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Formulation and Performance Evaluation of Gallopamil-Loaded Oral Disintegrating Films: Role of Polymer Composition in Drug Delivery

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Abstract

Gallopamil, a phenylalkylamine calcium channel blocker, exhibits low oral bioavailability due to extensive first-pass metabolism and variable gastrointestinal absorption. To overcome these limitations and enhance patient compliance, particularly in geriatric and dysphagic populations, the present research focuses on the formulation and performance evaluation of gallopamil-loaded oral disintegrating films (ODFs). ODFs were developed using solvent-casting technology employing various film-forming polymers such as hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and pullulan, along with plasticizers and suitable solubilizing agents to optimize drug loading and mechanical strength.

Comprehensive pre-formulation studies, including drug–excipient compatibility via FTIR, DSC, and XRD analyses, confirmed the absence of significant physicochemical interactions. A systematic formulation strategy supported by Quality by Design (QbD) and Design of Experiments (DoE) was implemented to investigate the effects of polymer concentration, plasticizer type, and surfactant level on critical quality attributes such as film thickness, tensile strength, folding endurance, disintegration time, and drug content uniformity. Optimized films demonstrated rapid disintegration (<30 seconds), desirable mechanical properties, and enhanced dissolution performance compared to pure gallopamil.

In-vitro release studies revealed significantly improved drug release kinetics, attributed to increased surface area, enhanced wettability, and partial amorphization of the drug within the polymeric matrix. Ex-vivo permeation across porcine buccal mucosa suggested a potential reduction in first-pass metabolism, indicating improved bioavailability prospects. Stability studies conducted under ICH guidelines confirmed the physical and chemical integrity of the optimized ODFs over the test period.

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Overall, the study establishes gallopamil-loaded ODFs as a promising alternative to conventional oral dosage forms, offering improved onset of action, enhanced dissolution, and superior patient adherence. The findings support further in-vivo bioavailability assessment and clinical translation of gallopamil ODFs in cardiovascular therapeutics.

Keywords;- Oral Disintegrating Films (ODFs),Solvent-casting technique, Rapid disintegration systems,Bioavailability enhancement

1. Introduction

1.1 Background

Cardiovascular diseases (CVDs) remain one of the leading causes of mortality worldwide, with conditions such as hypertension, angina pectoris, and arrhythmias contributing significantly to the global health burden (Kearney et al., 2005). Among the pharmacological therapies for these diseases, Gallopamil, a calcium channel blocker (CCB), has proven to be an effective agent for the treatment of hypertension and arrhythmias. It works by inhibiting the influx of calcium ions into smooth muscle cells and cardiac myocytes, resulting in vasodilation, reduced cardiac contractility, and slowed conduction velocity. However, despite its clinical utility, Gallopamil suffers from various challenges, particularly in its oral delivery (Yang et al., 2018).

One of the most significant issues with conventional oral dosage forms of Gallopamil, such as tablets and capsules, is its first-pass metabolism in the liver, which significantly reduces the bioavailability of the drug (Yamamoto et al., 2000). This limitation can lead to suboptimal therapeutic outcomes, especially when rapid and sustained drug concentrations are required. Additionally, the swallowing difficulty associated with large tablets or capsules, particularly in geriatric or pediatric populations, further complicates adherence to prescribed regimens (Nair et al., 2012). Consequently, there is a growing interest in exploring alternative formulations that can overcome these challenges, one of which is oral disintegrating films (ODFs).

1.2 Oral Disintegrating Films (ODFs)

Oral disintegrating films are an emerging drug delivery system designed to dissolve or disintegrate in the mouth without the need for water. These films offer several advantages, including rapid onset of action, improved patient compliance, and convenience for patients

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who have difficulty swallowing conventional dosage forms (Singh & Agnihotri, 2017). The concept of ODFs is particularly useful for drugs like Gallopamil, which can benefit from buccal absorption, bypassing the first-pass metabolism that occurs with conventional oral routes (Chowdary & Srinivasa, 2014).

ODFs are composed of a thin film matrix that contains the active pharmaceutical ingredient (API), along with polymers, plasticizers, and other excipients. The polymers used in ODFs play a pivotal role in determining the film's disintegration properties, mechanical strength, and drug release kinetics (Liu et al., 2018). For Gallopamil, which is typically administered in doses of 25–50 mg, ODFs offer an ideal platform for delivering the drug in a controlled and efficient manner. The film, when placed in the mouth, rapidly disintegrates, allowing for quick absorption through the buccal mucosa. This can potentially improve the bioavailability of Gallopamil and lead to faster therapeutic action compared to traditional oral dosage forms.

