies provide essential information for designing formulations and may indicate the need for molecular modifications. Before creating pharmaceutical formulations, it's crucial to consider the inherent chemical and physical properties of each drug, which serve as the foundation for combining them with other ingredients in dosage form production. The primary objective of preformulation studies is to create elegant, stable, effective, and safe dosage forms. This is achieved by establishing kinetic rate profiles, assessing compatibility with other components, and determining the physicochemical parameters of the new drug substances. Several properties play vital roles in preformulation studies, including drug solubility, partition coefficient, dissolution rate, polymorphic forms, and stability. Polymorphism, which includes crystal and amorphous forms, can lead to variations in the chemical, physical, and therapeutic characteristics of the drug molecule. This article provides insights into these properties and techniques for evaluating preformulation parameters of drugs.

INTRODUCTION

Formulation development plays a pivotal role in the product development of pharmaceuticals, influencing patent eligibility, product lifecycle, and overall success.

- Formulation development is a complex, multi-step process that involves blending the active drug with various components while considering factors like particle size, polymorphism, pH, and solubility to create the final effective medicinal product.
- Different companies incorporate formulation development functions and personnel into

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their product development processes in various ways.

- A successful formulation must be feasible for manufacturing, maintain chemical and physical stability during production and shelf life, and ensure the bioavailability of the active pharmaceutical ingredient, ensuring that the body can readily absorb the required amount in each dose. [1]

The ICH Q8 Pharmaceutical Development guidelines offer a platform to share insights acquired through the use of scientific methodologies and quality risk management in the creation of a pharmaceutical product and its manufacturing process. These guidelines should encompass the formulation's development, highlighting essential attributes crucial to the drug product's quality, all while considering the intended use and administration route. [2]

FDA PROCEDURAL STEPS:

- Conducting a literature review
- Assessing the active drug ingredient
- Choosing appropriate excipients
- Creating small batch formulations
- Engaging in production
- Developing analytical methods
- Performing bioequivalence studies
- Implementing scale-up techniques [3]

OBJECTIVES OF FORMULATION DEVELOPMENT:

1. Designing a high-quality product and its manufacturing process to consistently achieve the desired product performance
2. Creating a new drug that is safe, effective, stable, and hopefully, a best-seller.
3. Identifying material characteristics and process parameters that impact the quality attributes of the drug product.

cGMP (CURRENT GOOD MANUFACTURING PRACTICES):

Current Good Manufacturing Practices, abbreviated as cGMP, refer to standards that align with the guidelines put forth by regulatory authorities. These agencies oversee the authorization and licensing processes for the production and distribution of items like food, beverages, cosmetics, pharmaceuticals, dietary supplements, and medical devices. These guidelines establish the essential criteria that manufacturers are required to meet to ensure the consistent high quality of their products across different batches, meeting the intended purposes effectively. [4]

COMPONENTS OF cGMP:

1. Quality Assurance:

Quality Assurance (QA) is a term applicable in both manufacturing and service sectors, encompassing systematic measures taken to guarantee that the products delivered to customers conform to the agreed-upon performance, design, reliability, and maintainability expectations. [4]

2. Quality Control:

Quality Control (QC) refers to a set of procedures aimed at ensuring that a manufactured product or service complies with defined quality criteria and meets the requirements of the client or customer. [4]

3. Good Manufacturing Practices (GMP):

Good Manufacturing Practice (GMP) is a comprehensive system established to maintain consistent production and control of products in accordance with quality standards. It is designed to mitigate risks inherent in pharmaceutical production that cannot be entirely eliminated by simply testing the final product. GMP encompasses all facets of production, from the initial materials and facility to equipment, staff training, and personal hygiene. [4]

Importance of cGMP:

1. Current Good Manufacturing Practices (cGMP) serve as crucial guidelines for pharmaceutical companies, ensuring the

safety of their end products for human consumption. Typically, a product's safety cannot be determined through sensory factors like touch, smell, or appearance.

