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Multilayer Tablet: An Overview

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ABSTRACT

Multilayer tablets is a new era for development of controlled release formulation. They are an essential way to prevent chemical incompatibilities between APIs through physical separation and to make it easier to create various drug release profiles. Introduction, preformulation, excipient selection criteria, formulation, and preparation technique are all included in the domain formulation and characterization of the multilayer tablet. It also covers packaging, labelling, documentation, stability studies, and evaluation.

KEY WORDS: MULTILAYER TABLET

INTRODUCTION

Multilayer tablets are medications that combine two or more medications in one dose to effectively treat a patient's condition. For example, these tablets are frequently employed to physically separate formulation components in order to minimise chemical incompatibilities.

The active solute is included in the matrix core of a multi-layered matrix tablet, which also includes one or more barriers (modulating layers) that are added during the tableting process. By reducing the surface area accessible for the solute release and simultaneously regulating the rate at which the solvent permeates the matrix, the modulating layers serve to postpone the interaction of the active solute with the dissolving medium.[1]

TYPES OF MULTILAYER TABLET

1.Bilayer tablet: Bi-layer tablets can release two distinct APIs simultaneously or sequentially. There are two layers: the rapid release layer and the sustained release layer, which serves as a maintenance dose. A bi-layer tablet can deliver two medications simultaneously without causing pharmacological or physiological interactions.

2.Triple layer tablet: The first layer of a triple layer tablet is for immediate medication release, while the second layer is for continuous release. The middle barrier layer divides these two layers. This is a better way to distribute two medications that interact with one another.

ADVANTAGES

1. Cost is lower compared to all other oral dosage form.

2. Greatest chemical and microbial stability over all oral dosage form.

3.Objectionable odor and bitter taste can be masked by coating technique.

4. The tablet can be easily used for combination therapy.

DISADVANTAGES

1. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.

2. Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating.

3. Difficult to swallow in case of children and unconscious patients.[2]

PREFORMULATIONS

In order to create a stable, safe, and effective dosage form, preformulation scientists characterise the physical, chemical, mechanical, and biological properties of novel therapeutic substances. This stage of the research and development process is known as preformulation. In order to learn more about the physical and chemical characteristics of a medicinal ingredient, preformulation studies are crucial in the early phases of drug development.[1]

(A) IDENTIFICATION AND CHARACTERIZATION METHODS OF DRUG

Physical appearance

•Organoleptic properties of the candidate drug molecule, e.g.: color, odor, and taste.

•Bulk characterization. e.g.: particle size and surface area, powder flow properties, density, compressibility, crystallinity, polymorphism and hygroscopicity.

•Solubility analysis e.g.: ionization constant/ drug pka, partition coefficient, solubilization, thermal effect, common ion effect (Ksp) and dissolution.

•Stability analysis e.g.: solution-state stability testing, solid-state stability testing and drug excipient compatibility study

Determination of λmax

APIs was dissolved in solvent further diluted with the same and scanned for maximum absorbance in UV Visible spectrophotometer.

Solubility

Solubility study of a drug was prepared using 10ml of distilled water or any other organic solvent in 25ml volumetric flask. Precaution was taken so that the drug remains in medium in excess. Then by using mechanical shaker, the flask were for 24 hours. The sampling was done 24th and 48th hour. The sample withdrawn (1ml after filtration) was diluted with appropriate medium and was analyzed using UV spectrophotometer

Melting point

The melting point of the APIs was determined by capillary method in triplicate. Melting point of a drug was determined by taking a small quantity of drug in capillary tube sealed at one end and was placed in Thiel's melting point apparatus and temperature range at which the drug melted was noted. Average triplicate reading were noted.[4]

B) EXCIPIENT DRUG COMPATIBILITY STUDIES

Drug excipient compatibility studies are conducted to assess the compatibility between the active pharmaceutical ingredient (API) and various excipients used in the formulation of a drug product.

