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Review on Formulation and Evaluation of Bilayer Tablet: Metformin HCL and Glimepiride

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Abstract: The bilayer tablet is a type of pharmaceutical dosage form that has two different layers, each of which contains a different formulation of the active ingredient or ingredients; the two layers are usually separated by a thin barrier, allowing the controlled release of the active ingredients from each layer. The bilayer tablet design allows the combination of immediate-release (IR) and sustained-release (SR) formulations in a single tablet, providing a rapid onset of action followed by a prolonged release of the active ingredient, which has several advantages, such as increased therapeutic efficacy, decreased dosing frequency, and improved patient compliance. Bilayer tablets can be used to deliver a variety of active ingredients, including those for the treatment of chronic conditions like diabetes, hypertension, and cardiovascular disease. The goal of the current study was to create a formulation that would increase the effectiveness of oral therapy while maintaining optimal control over plasma drug levels. It included two antidiabetic medications, glimepiride and metformin HCl. A bilayer tablet formulation with two drug-containing layers—a sustained-release layer for metformin and an immediate-release layer for glimepiride—has been created.

Key Words: Sustained Release, Metformin HCL, Glimepiride, Matrix Formulation, Prolonged Release.

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I. INTRODUCTION

The goal of this study was to create a combination medication therapy for antidiabetic tablet formulations with distinct mechanisms of action that work in concert to successfully lower blood glucose levels. The combined action of metformin and glimepiride on type 2 diabetes's insulin resistance and insulin deficit may explain the medication's stronger effects on glycaemia. Compared to other sulfonylureas1, glimepiride retains a more physiological regulation of insulin secretion and carries a lower risk of hypoglycemia.

Wet granulation was used to independently create the extended-release form of metformin and the immediate-release form of glimepiride, which were then mixed to create a bilayer tablet. Two matrix formulations—one utilizing a hydrophobic polymer and the other using a hydrophilic matrix system, such as PEO and HPMC—were created in order to prepare

the metformin extended-release form. To create a tablet that would release over the course of 24 hours, researchers looked into the potential of hydrophobic and hydrophilic polymers (polyethylene oxide and hydroxypropyl methylcellulose) to function as a release controlling matrix for highly water-soluble metformin. As a result, adding a new medication makes more sense than replacing the current one. Combination therapy with two or three complementary oral anti-diabetic medications is quickly being introduced.

The medication concentration in the blood and tissues varies greatly with conventional dosage forms, leading to unfavorable toxicity and ineffectiveness. The idea of regulated medication delivery systems originated from these dynamics, which include irratic absorption and recurrent dosage. Reducing the frequency of dosage, increasing medication effectiveness via localization at the site of action, lowering the dose needed, or ensuring uniform drug distribution are the goals when building sustained or controlled delivery systems. Ensuring medication safety and efficacy while also increasing patient compliance1 are the primary goals of sustained release drug delivery.

In order to enable various forms of drug delivery of one or more medications, the layers are formulated utilizing several rate-controlling polymers. The drug may be delivered in the GI tract with targeted drug delivery or released as a bolus followed by a regulated rate. Bi-layer tablets come in a range of applications and can be made of multilayered matrices or monolithic partially coated materials. In the case of bi-layered tablets, if the medicine is included into the upper non-adhesive layer, its administration into the entire oral cavity can be made nearly unidirectional. Several problems arise in the manufacturing of tablets with two layers.

Bi-layer tablet development is required for the following reasons:

To monitor fixed dose combinations of medications, extend the life of drug products, create buccal/mucoadhesive delivery systems, and produce innovative drug delivery systems like chewing devices and floating tablets for gastro-retentive drug delivery systems.

1. Regulating the delivery rate of one or two distinct APIs.

2. To provide erodible/swellable barriers for controlled release, the API layer's total surface area can be modified by sandwiching it between one or two inactive layers.

3. Using the functional feature of the other layer (like the osmotic property) to regulate the release of one layer and to isolate incompatible APIs from one another.

