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Pharmaceutical Formulation Development

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Abstract: By ensuring product quality, safety, and efficacy, formulation development plays a crucial role in pharmaceutical research and is necessary for both therapeutic and commercial success. Up until and including market approval, the many components of formulation development interact with other phases in product development, such as discovery research. Every medication item requires a custom formulation because of the complexity of many routes that could impact product stability, the unique properties of the medicinal molecule, unique patient requirements, and even marketing concerns. Formulation development can be approached in a number of ways, relying on scientific theories and a logical design that applies these insights to thousands of components. This article reviews formulation development and explains pre-formulation and sop handling so that readers can understand the significance of these processes and recognize, respect.[1]

I. INTRODUCTION

The development of preformulation occurred in the late 1950s and early 1960s due to a change in the focus of industrial pharmaceutical products growth. Advancements in analytical techniques were the driving force behind the initial initiatives that may be referred to as "preformulation." Preformulation testing's overarching goal is to produce data that will assist the formulator in creating mass-produced, stable, and bioavailable dosage forms. The method of combining various chemicals, including the drug or drugs and excipients, to create a finished medication in the appropriate dose form.[3]

Pharmaceuticals are designed with precise dosage forms in mind to ensure effective product delivery and stability.The goal of formulation development is to identify the best dosage form, ingredient combination, and production process for pharmaceuticals. Pharmacological dosage forms come in a variety of forms, including oral tablets, capsules, solutions, suspensions, topical ointments, gels, and injections for subcutaneous (SC), intramuscular (IM), or intravenous (IV) administration.The physical shape that a drug dose is meant to be administered or consumed is called a dosage form.[2]

We first learned about the concept of pre- formulation in the 1950s as a result of industrial pharmaceutical product development. It is the phase in the development of pharmaceutical products where the drug's physicochemical characteristics are defined and characterized. The right formulation and distribution are made possible by the psychochemical and biopharmaceutical qualities techniques[1]

Defination: The successful creation of a commercial drug product is correlated with the discovery of a novel drug substance, according to pharmaceutical formulation development. Based on patient demand, formulation development experts must choose the best course of action for attaining successful drug delivery. They must then optimize the formulation's properties using information about the therapeutic product's bioavailability and prerequisites for processing.[1]

Keywords: Formulation Development, Preformulation, SOP, Tablet, Evaluation.

II. History

Natural materials such as plants, herbs, roots, vines, and fungi were used to make the first pharmaceuticals. The only means of relieving human pain and suffering up to the middle of the 1800s was through natural medications. As a sedative-hypnotic, chloral hydrate was the first synthetic medicine created; it is still in use today. It was discovered in 1869 in several nations currently. The first pharmaceutical enterprises were the textile and synthetic dye industries' mirror images, and they owed a great deal to the abundant supply of organic compounds that could be obtained by distilling coal (coal-tar). The first analgesics were antipyretics, which were made from coal tar byproducts called phenacetin and acetanilide, which are chemical derivatives of aniline and p-nitrophenol. A bark extract from the white willow tree was utilized.

III. Concept of cGMP

Current Good Manufacturing Practice (CGMP) rules are those that the US FDA enforces. The procedures to be followed, the facilities or controls to be utilized for, the production, processing, packing, or storage of a medicine to ensure that such drug satisfies the fulfills the act's standards, is strong and unique, and possesses the qualities and purity that are said to be present.The rules ensure that a product is both safe to use and has the ingredients and potency that are stated.A component of quality assurance known as "good manufacturing practice" guarantees that pharmaceuticals are regularly manufactured and managed to the quality standards suitable for their intended purpose.[2]

cGMP Requirements: Qualified and Trained Personnel, A Quality System (change control, validation), Buildings and facilities that are fit for purpose, as well as equipment that is appropriate, clean, well-maintained, and calibrated measures used to stop the deterioration or contamination of raw, processed, and finished materialsManufacturing
With in-process measures for tracking variances in performance, Identical and protective packaging and labelingLaboratory controls: parameters, specimens, and examinations.