It is imperative to guarantee that the drug's chemical or physical properties do not undergo any undesired changes as a result of the interaction with excipients, since this could potentially impact the drug's stability, safety, or efficacy.

Method of estimation of Drug –Excipient Compatibility

DSC Analysis

Thermal properties of the pure drug and the physical mixture of drug and excipients were analyzed by Different Scanning Calorimeter. The samples were heated in a thermatically sealed aluminum pan. Heat runs for each sample were set from 25 to 350 °C at a heating rate of 10 °C / min, using nitrogen as blanket gas.If no significant changes or shifts in peaks occur, it suggests compatibility.

FT-IR spectroscopy

FT-IR spectroscopy can be used for structural analysis. FTIR provides valuable information about the molecular structure of substances by measuring the absorption of infrared radiation.. Using the potassium bromide sample disk method, the core as well as the coated core can be analyzed by recording their IR spectra in the wave number range 4000 - 400 cm-1; the characteristic peaks observed are then matched with reference peaks. Identification of drug and drug excipients and physical mixture can also be confirmed by FT-IR analysis of the sample to reveal that there is no interaction between the drug and other excipients.

X-Ray Diffraction(XRD)

XRD is used to determine the crystalline structure of a substance. Changes in the XRD pattern can indicate alterations in crystallinity. Compare the XRD patterns of the drug and excipients individually with physical mixtures to identify changes in crystalline structure.[3]

C) CRITERIA FOR EXCIPIENT SELECTION

Inert materials called excipients are employed as diluents or delivery systems for drugs. It comprises a number of sub-groups in the pharmaceutical sector, such as glidant, lubricants, disintegrants, binders or adhesives, flavours, colours, and sweeteners. All of these must meet certain criteria as follows,

a) Physiologically inert

b) Acceptable to regulatory agencies.

c) Physiologically and chemically stable.

d) Free from bacteria.

e) Should not interfere with the bioavailability of the drug.

f) Commercially available in the form and purity commensurate with pharmaceutical standards.

g) Low cost, inexpensive.

h) Meet the standards of regulatory requirements.

(D) FORMULATION OPTIMIZATION TECHNIQUES

Optimization term is defined as "to make perfect" which means to make the perfect anything using different techniques and processes. To create high-quality products, many medicine formulations employ optimisation approaches. It deals with different drug product types and how they are made. Many problems with the pharmaceutical process and product, including formulation, manufacturing, excipient selection, novel drug development, and other pharmacy-related challenges, can be solved with optimisation techniques. Because of the optimisation method, we look at the different issues that arise while conducting research.

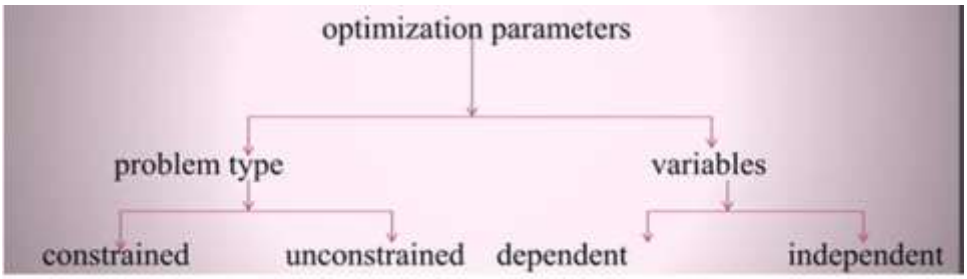

Fig no : 1

(I)Unconstrained

In this system, the restriction is not based on physical limitations. For example, one might want to make an uncoated tablet possible for a specific pharmaceutical system**.**

(II)Constrained

In this system the restriction is based on physical limitations. As a result, the constrained challenge is to make the uncoated tablet, but is should not be Disintegrate in the stomach.

(III)Independent variables

This type of variable comes under the supervision of a formulator like the force of compression, lubrication level, binder level etc.