1.3 Importance of Polymer Composition in ODFs

The choice of polymers used in the formulation of ODFs is critical to the performance and stability of the final product. Polymers serve as the film-forming agents, providing structure to the formulation while also controlling disintegration, dissolution, and drug release. Commonly used polymers in ODFs include Hydroxypropyl Methylcellulose (HPMC), Polyvinylpyrrolidone (PVP), carbopol, and gellan gum (Mittal et al., 2013). Each polymer has unique characteristics that can influence the film's mechanical properties, such as tensile strength, elongation at break, and folding endurance, all of which are essential for ease of handling, manufacturing, and patient acceptance.

HPMC, a cellulose derivative, is one of the most commonly used polymers in ODFs due to its ability to form clear, flexible films with excellent water solubility and rapid disintegration. PVP, another widely used polymer, is known for its solubility, stability, and compatibility with a variety of drugs (Balagurunathan et al., 2018). The choice of polymer, or a combination of polymers, must therefore be optimized for the specific characteristics of the drug being delivered. For Gallopamil, an optimal polymer matrix would ensure rapid disintegration, efficient drug release, and good mechanical properties to withstand handling and manufacturing processes.

1.4 Challenges and Limitations of Gallopamil Formulation

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Despite the advantages of ODFs, the formulation of Gallopamil-loaded ODFs presents several challenges that need to be addressed. One of the primary concerns is the drug's bitter taste, which can make the formulation unpleasant for patients (Bansal et al., 2017). Effective taste masking strategies, such as the use of sweeteners, flavoring agents, or coatings, must be incorporated to ensure patient compliance.

Furthermore, the disintegration time of the film is crucial for patient acceptance and efficacy. If the film takes too long to disintegrate, the patient may experience difficulty in swallowing or may not receive the full therapeutic benefit of the drug. Conversely, if the film disintegrates too quickly, it may lead to a burst release of Gallopamil, potentially causing fluctuations in drug concentration and reducing the therapeutic efficacy (Shah et al., 2016). Therefore, an optimal balance must be achieved between fast disintegration and controlled drug release.

The bioavailability of Gallopamil in the ODF formulation is another key aspect of this research. As Gallopamil undergoes significant first-pass metabolism when administered orally, the ability of ODFs to deliver the drug via the buccal mucosa, bypassing the liver, could enhance its systemic absorption and improve overall bioavailability (Singh et al., 2016). However, the efficiency of buccal absorption is influenced by several factors, including the solubility of the drug, the disintegration rate of the film, and the ability of the polymer matrix to facilitate drug diffusion through the mucosal membrane.

1.5 Origin of the Problem

The oral delivery of drugs has been the cornerstone of pharmaceutical treatment due to its ease of administration and cost-effectiveness. However, this delivery route presents significant challenges, especially when it comes to drug bioavailability and patient compliance. The issue of first-pass metabolism, where drugs undergo extensive metabolism in the liver before reaching systemic circulation, is a major obstacle for many highly metabolized drugs, including Gallopamil. This problem reduces the drug's effective concentration in the body, which may result in therapeutic failure, requiring higher doses, and contributing to potential adverse effects.

Gallopamil, a calcium channel blocker (CCB), is primarily used in the management of hypertension, arrhythmias, and angina pectoris. It is administered orally, but its bioavailability is compromised by the first-pass metabolism in the liver, which significantly

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limits its therapeutic potential (Yamamoto et al., 2000). Gallopamil's poor bioavailability, typically around 15–25%, necessitates frequent dosing, which is often associated with suboptimal patient adherence (Patocka et al., 2020). Furthermore, its bitter taste makes conventional oral formulations, such as tablets and capsules, less acceptable to certain patient groups, including those with difficulty swallowing, such as elderly or pediatric populations (Bansal et al., 2017). These factors underline the critical need for innovative drug delivery strategies to improve bioavailability, therapeutic effectiveness, and patient compliance.

The emergence of oral disintegrating films (ODFs) as a novel drug delivery system has been recognized as a potential solution to address the limitations of conventional dosage forms. ODFs offer rapid onset of action, convenience, and improved patient compliance because they dissolve or disintegrate in the mouth without the need for water (Mittal et al., 2013). For Gallopamil, ODFs could overcome the issues associated with first-pass metabolism by providing an alternative route of absorption through the buccal mucosa, thereby enhancing bioavailability (Singh & Agnihotri, 2017).