IV. Steps in formulation development

a. **Identification and characterization of drug**
b. **Excipients compatibility study**
c. **Formulation development**
d. **Formulation optimization**
e. **Evaluation of formulation**
f. **Stability study**

a. Identification and characterization of drug

Identification: The first step in the drug identification process is to isolate the function and involvement of a potential therapeutic target, such as a gene, protein, or nucleic acid, in the disease. Characterization of the molecular mechanisms that the drug targets comes after drug identification. A medication should be druggable, safe, effective, and meet all commercial and clinical requirements. Drug identification methods might be derived from concepts in molecular biology, biochemistry, genetics, biophysics, or other fields.

Characterization: The mechanism of action of the molecule can be better understood in the early phases of pharmacological research. Any novel pharmacological molecule that exhibits potential therapeutic efficacy is further examined for its size, shape, strength, weakness, application, toxicity, and biological activity.

b. Excipients compatibility study

Reactive functional groups present in excipients, or drug impurities, might react with other reactive functional groups in drug molecules during production or storage. As a result, drug-related impurities are created when excipient impurities react with active medicinal components.

c. Formulation development

The identification of a novel medicinal ingredient is associated with the successful development of a commercial therapeutic product. The active pharmaceutical ingredient (API) and inactive excipients need to be mixed to make a successful pharmaceutical formulation.

d. Formulation optimization

The company carries out formulation optimization during the product design phase because it believes that this approach helps bridge the gap between research and development and commercial manufacture of the finished pharmaceutical product.

e. Evaluation of formulation

The Hausner-ratio and compressibility index were calculated using the obtained values. It may be necessary to conduct many pre-formulation analyses to determine their mass and tapped density.A post-formulation evaluation was then carried out to evaluate the tablet's content consistency, hardness, thickness, friability, and weight changes.

f. Stability study

Stability is the ability of a medicine or product to continue meeting predetermined standards for identity, quality, and purity over an extended period of time.[2]

V. Procurement of equipment and instruments for formulation and analysis: It is the process of purchasing supplies of tools and equipment from suppliers, whether they are public or private, the manufacturer, or their representatives like distributors. acquiring apparatus and instruments for formulation:

1. Tablet Compression Machine
2. Friability Test apparatus
3. Monsato Hardness Tester
4. Hot air oven

VI. SOP Handling :

(a) Preparation of SOPs for different instruments and equipment's : A standard operating procedure is a written document that lists the routine tasks necessary to maintain the caliber of the inquiry.

The Standard Operating Procedure, or SOP, serves to outline the process for both preventative and instrument maintenance. There ought to be a SOP in place at the location of employment.

Goals: 1. A standard operating procedure (SOP) aims to give every employee comprehensive guidance on how to perform a task appropriately each and every time.

2. To continue maintaining quality assurance and control.

3. To function as training materials to instruct users on the procedure for which the SOP was created.

4. To promote data quality and enable constant adherence to quality system criteria.

5. To offer instructions for precise and prompt data collecting.

6. Consistency in performance.

Steps in the SOP preparation process:

1.Make a list of the procedures you feel require the creation of SOPs.

2. Arrange the procedure for creating and overseeing SOPs.

3. Gather data to support the information in your SOP.

4. Draft and check the SOP.

5. Adhered to standard operating procedures when using tools and equipment.

Handling of various instruments and equipment:

Tablet compression Machine :

A mechanical device with fast speed is the tablet press. It precisely compresses the components into the desired tablet shape.It has the ability to create the tablets come in a variety of shapes, though they are often oval or round.

Hydraulic pressure is the fundamental idea underlying the tablet compression machine. Through the static fluid, this pressure is conveyed without being decreased. Static fluid distributes any externally applied pressure in a same amount in every direction. Additionally, it enables the force to be multiplied as necessary.

Various phases of the compression procedure:
1. Filling
2. Measuring
3. Compression
4. Ejection

b. Tablet coater Tablet coating works on a straightforward concept. The process of coating tablets involves applying coating material to a moving bed of tablets while using heated air at the same time. promote the solvent's evaporation. The tablets are moved in two directions to distribute the coating: vertically (air suspension) or perpendicularly (coating pan).