2. To guarantee the safety and adherence to manufacturing standards, the FDA conducts laboratory tests and random inspections of production facilities. This rigorous oversight is in place to ensure that pharmaceuticals in the market are safe for human consumption and meet recommended manufacturing protocols.
3. The presence of an unsafe product in the market can result in expensive legal issues, loss of licensure, and significant damage to a company's reputation. To mitigate these risks, cGMP is diligently implemented, effectively preventing instances of contamination, mix-ups, deviations, failures, and errors. This ensures that drug products consistently meet stringent quality standards, providing assurance of quality, safety, and purity in pharmaceutical products. [4]

Steps in Formulation Development:

1. Identification and Characterization of the Drug: This step involves conducting identification tests to confirm the identity of the active pharmaceutical ingredient (API) in the pharmaceutical tablet. These tests are designed to differentiate between compounds with closely related structures, ensuring specificity for new drug substances, often utilizing techniques like infrared spectroscopy.
2. Drug-Excipient Compatibility: Excipient compatibility studies aim to select components for the dosage form that are compatible with the drug. These systematic experiments also yield insights into the drug's stability profile, helping identify degradation products and mechanisms.
3. Formulation Development: Formulation development is a critical phase of product development, influencing patent eligibility, product lifecycle, and overall pharmaceutical product success. During this stage, the specific chemical substances to be combined with the active drug are determined to create the final pharmaceutical product.
4. Pharmaceutical Optimization: Optimization is geared toward achieving the best product with desired bioavailability criteria and the potential for mass production. The more optimal the product, the higher the company's profit potential.
5. Formulation Evaluation: Evaluation involves the analysis of various aspects of the drug, such as colour, odour, taste, and shape, to ensure the effectiveness and safety for patients.
6. Stability Study: Stability testing establishes the product's shelf-life by determining how long it remains safe for use and maintains its therapeutic value, considering the active ingredient's level over time. [5]

Requirement Identification and Procurement:

Procurement is the defined process of obtaining supplies through purchases from manufacturers, their agents, such as distributors, or from private and public suppliers. The procurement of medicines initiates with the establishment of procurement policies and concludes with the receipt, storage, and payment processes. This comprehensive process requires the application of specialized skills and knowledge, considering both professional and legal perspectives. [3]

Objectives of Procurement:

1. Ensuring the availability of the correct drugs in the appropriate quantities.
2. Guaranteeing the quality assurance of stocked pharmaceuticals.
3. Timely delivery of pharmaceutical supplies.

4. Obtaining most cost-effective prices from reputable suppliers, (value for money).
5. Maintaining safety stock levels [3]

SOP HANDLING:

SOP, which stands for Standard Operating Procedure, is a comprehensive set of step-by-step instructions created by an organization to assist employees in executing routine tasks These procedures go beyond mere written instructions; they serve as documents containing detailed steps to guide employees through technical and repetitive processes within the organization.

The primary objectives of SOPs are to enhance efficiency, ensure high-quality output, and maintain consistency in performance, all while reducing miscommunication and ensuring compliance with industry regulations. [6]

Specifically, the aims of SOPs are as follows:

1. Ensuring consistent and high-quality output. ii. Establishing a cohesive organizational framework for the collection of comparable monitoring data related to hazardous substances.
2. Maintaining quality control and assurance.
3. Providing guidelines for accurate and punctual data collection. [6]

SOP Writing Style:

Standard Operating Procedures (SOPs) should adhere to a concise, step-by-step, easy-to-read, and straightforward format. Information should be kept uncomplicated, using active voice and present verbs. SOPs should be kept simple and brief. For lengthy procedures with more than 10 steps and a few decision points, consider presenting them in a graphical or hierarchical format. Procedures involving numerous decisions can benefit from the inclusion of flowcharts. Every SOP should include requirements for document identification and control, as well as responsibilities for accountability and traceability. Maintaining a consistent format achieves this. It's important to emphasize warnings in the SOPs and alert users to exercise caution in specific scenarios. Avoid using terms like "may" or "if possible," as they imply flexibility under certain conditions. [6]

Various equipment and instruments handling:

1) Tablet compression machine:

➢ **Working principle:**

The basic principle behind the tablet compression machine is hydraulic pressure. This pressure is transmitted unreduced through the static fluid. Any externally applied pressure is transmitted via static fluid to all the directions in the same proportion. It also makes it possible to multiply the force as needed.

➢ **Applications:**

A tablet compressing machine converts granulated powder into pressed tablets of uniform size and weight. [7]

2) Tablet coater:

➢ **Working principle:**

The working principles of tablet coating machines are relatively simple. Tablet coating machines work by applying coating ingredients in the form of a solution to a group of tablets in a bed that may move horizontally or vertically. A concurrent flow of heated air facilitates evaporation of the solvents.

