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Review Paper

Formulation and Evaluation of Mouth Dissolving Film of Azilsartan Medoxomil using Novel Polymer Combination (HPMC, Soluplus, and beta-Cyclodextrin): A Review

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ABSTRACT

Azilsartan Medoxomil (AZL) is a potent, long-acting angiotensin II receptor blocker (ARB) used primarily for the management of hypertension. Despite its clinical efficacy, its therapeutic potential is significantly limited by its low aqueous solubility and poor oral bioavailability, categorized under the Biopharmaceutics Classification System (BCS) as a Class II drug. To overcome these challenges, Mouth Dissolving Films (MDFs) have emerged as an innovative drug delivery system that offers rapid disintegration in the oral cavity without the need for water, bypassing first-pass metabolism and potentially enhancing bioavailability. This review explores the formulation strategies for AZL-MDFs focusing on a novel synergistic polymer combination consisting of Hydroxypropyl Methylcellulose (HPMC), Soluplus, and beta-Cyclodextrin (beta-CD). HPMC serves as a robust film-forming agent, Soluplus acts as a polymeric solubilizer and stabilizer for solid dispersions, and beta-Cyclodextrin facilitates inclusion complexation to enhance the solubility of the hydrophobic drug moiety. The paper discusses the physicochemical properties of these materials, the techniques for film preparation, specifically solvent casting—and the critical evaluation parameters including mechanical properties, disintegration time, and in-vitro dissolution profiles. By integrating these novel excipients, a superior delivery platform for AZL can be achieved, ensuring better patient compliance and optimized therapeutic outcomes.

INTRODUCTION

Hypertension remains a global health challenge, serving as a primary risk factor for cardiovascular diseases, stroke, and renal failure. Azilsartan Medoxomil (AZL) is an ester prodrug that is hydrolyzed to its active moiety, azilsartan, which selectively inhibits the binding of angiotensin II receptor. While it demonstrates superior blood

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pressure-lowering efficacy compared to olmesartan and valsartan, its clinical application is hindered by its poor solubility in water, leading to inconsistent absorption patterns [1], [2].

In recent years, the pharmaceutical industry has shifted focus toward patient-centric dosage forms. Mouth Dissolving Films (MDFs) or Oral Lyophilisates are thin, elegant strips that hydrate rapidly when placed on the tongue, releasing the medicament within seconds [3]. This dosage form is particularly advantageous for geriatric patients who suffer from dysphagia, pediatric populations, and patients who lack immediate access to water. Furthermore, the sublingual or pregastric absorption potential of MDFs can bypass hepatic first-pass metabolism, directly entering the systemic circulation [4].

The primary challenge in formulating AZL as an MDF lies in its hydrophobicity. Traditional film-forming agents may not provide sufficient solubility enhancement. Therefore, this review proposes a novel ternary approach using HPMC (as the structural matrix), Soluplus (as a solubility enhancer), and beta-Cyclodextrin (as a complexing agent). The synergy between these three components aims to bridge the gap between rapid disintegration and high drug loading with optimized dissolution rates.

2. Drug Profile: Azilsartan Medoxomil

Azilsartan Medoxomil, chemically known as (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate, has a molecular weight of 568.5 g/mol [5]. It is a BCS Class II drug, characterized by high permeability but low solubility.

2.1 Mechanism of Action

AZL acts by blocking the vasoconstrictor and aldosterone-secreting effects of angiotensin II. It binds more tightly to the AT receptors and dissociates more slowly than other ARBs, providing 24-hour blood pressure control [6].

2.2 Rationale for MDF Formulation

Conventional oral tablets of AZL exhibit a bioavailability of approximately 60%. By formulating AZL into an MDF, the drug can be partially absorbed through the oral mucosa. The high vascularization of the oral cavity allows for direct entry into the jugular vein.

3. Novel Polymer Combination

The success of an MDF depends heavily on the selection of polymers that provide mechanical strength, flexibility, and rapid dissolution.

3.1 Hydroxypropyl Methylcellulose (HPMC)

HPMC is a semi-synthetic, hydrophilic, and biodegradable polymer. Grades such as E5, E15, and K100 are commonly used in MDFs due to their excellent film-forming properties [8]. HPMC provides the necessary tensile strength to the film, ensuring it does not tear during packaging or handling. However, used alone, HPMC may not significantly improve the solubility of AZL [9].

3.2 Soluplus

Soluplus is a relatively new graft copolymer consisting of polyvinyl caprolactam, polyvinyl acetate, and polyethylene glycol (PCL-PVAc-PEG). It is specifically designed for the solid dispersion of poorly soluble drugs. In an MDF formulation, Soluplus acts as a polymeric emulsifier and solubilizer, maintaining the drug in an amorphous state within the HPMC matrix, thereby preventing recrystallization and enhancing the dissolution rate [10], [11].

3.3 beta-Cyclodextrin (beta-CD)

beta-Cyclodextrin is a cyclic oligosaccharide with a hydrophobic interior cavity and a hydrophilic exterior. It forms "host-guest" inclusion complexes with hydrophobic drugs like AZL. The

inclusion of the hydrophobic tail of AZL into the beta-CD cavity masks the bitter taste of the drug and significantly increases its apparent solubility in the saliva [12].

