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Research Article

Design and evaluation of bi-layered tablet of Ramipril and hydrochlorothiazide for the Treatment of hypertension

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Abstract:

Hypertension is a widespread cardiovascular disease that requires effective management through combination therapy. The complexity of hypertension necessitates a multifaceted approach, often involving the concurrent administration of multiple antihypertensive agents. This study aims to design, formulate, and evaluate bi-layered tablets of Ramipril and Hydrochlorothiazide, leveraging the benefits of sequential drug release and stability enhancement. The bi-layer tablet formulation comprises an immediate-release layer for rapid therapeutic onset and a sustained-release layer for prolonged plasma drug concentration, thereby providing a synergistic effect in reducing blood pressure. Ramipril, an angiotensin-converting enzyme (ACE) inhibitor, and Hydrochlorothiazide, a diuretic, are commonly used in combination therapy for the treatment of hypertension. The rationale behind this combination lies in their complementary mechanisms of action, which together provide a more effective reduction in blood pressure than either drug alone. The proposed formulation utilizes a range of excipients, including Pregelatinized Starch, Microcrystalline Cellulose, Lactose Anhydrate, Sodium Bicarbonate, Sodium Stearyl Fumarate, Cross Carmellose Sodium, Talc, Povidone, and Hydroxy Propyl Methyl Cellulose (HPMC), carefully selected to achieve the desired drug release profiles. The bi-layer tablet technology offers several advantages, including the ability to separate two incompatible drugs, provide sequential release of two drugs in combination, and achieve sustained release of one drug while the other provides immediate therapeutic effects. This study focuses on formulating and characterizing monolayer and bilayer tablets to enhance stability, improve patient compliance, and provide a synergistic therapeutic effect. The proposed research will involve the optimization of formulation variables, such as the ratio of excipients and the compression force, to achieve the desired drug release profiles. The tablets will be evaluated for various physicochemical parameters, including hardness, friability, weight variation, and content uniformity. In vitro drug release studies will be conducted to assess the release profiles of Ramipril and Hydrochlorothiazide from the bi-layer tablets. By developing a bi-layer tablet formulation of Ramipril and Hydrochlorothiazide, this study aims to provide a more effective and convenient treatment option for patients with hypertension, ultimately improving patient outcomes and quality of life.

Key Highlights:

1. Bi-layer tablet formulation for sequential release of Ramipril and Hydrochlorothiazide.
2. Immediate-release layer for rapid therapeutic onset.
3. Sustained-release layer for prolonged plasma drug concentration.
4. Excipient selection for enhanced stability and drug release.
5. Optimization of formulation variables for desired drug release profiles.
6. Evaluation of physicochemical parameters and in vitro drug release profiles.

Introduction

Introduction to Tablet Oral route has been the most commonly adopted and the most convenient route for drug delivery. Oral route of administration has received more attention in the pharmaceutical field because of more flexibility in the designing of dosage form than the drug delivery design for other routes. It is probable that at least 90% of all drugs used to produce systemic effects are administered by the oral route. The oral route of administration still continues to be the most preferred route due to its manifold advantages including ease of ingestion, pain avoidance, versatility, and most importantly patient compliance. The most popular dosage forms being tablets and capsules, one important drawback of these dosage forms however is the difficulty to swallow (1)

Bi-layered tablets have emerged as a versatile and innovative drug delivery system, offering numerous benefits in the management of various diseases. This technology involves the compression of two distinct layers of drugs and/or excipients into a single tablet, allowing for the simultaneous or sequential release of multiple active pharmaceutical ingredients (APIs). Bi-layered tablets provide a range of advantages, including improved patient compliance, enhanced therapeutic efficacy, and increased flexibility in drug delivery.

Ideal Properties of Tablet Dosage Form:

1. Should be an elegant product having its own identity while being free of defects such as chips, cracks, discoloration, contamination, and the like.
2. Should have the strength to withstand the rigors of mechanical shocks encountered in its production, packaging, shipping and dispensing.
3. Should have the chemical and physical stability to maintain its physical attributes over time.

On the other hand, the tablet

1. Must be able to release the medicinal agents in the body in a predictable and reproducible manner, and
2. Must have a suitable chemical stability over times so as not to allow alteration of the medicinal agents. (2)

Types of Delivery Systems

1. Systemic Release Dosage Form
2. Drug Targeting Dosage Forms

The former system releases the drug in a controlled or modified manner in the GIT for the systemic uptake with no particular area of GIT specified. While the later targets the drug to a specified part of body.