Advantages of bi-layer tablets:

1. Bi-layer operation with a single layer conversion kit available as an option.

2. Inexpensive in comparison to alternative dose forms.

3. The highest level of microbiological and chemical stability when compared to other oral dosing methods.

4. Coating methods can disguise undesirable taste and odor.

5. Adaptable idea.

6. Provide the least amount of content uniformity and the highest level of precision.

7. Simple to swallow, with minimal hang-up issues.

8. Suitable for large scale manufacturing.

9. A bi-layer tablet can be used to maximize the effectiveness of a medicine combination by preventing direct contact between the two substances.

10. Because one of the layers can be kept extended and the other as immediate release, bi-layer tablets can be made to have a modified release.

11. A traditional technology's expansion.

12. The potential application of feed granules for a single entity.

13. Distinguishing incompatible parts.

14. Better patient compliance results in more effective medication regimens.

Disadvantages of Bilayer Tablet:

1. Bi-layer rotary presses are costly and add complexity.

2. Reduced yield, layer separation, and inadequate hardness.

3. Inaccurate weight management for individual layers.

4. Inter-layer cross-contamination.

5. Difficult for people who are unconscious or children to swallow.

6. Because of their low density and amorphous nature, several medications are resistant to compaction into dense compacts.

7. It may be challenging to produce a tablet that will nevertheless have sufficient drug bioavailability for medications with poor wetting, slow dissolution characteristics, and optimal absorption high in the GIT.

Fig 1: Bilayer Tablet

General characteristics of dose formulations for bi-layer tablets:

1. The product should be elegantly designed and free of flaws such as contamination, chipping, fractures, and discoloration.

2. It should be strong enough to withstand mechanical shock while being made, packaged, shipped, and dispensed.

3. It should be stable both chemically and physically.

4. The medicine must be released from the bi-layer tablet in a predictable and repeatable way.

5. The shelf life needs to be chemically stable in order to prevent the therapeutic substances from changing.

Types of bi-layer tablet presses:

* Single sided tablet press.

* Double sided tablet press.

* Bi-layer tablet press with displacement.

Class of Metformin HCL: Biguanide

Action Mechanism:

Metformin mainly acts by lowering hepatic gluconeogenesis, the liver's process of producing glucose.

Additionally, it improves glucose absorption by making muscle cells more sensitive to insulin.

It can also somewhat lessen the amount of glucose that the intestines absorb from food.

Indications:

It is typically prescribed for Type 2 diabetes, especially for people who are overweight or have insulin resistance.

Metformin is often used as a first-line treatment due to its effectiveness and low risk of causing low blood sugar (hypoglycemia).

Glimepiride

Class: Sulfonylurea

Glimepiride's mode of action involves inducing an increase in insulin production by the pancreas. It causes an increase in insulin secretion by binding to certain receptors on pancreatic beta cells.

By raising blood insulin levels and encouraging cells to absorb glucose, this drug lowers blood sugar.It is used to treat Type 2 diabetes, frequently when metformin and other drugs are insufficient to manage blood glucose levels.

Combination Use:

Glimepiride and metformin together can offer a more thorough method of controlling blood sugar in people with Type 2 diabetes. Glimepiride aids in boosting insulin production, whereas metformin mainly treats insulin resistance. Nevertheless, the combination raises the possibility of hypoglycemia, particularly in cases where meals or exercise are not scheduled consistently.

II. EVALUATION PARAMETER OF BILAYER TABLET

1. Weight Variation Test.

2. Hardness Test.

3. Friability Test.

4. Dissolution Test.

5. Disintegration Test.

1.Weight Variation Test:

Twenty (20) tablets from each batch were individually weighed in grams(gm) on an analytical balance. The average weight, standard deviation and relative standard deviation were reported. The tablet compression machine was suitably adjusted to produce tablets of uniform weight. The tablet weight test is a critical quality control measure ensuring uniformity in tablet weight, which directly affects dosage accuracy. According to USP guidelines, tablet weight variation should not exceed ±5% of the average weight. To conduct the test, a random sample of 20-30 tablets is selected, and each tablet is individually weighed. The average weight is calculated, and the percentage deviation for each tablet is determined.15

Acceptance Criteria:

i. The average weight should be within ±5% of the labeled weight.

ii. No single tablet weight should deviate by more than ±10% from the average weight.

iii. Not more than two tablets should deviate by more than ±5% from the average weight

2. Hardness Test:

The hardness test is typically performed using a tablet hardness tester (e.g., Monsanto, Dr. Schleuniger).