COATING EQUIPMENTS For the coating process there are 3 types of following equipments..

1. The perforated coating pan.
2. The fluidized bed coater.
3. Conventional coating pan.

c. Capsule filling machine

A type of pharmaceutical processing equipment called a capsule filling machine, also called a capsule filler, encapsulator, or encapsulation machine, is used to fill empty capsules with various substances that contain active pharmaceutical ingredients (APIs), such as powder, pellets, tablets, granules, liquids, or different combinations of these.

1. Based on their applications and features, capsule filling machines can be divided into two groups: personal and professional capsule filling machines.
2. While semi- and fully-automated capsule fillers are frequently used for pilot production or medium volume manufacture, manual capsule fillers are primarily intended for personal usage in manufacturing processes requiring less or an exact amount of prescribed components to be placed in the capsule.[5]

VII. Preformulation studies

In the latter half of the 1950s and the early part of the 1960s, preformulation evolved as a result of a shift in emphasis in industrial pharmaceutical product development. The first programs that may be referred to as "preformulation" were motivated by developments in analytical methods. The principal aim of preformulation testing is to gather information that the formulator can employ to make mass-producible, stable, and bioavailable dosage forms. Synthetic chemists, working alone or in conjunction with specialists from other fields, may obtain data that is appropriately classified as preformulation data in the early phases of developing a novel medicinal chemical.

Preformulation's goals are to:

1) Provide the formulator with essential information
2) Minimize compatibility problems with excipients.
3) To increase the bioavailability of drugs.
4) To create aesthetically pleasing dosage forms that are dependable, effective, and safe.[6]
5) To see whether it works well with typical excipients.
6) It describes how to prepare and store drug items so that their quality is maintained.[7]

A) PHYSICAL PROPERTIES

Before developing a dosage form, it is critical to comprehend the physical characteristics of a drug substance, whether it is liquid, semisolid, or solid. The majority of medications used nowadays are fewer materials are liquid in nature and more are solid.

Principal Areas of Preformulation :

(I) Nature of Solid Drug:

1. Crystallinity and polymorphism
2. Hygroscopicity
3. Fine particle characterization
4. Powder flow

(II) Solubility Data:
1. Ionization constant – pKa v (- log Ka)
2. pH solubility profile
3. Common ion effect – KSP.
4. Thermal effects
5. Solubilization
6. Partition coefficient
7. Dissolution

(III) Stability Analysis:
1. Stability in toxicology formulation
2. Solution stability
   (a) pH stability profile
3. Solid state stability
   (a) Bulk stability
   (b) Compatibility

B) CHEMICAL PROPERTIES
1. Hydrolysis
2. Oxidation and Reduction
3. Racemization[8]

Formulation of conventional or novel drug delivery systems

i. Tablets

Tablets are solid pharmaceutical dosage forms that are made by molding or compression and include medication(s) with or without appropriate excipients.

Classification of Tablets

1) Tablets ingested orally.
- a) Compressed tablet
- b) Multiple compressed tablet
  - i) Layered Tablet
  - ii) Compression coated Tablet
- c) Repeat action Tablet
- d) Delayed action and enteric coated Tablet
- e) Sugar and chocolate coated tablet
- f) Film coated tablet
- g) Chewable Tablet

2) Tablets used in the oral cavity.
- a) Buccal Tablet
- b) Sublingual Tablet
- c) Troches and Lozenges
- d) Dental cones

3) Tablets administered by other routes.
- a) Implantation Tablet
- b) Vaginal Tablets[9]

ii. Capsules

The term "capsule" refers to a unit solid dosage form of medication that comes in the form of tiny shells composed of gelatin that contain precisely calculated amounts of medicinal material. The Latin word capsula, which means a little container, is where the word "capsule" originates.