4. Formulation Methodology

4.1 Inclusion Complex Preparation

Before film formation, AZL is often complexed with beta-CD using techniques such as kneading, co-precipitation, or spray drying. The 1:1 molar ratio is typically optimized to ensure maximum entrapment efficiency. This complex acts as the "active" phase to be dispersed in the polymer solution [13].

4.2 Solvent Casting Technique

The most widely used method for MDF preparation is the solvent casting method.

1. **Preparation of the Aqueous Solution:** HPMC is dissolved in warm water.
2. **Solubilization:** Soluplus is added to the HPMC solution under continuous stirring.
3. **Drug Incorporation:** The AZL-beta-CD complex is dispersed into the polymeric solution.
4. **Addition of Plasticizers:** Glycerol or Propylene Glycol (PG) is added at concentrations of 10-20% w/w of the polymer to provide flexibility.
5. **Casting:** The solution is de-aerated to remove air bubbles and cast onto a glass mold or a Teflon-coated plate.
6. **Drying:** The films are dried in a controlled environment (usually 40-50°C) until a constant weight is achieved [14], [15].

5. Physicochemical Evaluation Parameters

To ensure the quality and performance of the AZL-MDF, several evaluation parameters must be standardized.

5.1 Morphological and Organoleptic Properties

Films must be checked for color, odor, and surface texture. Scanning Electron Microscopy (SEM) is used to observe the surface morphology to ensure the drug is uniformly distributed and the surface is non-porous [16].

5.2 Mechanical Properties

1. **Thickness:** Measured using a micrometer screw gauge at multiple points to ensure uniformity (typically 0.05 to 0.1 mm).
2. **Tensile Strength:** The maximum stress a film can withstand before breaking. A balance between flexibility and toughness is required.
3. **Folding Endurance:** Calculated by repeatedly folding the film at the same place until it breaks. An endurance value of >200 is generally considered ideal [17], [18].

5.3 Disintegration and Dissolution

1. **In-vitro Disintegration Time:** The film is placed in a beaker containing 10 ml of simulated salivary fluid (pH 6.8). For a standard MDF, disintegration should occur within 30 seconds [19].
2. **In-vitro Dissolution Study:** Conducted using USP dissolution apparatus (Type II - Paddle) in 900 ml of phosphate buffer (pH 6.8). Because AZL is poorly soluble, the addition of Soluplus and beta-CD is expected to result in >85% drug release within 10 minutes [20].

5.4 Solid State Characterization

1. **Differential Scanning Calorimetry (DSC):** Used to detect the crystallinity of AZL. The disappearance of the drug's endothermic peak suggests its conversion to an amorphous form within the polymer matrix.
2. **X-Ray Diffraction (XRD):** Confirms the amorphous or crystalline nature of the drug in the film [21].
3. **FTIR Spectroscopy:** Used to check for chemical interactions between AZL, HPMC,

Soluplus, and beta-CD. The absence of new peaks or significant shifts indicates compatibility [22].

6. Discussion: The Synergistic Mechanism

The combination of HPMC, Soluplus, and beta-CD creates a multi-layered approach to drug delivery. HPMC provides the structural integrity (The "Skeleton"), creating a thin, manageable strip. beta-Cyclodextrin addresses the molecular-level solubility issues by encapsulating the AZL molecules, shielding their hydrophobic nature from the aqueous environment of the saliva [23]. Soluplus then acts as a secondary stabilizer, inhibiting the precipitation of the drug once the film hydrates.

Research suggests that Soluplus can form micelles that further solubilize complexed drugs, creating a supersaturated state in the localized oral environment. This leads to a higher concentration gradient across the oral mucosa, facilitating passive diffusion. Furthermore, the use of beta-CD is instrumental in taste masking, as AZL has a slightly bitter aftertaste which could lead to patient non-compliance if not addressed [24-25].

7. Challenges and Regulatory Considerations

While MDFs offer numerous advantages, challenges include:

1. **Drug Loading:** Only low doses of drugs (typically <30 mg) can be effectively incorporated into a standard-sized film. Since AZL doses are usually 40 mg or 80 mg, the thickness and size of the film must be carefully optimized or high-potency versions must be explored [26].
2. **Moisture Sensitivity:** Due to the hygroscopic nature of HPMC and Soluplus, the films require specialized moisture-proof packaging (e.g., aluminum pouches) to prevent stickiness or degradation [27].

From a regulatory standpoint, the FDA and EMA require stringent testing for "Uniformity of Dosage Units" and "Residual Solvents" if organic solvents are used during the casting process, although aqueous-based casting is preferred for HPMC [28].

CONCLUSION

The formulation of Azilsartan Medoxomil into a Mouth Dissolving Film using a combination of HPMC, Soluplus, and beta-Cyclodextrin represents a significant advancement in antihypertensive therapy. This ternary system effectively addresses the poor solubility of AZL through inclusion complexation and polymeric stabilization while maintaining the rapid disintegration characteristics required for an MDF. The synergy between the film-forming ability of HPMC, the solubilizing power of Soluplus, and the complexing efficiency of beta-CD provides a robust platform for enhancing the bioavailability of BCS Class II drugs. Future studies involving in-vivo pharmacokinetics and long-term stability under various climatic conditions are essential to translate this delivery system from the laboratory to the clinical market.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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