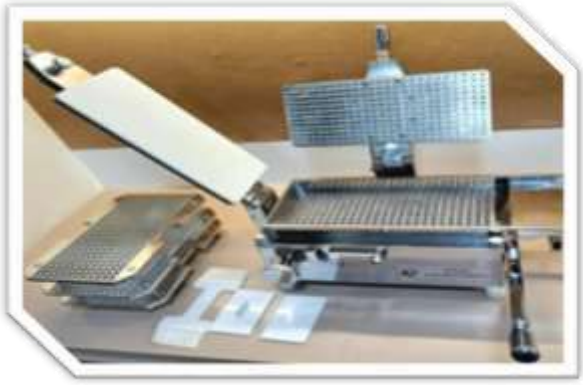
➢ **Application:**

Tablet coating machines are used to coat the surface of tablets with a thin coating of film. [8]

3) Capsule filling machine:

➢ **Working principle:**

The capsule filling machine work on certain principles. The principles of the machines are as follows. First, the capsule caps are divided from their bodies. After that, the material is filled in the capsules with the help of powder/granule filler present in the capsule filler machine, then the caps and body are rearranged in the machine itself. And, then the capsules are processed out as the ready material.



➢ **Applications:**

A capsule filler is a type of machine used to fill empty capsules with pharmaceutical ingredients. Fig.2.4 Capsule filling machine. [7]

4) Dissolution test apparatus:

➢ **Working principle:**

Dissolution testing measures the extend and rate of solution formation from a dosage Form single tablet is placed in a small wire mesh bask attached to the bottom of the shaft connected to a variable ed motor. The basket is immersed in a dissolution medium (as specified in monograph) contained in a 1000 ml flask; The flask is cylindrical with a hemispherical bottom. The flask is maintained at 37 ± 0.50C by a constant temperature bath, the motor is adjusted to turn at the specified speed and sample of the fluid are withdrawn at intervals to determine the amount of drug in solutions.

➢ **Application:**

Dissolution testing apparatus applicable for measuring the extent and rate of solution formation from a dosage form, such as tablet, capsule. Used to evaluate the performance of the product. [8]

Physicochemical parameters:

A. Organoleptic properties:

B. Bulk characterization studies:

- Crystallinity and polymorphism
- Hygroscopicity
- Fine particle characterization
- Bulk density
- Powder flow properties
- Compression properties
- Physical description

C. Solubility analysis:

- Intrinsic solubility determination
- PKa determination
- Partition coefficient
- Dissolution studies
- Common ion effect

D. Stability analysis:

1. In toxicology formulations

2. Solution stability
3. Solid state stability

A. Organoleptic properties:

Addressing Odour and Taste:

To manage the unpalatable nature of certain drugs with low solubility, it is essential to either alter their chemical form or mask their taste using flavours, excipients, or coatings. It's also crucial to handle drug substances that may irritate the skin with care. However, it's important to note that the use of flavour's, dyes, and excipients can impact the stability and bioavailability of the drug. Additionally, the drug's colour may vary, appearing as off-white, cream yellow, tan, or shiny, while its odour can range from pungent and sulfurous to fruity, aromatic, or odourless. Similarly, the taste may vary, being acidic, bitter, bland, intense, sweet, or tasteless. [9]

B. Bulk Characterization Studies:

Bulk characterization studies are essential for identifying all possible solid forms that may arise during the drug synthesis process, including the presence of polymorphs. These studies also assess bulk properties like particle size, bulk density, and surface morphology. Changes in these properties during drug development can affect solubility and stability predictions, which are closely linked to the specific crystalline form of the drug. Bulk characterization testing is a crucial step in ensuring the quality and performance of pharmaceutical products. [10]

1. Hygroscopicity:

Many drug substances have a propensity to absorb moisture. This involves measuring the amount of moisture absorbed by a specific weight of an anhydrous sample in equilibrium with the surrounding air's moisture at a given temperature. These substances can be classified as Deliquescent (absorbing enough moisture to dissolve themselves in high humidity conditions), Efflorescent (losing water to form a lower hydrate or becoming anhydrous in low humidity conditions), or Hygroscopic (existing in a dynamic equilibrium with water). The degree of moisture absorption depends on the relative humidity of the environment. Hygroscopicity is typically assessed using methods like Karl Fischer titration, gravimetric analysis, thermogravimetric analysis (TGA), or gas chromatography. This property is significant because changes in moisture content can impact stability, flow characteristics, compatibility, and other critical factors in drug development. [10]

2. Fine particle characterization:

It is a critical aspect of understanding drug substances. The particle size distribution of these substances influences various physical and chemical properties, including drug dissolution rate, bioavailability, content uniformity, taste, texture, colour, and stability. Additionally, particle size affects properties like flow characteristics and sedimentation rates, which are vital for formulation and product efficacy.