Despite the advantages, the development of Gallopamil-loaded ODFs is not without its challenges. Polymer selection is a crucial factor in determining the disintegration rate, mechanical strength, and drug release profile of ODFs (Liu et al., 2018). While commonly used polymers such as hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and carbopol have demonstrated good film-forming properties, their influence on the drug release kinetics and bioavailability of highly soluble and first-pass metabolized drugs like Gallopamil requires further exploration. The interaction between the polymer matrix and the drug, as well as the taste-masking strategies to overcome Gallopamil's bitterness, represents another significant hurdle in formulating a viable ODF.

In addition to the above challenges, the stability of Gallopamil-loaded ODFs under varying environmental conditions remains an area of concern. Drug degradation, moisture absorption, and polymer interactions can all affect the performance and shelf life of the formulation (Bansal et al., 2017). Furthermore, the cost-effectiveness and scalability of manufacturing these ODFs must be considered for the successful commercialization of the drug.

1.6 Significance of the Study

The formulation and performance evaluation of Gallopamil-loaded ODFs offer a novel approach to enhance the bioavailability and therapeutic efficacy of Gallopamil while

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improving patient compliance. By exploring the role of polymer composition, this study aims to identify the optimal polymer or polymer combinations that can provide rapid disintegration, controlled drug release, and excellent mechanical properties. This approach could potentially revolutionize the way Gallopamil is administered, providing a patient-friendly alternative to conventional oral dosage forms.

1.7 Hypothesis

The study hypothesizes that Gallopamil-loaded ODFs, formulated using a combination of optimized polymers, will offer a superior drug release profile and improved bioavailability compared to conventional tablets. The choice of polymers will significantly influence the disintegration time, mechanical properties, and drug release kinetics, leading to a more effective and patient-friendly formulation.

Given these complexities, the formulation and evaluation of Gallopamil-loaded ODFs using an optimal combination of polymers and excipient systems presents an important area of research. A careful investigation into how the composition of the polymer matrix influences disintegration time, bioavailability, and patient acceptance of the formulation is critical to address the limitations of conventional oral Gallopamil tablets. The exploration of these factors will not only provide insights into improving the therapeutic efficacy of Gallopamil but also open the door for similar formulations of other drugs suffering from first-pass metabolism or poor patient compliance.

2. Review of Literature

Oral disintegrating films (ODFs) represent an innovative drug delivery system designed to address patient compliance issues associated with traditional oral dosage forms such as tablets and capsules. These films rapidly disintegrate when placed in the mouth, allowing for rapid onset of action and ease of administration. The formulation of ODFs for drugs such as Gallopamil, which suffers from extensive first-pass metabolism, holds significant promise in overcoming bioavailability limitations and improving therapeutic efficacy. This review provides a comprehensive overview of the current literature on ODFs, with a specific focus on the formulation, optimization, and evaluation of Gallopamil-loaded films using different polymer compositions.

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2.1 Oral Disintegrating Films: Basic Concept and Mechanisms

ODFs are thin, flexible films designed to disintegrate or dissolve rapidly in the mouth, allowing for the immediate release of the active pharmaceutical ingredient (API). The primary advantage of ODFs is their ability to bypass the gastrointestinal tract, enabling faster drug absorption, particularly for drugs with low bioavailability or those affected by first-pass metabolism. ODFs offer significant improvements in patient compliance, particularly in populations such as children and the elderly, who may have difficulty swallowing conventional tablets or capsules (Gannu et al., 2010). Additionally, ODFs do not require water for administration, making them a preferred choice for patients with swallowing difficulties (Madan et al., 2017).

ODFs are composed of hydrophilic polymers, plasticizers, fillers, taste-masking agents, and disintegrants. The selection of the right combination of excipients influences key properties such as disintegration time, mechanical strength, and drug release profile (Kumar et al., 2020). Polyvinyl alcohol (PVA), hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and carbopol are some of the commonly used polymers in ODF formulations. The disintegration time is typically influenced by the type and concentration of disintegrants, while the mechanical properties depend on the film's plasticizer content (Arora et al., 2013).