(IV)Dependent variables

The formulator has no direct control over this type of variable. They are reliant on an unrelated variable. These are responses like hardness, flow property, and friability, among others.[4]

FORMULATION

In addition to active ingredients, tablets containseveral inert materials known as additives or excipients.

1) Diluents

When the drug dosage is insufficient to provide the necessary bulk for the tablet, diluents are fillers that are added to make the appropriate bulk. Better tablet characteristics, such as increased cohesiveness, the ability to employ direct compression production, or flow promotion, are the secondary motivation.

Example: Lactose, microcrystalline cellulose (MCC), mannitol.

2) Binders and Adhesive

Binders and granulators are agents that are employed to give the powdered material cohesive properties.

Example Hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP).

3) Disintegrants

A disintegrant is a compound or combination of substances that is added to a tablet to help it dissolve or break down in the GIT after it has been administered.

Example: Croscarmellose sodium, crospovidone, sodium starch glycolate.

4) Lubricants and glidants

Lubricants are intended to prevent adhesion of the tablet materials to the surface of dies and punches, reduce inter particle friction and may improve the rate of flow of the tablet granulation.

Example: Magnesium stearate, stearic acid, colloidal silicon dioxide.

Glidants are intended to promote the flow of granules or powder material by reducing the friction between the particles.

Example: Colloidal silicon dioxide, talc.

5) Coloring agent

The use of colors and dyes in a tablet has three purposes:

(1) Masking of off-color drugs

(2) Product Identification

(3) Production of more elegant product

All coloring agents must be approved and certified by the FDA.

Example: Iron oxide pigments, titanium dioxide.

6) flavoring agent

Flavoring agent also referred to as flavorings, Flavors are pharmaceutical excipients used to impart a pleasant flavor and often odor to pharmaceutical formulations. They may be derived from natural sources (e.g.: fruit components) or, prepared artificially.

Example : Artificial flavors, sweeteners.

7) sweetening agent

Sweetening agents are incorporated in tablets to impart sweetness to the product and hence the acceptability of tablets. The excipients are of particular importance if the conventional tablet contains bitter drug substances.

Examples of sweeteners that are found in tablet manufacture include aspartame, dextrose, fructose, mannitol. Saccharine, sorbitol, sucrose etc.

8) Coating agent

Used in film coating to provide a protective layer, control drug release, and improve stability.

Example: Hydroxypropyl methylcellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), ethyl cellulose.

9) Plasticizer

Enhance flexibility and reduce brittleness in coating materials.

Example: Triethyl citrate, acetyl tributyl citrate.

10) Sustained release matrices

Control drug release over an extended period.

Example: Hydrophilic matrices (e.g., HPMC), hydrophobic matrices (e.g., ethyl cellulose).[5]

METHOD OF PREPARATION

- Premixing drug with other ingredient using mixer
- Transferring the mixture into granulator where binder solution is sprayed until a certain consistency attain
- Wet sieving of granules through desired screen size
- Drying of granules
- Dry sieving of granules to certain particle size distribution
- Addition of lubricant to dry granules
- Compressing the granules into tablet

EVALUATION OF FORMULATION

Weight Variation Test:

To study weight variation, 20 tablets of each formulation were weighted using electronic balance and the test was performed according to the official method.

SL NO.	AVERAGE WEIGHT OF TABLET (mg)	% OF DEVIATION
1	< 80	10
2	< 80 – 250	7.5
3	≥ 250	5

Table no:1

Hardness:

The resistance of tablets to shipping or breakage under condition of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in the terms of kg/cm2. 5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.[10]

Friability:

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. 10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator dusted off the fines and again weighed and the weight was recorded. Percentage friability was calculated by using the formula.

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}}$$

Tablet thickness:

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation. Vernier caliper consists of metric and imperial scales. The main matric scale is read first then read “hundredths of mm” of imperial scale (count the number of division until the lines concedes with the main metric scale. The imperial scale number is multiply with 0.02. Then that number obtained from imperial scale added with main metric scale to get final measurement.