Acceptance criteria for bilayer tablets:

i. Minimum hardness: 6-12 kg (kiloponds) or 60-120 N (Newtons)

ii. Average hardness: 8-15 kg or 80-150 N

iii. Variance: ±10-20% of the average hardness

iv. Layer separation force: ≥2 kg or 20 N

Fig 2: Hardness Tester

3. Friability Test:

The friability test evaluates the ability of bilayer tablets to withstand abrasion and resistance to powdering. This test ensures the tablet's mechanical strength and stability during handling, transportation, and storage.

Test Procedure:

1. Weigh 20-30 bilayer tablets.

2. Place tablets in a friabilator (e.g., Roche friabilator).

3. Rotate friabilator 100 times.

4. Re-weigh tablets.

5. Calculate friability (%) = (Initial weight - Final weight) / Initial weight × 100.

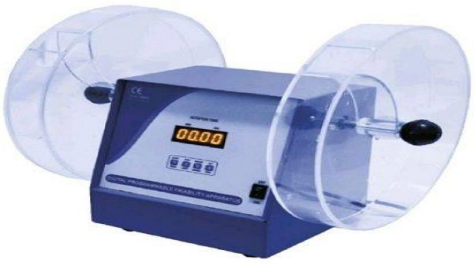

Fig 3: Friability Test Apparatus.

Acceptance Criteria:

i. Friability: ≤1% weight loss.

ii. Maximum allowable weight loss: 1.5%.

4. Dissolution Test

The dissolution test for bilayer tablets evaluates the release of active pharmaceutical ingredients (APIs) from both immediate-release (IR) and sustained-release (SR) layers. This test ensures the tablet's bioavailability, efficacy, and safety.

Test Procedure:

1. Use USP Apparatus 1 (Basket) or 2 (Paddle).

2. Select appropriate dissolution medium (e.g., water, phosphate buffer).

3. Operate at 37°C ± 0.5°C.

4. Measure API release at specified time points (e.g., 15, 30 minutes, 1, 2, 4, 8, 12 hours).

Acceptance Criteria:

i. IR layer: ≥85% API release within 30 minutes.

ii. SR layer: API release over 12 hours, following a predetermined profile (e.g., zero-order, firstorder).

Fig 4: Dissolution Tesr Apparatus.

5. Disintegration Test:

The disintegration test for bilayer tablets is a quality control measure that assesses the tablet's ability to break down into smaller particles within a specified time frame, allowing for proper release of the active ingredients. The test involves placing 1-6 bilayer tablets in a cylindrical basket with a mesh bottom, suspending it in a water bath at 37°C, and moving the basket up and down at a specified frequency. The time it takes for the tablets to disintegrate completely is recorded, with acceptance criteria typically ranging from 15-30 minutes for immediate-release layers and 1-2 hours for sustained-release layers.

III. CONCLUSION

A bi-layer tablet is an enhanced, useful technology that gets around the drawbacks of a single-layered tablet. The bi-layer tablet, which consists of monolithic partially coated or multilayered matrices, has a variety of applications. A bi-layer tablet can be used to segregate two incompatible substances, release two medications in succession, or create a sustained release tablet with a maintenance dose in the second layer and an immediate release as the initial dose in the first layer. In order to give controlled release tablet preparations with surrounding or multiple swelling layers, and to create systems for the administration of medications that are incompatible, tablets are prepared in the shape of several layers. Pharmaceutical development and quality risk management are two scientific and quality risk management strategies that must be applied in order to establish a comprehensive mechanistic understanding for the creation of a dynamic bi-layer tablet. GMP regulations and the quality of bi-layer tablets can differ greatly. This explains why a wide variety of presses, from basic single-sided presses to extremely complex devices, are utilized to create bi-layer tablets. The employment of a "air compensator" in conjunction with displacement control seems to be the ideal option where high-quality bi-layer tablets need to be manufactured quickly.

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