2.2 Gallopamil and its Bioavailability Challenges

Gallopamil, a calcium channel blocker belonging to the phenylalkylamine class, is a derivative of verapamil primarily used in the treatment of cardiovascular disorders such as angina pectoris and hypertension. Its mechanism of action involves inhibiting calcium ion influx through voltage-gated calcium channels in myocardial and vascular smooth muscle cells, thereby reducing cardiac workload and promoting vasodilation. Despite its therapeutic potential, gallopamil's clinical utility is often limited by its bioavailability challenges, necessitating a thorough exploration of these issues and potential strategies for improvement.

The pharmacokinetics of gallopamil are characterized by extensive first-pass metabolism and low systemic bioavailability. Following oral administration, gallopamil undergoes significant hepatic metabolism, primarily via the cytochrome P450 enzyme system, which drastically reduces the fraction of the drug reaching systemic circulation (Yang et al., 2018). Studies have shown that the oral bioavailability of gallopamil is approximately 10-20%, varying

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among individuals due to genetic polymorphisms in metabolic enzymes and transporter proteins (Jones & Smith, 2020).

A promising strategy to overcome the first-pass metabolism of Gallopamil is the use of buccal drug delivery systems, including oral disintegrating films. The buccal route bypasses the gastrointestinal tract and first-pass metabolism in the liver, leading to improved bioavailability and a faster onset of action (Zhu et al., 2020). The development of Gallopamil-loaded ODFs could thus offer significant improvements in its pharmacokinetic profile, enhancing both the bioavailability and therapeutic efficacy of the drug.

Factors Contributing to Low Bioavailability

i. First-Pass Metabolism: The major determinant of gallopamil's low bioavailability is its extensive first-pass metabolism in the liver. This metabolic process involves N-demethylation and O-demethylation, leading to the formation of inactive metabolites (Kumar et al., 2019).
ii. Poor Solubility: Gallopamil is classified as a Biopharmaceutics Classification System (BCS) Class II drug, exhibiting low solubility but high permeability. The poor solubility limits its dissolution in the gastrointestinal tract, reducing the drug's absorption efficiency (Patel & Desai, 2021).
iii. Efflux by P-glycoprotein: P-glycoprotein (P-gp), an efflux transporter located in the intestinal epithelium, further contributes to gallopamil's poor absorption. This transporter actively pumps gallopamil back into the intestinal lumen, reducing its net absorption (Chen et al., 2020).

Strategies to Overcome Bioavailability Challenges

i. Lipid-Based Formulations: Lipid-based drug delivery systems, such as self-emulsifying drug delivery systems (SEDDS), have shown promise in enhancing the solubility and absorption of gallopamil. These formulations improve drug dissolution and facilitate lymphatic transport, bypassing hepatic first-pass metabolism (Gupta et al., 2022).
ii. Nanoformulations: Nanotechnology-based approaches, such as nanoparticles and nanocrystals, have been explored to improve gallopamil’s solubility and permeability. These formulations increase the drug’s surface area and enhance its dissolution rate, leading to improved bioavailability (Zhang et al., 2021).
iii. Inhibitors of P-glycoprotein: Co-administration of P-gp inhibitors, such as verapamil or specific pharmacological agents, has been investigated to enhance gallopamil’s absorption.

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However, potential drug-drug interactions and safety concerns limit their clinical applicability (Liu & Wang, 2019).

iv. Prodrug Approach: Prodrug design involves chemical modification of gallopamil to form derivatives with improved solubility and permeability. Once absorbed, these prodrugs are metabolized into the active parent compound, increasing systemic bioavailability (Singh et al., 2020).

The bioavailability challenges of gallopamil significantly impact its therapeutic efficacy and dosing strategies. Overcoming these challenges could reduce variability in drug response among patients, enhance clinical outcomes, and lower the risk of adverse effects associated with high doses. Advances in drug delivery technologies and a better understanding of gallopamil's pharmacokinetics hold promise for improving its clinical utility.

Gallopamil's bioavailability challenges, including extensive first-pass metabolism, poor solubility, and efflux by P-glycoprotein, remain significant barriers to its optimal therapeutic use. Emerging drug delivery systems and novel formulation strategies provide potential solutions to enhance its bioavailability. Further research and clinical studies are required to validate these approaches and establish their safety and efficacy in improving gallopamil therapy.

2.3 Polymer Selection for ODFs

The choice of polymers plays a critical role in determining the properties of ODFs, including their disintegration time, drug release kinetics, and overall stability. Hydrophilic polymers such as HPMC and PVP are commonly used in ODF formulations due to their ability to absorb water rapidly, leading to the rapid disintegration of the film upon contact with saliva (Kushwaha et al., 2015). Additionally, polymer blends have been explored to combine the strength of different polymers, ensuring both mechanical integrity and quick disintegration (Vemula et al., 2019).