Capsule types
1) Soft gelatin capsules
2) Hard gelatin capsules
3) Coating capsules
4) Sustained release capsules

5) Liquid filled hard gelatin capsules
6) Starch Capsules
7) Non-Gelatin Capsules[10]

iii. Oral liquids

Pharmaceutical liquid dosage forms are prepared substances that are used as drugs or medications. They consist of a mixture of active drugs and excipients (stabilizing, emulsifying, dispersing, solubilizing, suspending, wetting, thickening agent, preservative, sweetening agent, flavoring agent, and coloring agent) that are dissolved or suspended in suitable solvents.

Liquid Dosage Form

1) Solutions
2) Syrup
3) Linctus
4) Elixirs
5) Gargles
6) Mouthwash
7) Lotions
8) Liniment
9) Nasal drops
10) Ear drop
11) Throat paints
12) Eye drops
13) Suspension
14) Emulsion[11]

iv. Semisolids like Ointments, creams, lotions etc.

Topical dose forms in semisolid form are utilized for both protective and therapeutic purposes. It can be administered to the nasal, vaginal, rectal, or cutaneous cavities. A semisolid pharmaceutical system consists of a body of products that, when applied to the skin or mucous membranes that are accessible, help cure or alleviate a pathological condition or provide further protection from the environment.[12]

v. Parenterals

Parenteral preparations are solid dosage forms or sterile, non-pyrogen liquids that are delivered in single- or multidose
containers.[13]

VIII. Evaluation

Verifying a drug's identity and evaluating its quality and purity is the process of evaluation.

Solid dosage forms

i. Dissolution test

A medication must be in solution in order for it to be absorbed from a solid dosage form following oral administration. Breaking apart the tablet, often referred to as disintegration, is typically the first crucial step toward achieving this condition.

ii. Dissolution Test

The formulations' release characteristics were measured at 50 and 100 rpm in pH 6.8 phosphate buffer or 0.1 M HCL, both maintained at 37°C, using the USP APPARATUS II.
A spectrophotometer with a wavelength of 238 nm was used to measure the amount of medication released after six tablets underwent dissolution testing.

iii. Friability test

The hardness test and the friability test, which gauge a tablet's resistance to abrasion during handling, packing, and shipping, are closely related. It is measured with Roche Friabilitor.

iv. Hardness Test

Measurements of hardness or crushing strength are made during the tablet-making process to determine whether the pressure inside the tablet machine has to be changed. A tablet's crushing strength is expressed in kilograms, and four kilogrammes is usually thought to be the minimal amount required for tablets to work. The hardness of oral pills varies from 4 to 10 kg. While hypodermic and chewable pills are frequently significantly softer (10–20 kg), some continuous release tablets are noticeably tougher (3 kg). Other tablet attributes have been connected to tablet density, porosity, and hardness.

v. Weight variation

Twenty tablets were randomly selected from each batch and weighed separately in order to check for weight variation. The USP has set limitations on the average weight of uncoated, compressed tablets.Within a batch, there is minimal variance among the tablets and each tablet has the recommended quantity of therapeutic ingredients. For the uniformity test, ten of the thirty tablets that make up the typical sample are evaluated separately. Nine out of ten pills must have NLT 85% or more than 115% of the drug content listed on the label.

vi.content uniformity

Within a batch, there aren't many differences between the tablets, and each one has the recommended dosage of active ingredients.For the uniformity test, ten of the thirty tablets that make up the typical sample are evaluated separately. Nine out of ten pills must have NLT 85% or more than 115% of the drug content listed on the label.

The three components that directly result in problems with consistency of content.[14]

IX.Conclusion

The introduction to formulation development, concepts of cGMP, steps in formulation development, requirements listing and procurement, handling SOP, handling various equipment and instruments, pre-formulation studies and preparation of pre-formulation data sheet, formulation of novel drug delivery system, and its evaluation were all clear to us after the report on formulation development was finished.The pharmaceutical industries depend heavily on the formulation development studies, pre-formulation studies, various tests, and SOP handling. Without these, the industries cannot function properly, and neither can quality efficacy nor novel solutions to problems that arise during development be found. One can understand that the significant amount of work required with knowledge necessary for the development of formulations since "small mistakes have big consequences"

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