Immediate Release System: In this system which releases the drug immediately after administration.

Extended Release System: Also known as delayed-release system, are those that use repetitive, intermittent dosing of a drug from one or more immediate-release units incorporated in to a single dosage form. A dosage form that allows at least a twofold reduction in dosage frequency as compared to that presented as an immediate release (conventional) dosage form.

Modified Release System: The term modified-release drug product is used to describe products that after the timing and/or release of the drug

substances. A modified- release dosage form is defined "as for which the drug-release characteristics of time course and/or locations are choose to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized. (3)

Quality and GMP-requirements for Bi-layer tablets.

To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of:

1. Preventing capping and separation of the two individual layers that constitute the bi-layer tablet.
2. Providing sufficient tablet hardness.
3. Preventing cross-contamination between the two layers.
4. Producing a clear visual separation between the two layers.
5. High Yield.
6. Accurate and individual weight control of the two layers. (4)

Advantages

1. This dosage form has the advantage of separating two incompatible substances.
2. It makes possible sustained-release preparations with the immediate-release quantity in one layer and the slow-release portion in the second.
3. The weight of each layer can be accurately controlled, in contrast to putting one drug of a combination product in a sugar coating.
4. Two-layer tablets require fewer materials than compression coated tablets, weight less, and may be thinner.
5. Monograms and other distinctive markings may be impressed on the surfaces of the multilayer tablets. Coloring may possibilities for unique tablet identity.
6. Analytical work may be simplified by separating of the layers prior to assay.
7. Since there is no transfer to second set of punches and dies, as with the dry- coating machines, add shapes (such as triangles, squares, and ovals) present no operating problems except for those common to keyed tolling.
8. Bi-layer tablets are prepared with one layer of drug for immediate release with second layer design to release drug, later, either as second dose or in an extended-release manner. Bi-layer tablets are tablet, made by compressing two different granulations fed into a die succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet press can be set up for two or three layers. More are possible but the design becomes very special. (5)

Mechanism of Action:

1. Layered Structure: Bi-layered tablets consist of two distinct layers, each containing a specific drug or excipient. This layered structure allows for the simultaneous or sequential release of multiple active pharmaceutical ingredients (APIs).
2. Drug Release: The drug release mechanism depends on the formulation and design of each layer. Common mechanisms include:
   - Immediate Release (IR): One layer can be formulated for immediate release, providing a rapid onset of action.
   - Sustained Release (SR): The other layer can be designed for sustained release, providing a prolonged therapeutic effect.
   - Delayed Release: One layer can be formulated to delay the release of the drug, allowing for targeted delivery or reduced side effects.
3. Excipient Selection: The choice of excipients in each layer plays a crucial role in controlling drug release. Excipients can be selected to:
   - Enhance Solubility: Improve the solubility of poorly soluble drugs.
   - Modify Viscosity: Control the viscosity of the layer to influence drug release rates.

- Target Specific Sites: Deliver drugs to specific sites in the body, such as the colon or stomach.

Benefits

1. Improved Patient Compliance: Bi-layered tablets can reduce the number of pills a patient needs to take, improving compliance.
2. Enhanced Therapeutic Efficacy: The combination of multiple drugs or release profiles can lead to improved therapeutic outcomes.
3. Increased Flexibility: Bi-layered tablets offer flexibility in drug delivery, allowing for tailored release profiles and targeted delivery.

Applications

1. Chronic Diseases: Bi-layered tablets are suitable for managing chronic diseases, such as hypertension, diabetes, or asthma.
2. Combination Therapy: They are ideal for combination therapy, where multiple drugs are used to treat a single condition.
3. Targeted Delivery: Bi-layered tablets can be designed for targeted delivery, reducing side effects and improving efficacy. (6)

Formulation Evaluation (7)

1. Physical Properties:
   - Weight variation
   - Thickness
   - Hardness
   - Friability
2. Content Uniformity:
   - Assay of active ingredients in each layer
   - Uniformity of dosage units
3. In Vitro Drug Release:
   - Dissolution testing for each layer
   - Release profiles (e.g., immediate, sustained, delayed)
4. Stability Studies:
   - Short-term and long-term stability testing
   - Evaluation of degradation products
5. Compatibility Studies:
   - Excipient compatibility with active ingredients
   - Interaction between layers

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