It is crucial to determine early on how the particle size of a drug substance can impact the final product. Several methods are employed to evaluate particle size and distribution, such as using a light microscope with a calibrated grid, sedimentation techniques, stream scanning, Coulter counter, and surface area determination through the BET nitrogen adsorption method. These methods help in characterizing and optimizing drug particle sizes for optimal pharmaceutical outcomes. [10]

3. Bulk Density:

Understanding the true and bulk densities of a drug substance is valuable in estimating the size of the final dosage form. This parameter is particularly critical for low-potency drugs, which may constitute a significant portion of the final granulation or tablet. The bulk density of a compound can vary significantly based on the method of crystallization, milling, or formulation. When density-related issues arise, they can often

be easily resolved through processes like milling, slugging, or adjusting the formulation. Bulk density has a direct impact on the flow properties of powders and can influence the size of high-dose capsule products or the uniformity of low-dose formulations where there are significant differences in the densities of the drug and excipients. [11]

4. Powder Flow Properties:

Efficient tablet manufacturing relies on the smooth flow of powders. When evaluating a drug substance in the preformulation stage, it's essential to study its flow characteristics, particularly if the intended drug dose is substantial. Powders can fall into two categories: free-flowing or cohesive (non-free-flowing). Several factors influence flow properties, including changes in particle size, density, shape, electrostatic charges, and absorbed moisture. These properties are typically assessed using methods such as Carr's index, the Hauser ratio, the angle of repose, rheology, and thixotropy. Understanding and optimizing powder flow properties are crucial for effective tablet production. [11]

5. Compression Properties:

Evaluating the compression properties, which include elasticity, plasticity, fragment ability, and punch filming propensity, can be established for small amounts of a new drug candidate. These properties play a crucial role in selecting the appropriate formulation ingredients. [10]

6. Physical Description:

The physical characteristics of a substance can be determined by observing its size, shape, appearance, and can be assessed either instrumentally or visually. [11]

Solubility Analysis:

A key objective in the pre-formulation process is to develop a method for creating drug solutions. A certain level of aqueous solubility is essential for a drug to be therapeutically effective. To exert its therapeutic action by entering the systemic circulation, a drug must initially be in a solution form. Compounds with low solubility often result in incomplete absorption. When a solute dissolve, it involves overcoming the intermolecular forces of attraction within the substance by the forces of attraction between the solute and solvent molecules. [12]

Intrinsic Solubility Determination: The process involves several steps:

- Identify all factors influencing solubility and dissolution.
- Disperse an excess amount of the drug in the medium and agitate it at a constant temperature.
- Withdraw samples of the slurry at various time intervals.
- Clarify ampoules through filtration or centrifugation.
- Analyse the clear samples for their drug content to establish a plateau concentration, typically using methods like UV, HPLC, GC, and others. [13]

7. pKa Determination:

Understanding the relationship between the dissociation constant (pKa), lipid solubility, and pH at the absorption site is foundational to the pH-partition theory, which explains the absorption characteristics of various drugs. Determining pKa is typically achieved through potentiometric titration.

Many drugs in use today are weak organic acids or bases. Knowledge of their individual ionization or dissociation characteristics is crucial because their absorption depends largely on their degree of ionization when they encounter biological membranes. A drug's ionization is influenced by both the pH of the solution at the membrane interface and the drug's pKa (whether it's an acid or base).