In Vitro dissolution studies:

The release rate of tablet (n=3) was determined using The United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 □ 0.5□C and 75rpm.

Disintegration Time.

The disintegration time was determined at 37±0.5∘ C using disintegration test apparatus in 0.1 N HCl.[6]

STABILITY STUDIES

Pharmaceutical stability studies can be defined as the amount of time that a pharmaceutical product maintains its physical, chemical, microbiological, and pharmacokinetic features and characteristics during the course of its shelf life after it is manufactured.

The product's shelf life is determined by the substance's reduction to 90% of its initial concentration. The technical word for the product's stability, shelf life, is expressed as the date of expiration.

STABILITY TESTING METHODS

Stability testing is a procedure performed for all the pharmaceutical products at various stages of the product development.

1. Real-time stability testing

Real-time stability testing is normally performed for a long duration of time to allow significant degradation of the product under the storage conditions recommended. The period of time for the test of the product depends on the stability of the product which clearly tells that the product is not degraded or decomposed for a long time.

2. Accelerated stability testing

This type of stability testing is done at higher temperatures and that decomposition the product is determined. The information is used to predict the shelf life or used to compare the relative stability of alternative formulations. The accelerated stability studies are easily predicted by the Arrhenius equation

K = Ae -Ea/RT Log

where

K= Specific rate constant

A= Frequency factor or Arrhenius factor

Ea= Energy of activation

R= Real gas constant 4.184 j/mol. k

T= Absolute temperature

3. Retained sample stability testing

In this type of testing, the stability is done by selecting one batch for a year. If the number of samples exceeds more than 50 then they are divided into two batches. The samples stability studies help to predict the shelf life. The maximum shelf life of every product predicted could be 5 years which is conventional to the test samples at 3, 6. 9, 12, 18, 24, 36, 48 and 60 months. This method of testing is also known as constant interval method

4. Cyclic temperature stress testing

In this method, cyclic temperature stress tests are designed knowledge of the product so as to mimic likely conditions in the market place storage. In this testing the sampling is considered to be conducted by a cycle of 24 hours which is known as the rhythm of the earth is 24 hours.[7]

PACKAGING AND LABELLING OF TABLETS

PACKAGING

A device or material that holds a pharmaceutical product, whether or not it comes into direct touch with the substance, is called a pharmaceutical package container.

TYPES OF PACKAGES

Primary Packaging

Packages that come into direct contact with the pharmaceutical formulation are referred to as primary packaging. Protecting the formulation against mechanical, chemical, environmental, and/or other risks is the primary goal of the primary package**.**

Secondary Packaging

The secondary package is the one that is external to the primary package. In addition to offering extra security during storage, this package contains information on pharmaceutical products. For example, leaflets

Tertiary packaging

It shields the products from damage and is the outer package of secondary packing. It is employed in bulk transportation and handling. Barrel, crate, container, pallets, and slip sheet are a few examples.

TYPES OF PACKAGING FOR TABLETS

• Blister packaging: Blister packaging is a type of packaging produced by heating a sheet of plastic and molding it into shape to form a bubble or pocket the blister that completely covers the product[11]

LABELLING

LABEL:

Label means a display of written,printed or graphic matter upon immediate container or the wrapper of a drug package

LEGAL REQUIRMENTS OF A LABEL

✓ The name of preparation

✓ Strength and dosage form.

✓ Quantity.

✓ Instructions for the use.

✓ Precautions & warnings.

✓ Registration number.

✓ Batch number.

✓ Manufacturing & Expiry date.

✓ Price

✓ The name and address of pharmaceutical industry

Conclusion

The detailed study of multilayer tablet was studied. A thorough examination of the multilayer tablet was conducted. A multilayer tablet comprises two layers of formulation, one for quick drug release and the other for prolonged drug release. We also looked at tablet formulation and preformulation in this study. The preparation process for the multilayer tablet was examined, along with its evaluation, stability tests, packing, and labelling.

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