The concept of pKa is related to the Henderson-Hasselbalch equation. For acidic compounds, it is expressed as pH = pKa + log (ionized

drug/unionized drug), while for basic compounds, it is pH = Pkw - pKb + log (unionized drug/ionized drug). In parenteral products, the ideal pH is typically set at 7.4. If the pH is above 9, it can lead to tissue necrosis, and if it falls below 3, it may cause pain and phlebitis in the tissue. To maintain the pH of parenteral products, buffers such as citrates and phosphates are included in injections. [14]

8. Partition Coefficient:

The oil/water partition coefficient is a measure of a molecule's preference for either the hydrophilic or lipophilic phase, indicating its lipophilic characteristics. This coefficient plays a significant role in the development of a drug substance into a dosage form. When a solute is introduced into a mixture of two immiscible liquids, it will distribute itself between the two phases and reach equilibrium at a constant temperature. This distribution of the solute, which is in an unaggregated and undissociated state, can be explained as the ratio of the unionized drug distributed between the organic (upper phase) and aqueous (lower phase) layers at the equilibrium temperature. This parameter is essential for understanding how a substance interacts with different phases in a system. [15]

Determination of Partition Coefficient:

Using the shake flask method, the drug dissolved in one solvent is mixed with another partitioning solvent, and the mixture is shaken for 30 minutes. Afterward, the mixture is allowed to settle for 5 minutes. The aqueous solution is then centrifuged, and the drug content is assayed. This technique has several advantages in assessing the partition coefficient. [15]

Dissolution Studies:

Dissolution rate refers to the speed at which a drug substance dissolves in a given medium. When dissolution rate data is combined with information on a drug's solubility, dissociation constant, and partition coefficient, it offers insights into the drug's potential for absorption after administration. Importantly, these studies typically maintain a constant surface area of the drug during the dissolution process. [16]

Common Ion Effect:

When a common ion is introduced, it decreases the solubility of a slightly soluble electrolyte. This effect, known as salting out or drug precipitation, occurs because the common ion disrupts the solvent molecules from the electrolyte's surface through hydration. Conversely, the presence of larger anions, such as benzoates and salicylates, can promote the solubility of poorly water-soluble drugs by allowing water molecules to facilitate their dissolution. [16]

STABILITY ANALYSIS

In Toxicology Formulations:

Conducting stability analyses is essential when dealing with toxicology formulations to assess potential issues related to stability and homogeneity. Typically, drugs are administered to animals through their feed or by oral gavages, involving a solution or suspension of the drug in an aqueous vehicle. Factors like water, vitamins, minerals (metal ions), enzymes, and moisture levels in the feed can significantly impact the shelf life and stability of a drug. For solution and suspension toxicological preparations, it's crucial to evaluate ease of manufacturing and store them in flame sealed ampoules at various temperatures. In terms of chemical stability, suspensions should undergo periodic shaking to verify dispersibility, and drug solubility can be assessed through pH decomposition analysis. [17]

Solution Stability:

Exploring solution stability involves assessing various factors such as pH, ionic strength, co-solvent presence, exposure to light, temperature variations, and oxygen levels. Typically, these studies begin with initial experiments to confirm the degradation of the drug under extreme conditions, such as exposure to 0.1 N HCl, water,

and 0.1 N NaOH, all at a high temperature of 90°C. [17]

Solid State Stability:

The main objective of this study is to investigate and identify the optimal storage conditions for a drug in its solid state and to identify compatible excipients for a formulation. In solid dosage formulations, there is usually some free moisture contributed by both excipients and the drug itself. In tablets, for example, a significant percentage, typically 2% w/w, is needed for proper compression. This free moisture can potentially facilitate chemical reactions between the drug and excipients. [18]

In solid state stability, the absorbed moisture films in solid dosage forms are saturated with the drug, which is different from the dilute solutions found in injectable products. Stability testing for pharmaceutical products is the initial quantitative assessment of a new drug's chemical stability. It is defined as the drug product's ability to maintain its physical, chemical, microbiological, therapeutic, and toxicological specifications throughout its shelf life. [18] The purpose of stability studies includes ensuring the efficacy, safety, and quality of the active drug substance and dosage forms, establishing shelf life, supporting label claims, gaining insights into packaging, assessing product condition over an extended period, determining the compatibility of the drug with excipients and additives, and identifying the most suitable dosage form for the drug. [18]

CONCLUSION:

Formulation development is a critical process that enables the creation of stable, effective, and high-quality dosage forms tailored to meet patient requirements. This goal can be achieved by adhering to the formulation development process, following relevant guidelines, acquiring expertise in the operation of various instruments, and recognizing the significance of pre-formulation and quality control approaches.

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