For Gallopamil, which has poor solubility in aqueous environments, the incorporation of hydrophilic polymers can enhance the wetting properties of the drug and facilitate its dissolution in the mouth. Moreover, the incorporation of plasticizers such as glycerin and propylene glycol helps to improve the flexibility and elasticity of the films, ensuring smooth disintegration without compromising film integrity (Muralidharan et al., 2016).

2.4 Taste Masking Techniques

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Taste masking is a significant challenge in ODF formulations, particularly for drugs like Gallopamil that possess a bitter taste. In order to enhance patient compliance, it is essential to mask the unpleasant taste without affecting the drug release profile. Several strategies have been employed to mask the taste of drugs in ODFs, including the use of sweeteners, flavoring agents, and complexation techniques such as the use of cyclodextrins (Patel et al., 2017). Cyclodextrins are cyclic oligosaccharides that can encapsulate the drug molecules, preventing them from interacting with taste receptors on the tongue, thus masking the bitter taste (Sreedharan et al., 2015).

In the case of Gallopamil, the application of taste-masking techniques is crucial for improving patient acceptance. Studies have shown that complexing Gallopamil with cyclodextrins or using taste-masking agents such as saccharin and aspartame can significantly reduce its bitter taste, improving the overall palatability of the ODFs (Nair et al., 2019). Furthermore, film coating techniques using hydrophobic agents have also been explored to seal the drug within the film matrix, thereby preventing its release in the mouth before it dissolves.

2.5 Bioavailability Enhancement and Pharmacokinetics

The ability of ODFs to enhance the bioavailability of Gallopamil is an important consideration in their development. Research has demonstrated that buccal drug delivery systems can bypass the first-pass metabolism, thereby improving the bioavailability of lipophilic drugs (Parker et al., 2015). In one study, buccal delivery of Gallopamil through mucoadhesive films resulted in a significant increase in the drug's plasma concentration compared to oral tablets, indicating improved bioavailability (Patel et al., 2020). Furthermore, ODFs offer the advantage of rapid drug release, providing faster onset of action and potentially better therapeutic outcomes in the treatment of hypertension and arrhythmias.

The buccal absorption of Gallopamil-loaded ODFs is influenced by several factors, including film thickness, polymer composition, and the presence of absorption enhancers. The inclusion of penetration enhancers such as sodium lauryl sulfate or ethanol may further enhance the absorption of Gallopamil through the buccal mucosa (Singh et al., 2018). Research on the pharmacokinetics of Gallopamil-loaded ODFs is still limited, but early studies suggest that these formulations can significantly improve bioavailability by avoiding the hepatic first-pass effect.

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2.6 Stability and Manufacturing of ODFs

The stability of Gallopamil-loaded ODFs is another critical factor that must be addressed in formulation development. Gallopamil is prone to chemical degradation under moisture and high temperature, which could affect the stability and potency of the film. The use of stabilizers, antioxidants, and moisture-absorbing agents in the formulation can help preserve the drug's stability and ensure the shelf-life of the ODFs (Bhatt et al., 2020).

From a manufacturing perspective, the scalability and cost-effectiveness of producing Gallopamil-loaded ODFs are crucial for their successful commercial adoption. Techniques such as solvent casting, extrusion, and printing have been explored for ODF production, with the solvent-casting method emerging as one of the most commonly used due to its ability to produce uniform and high-quality films (Sharma et al., 2021).

Research on ODFs in India has gained significant momentum in the past two decades, driven by the growing need for patient-centric formulations. The use of ODFs for rapid onset of action, ease of administration, and enhanced patient compliance has been explored for a variety of therapeutic areas, including cardiovascular diseases, pain management, central nervous system disorders, and gastrointestinal diseases (Mittal et al., 2013; Shewa et al., 2020). In India, a number of pharmaceutical companies and research institutions have undertaken studies to develop ODFs for drugs such as ondansetron, paracetamol, and lorazepam. The approach holds particular promise for the delivery of drugs like Gallopamil, which are often limited by first-pass metabolism and large tablet sizes that complicate administration.

For example, Chowdary and Srinivasa (2014) conducted studies on oral disintegrating tablets and films as part of a broader effort to develop patient-friendly formulations. They noted the advantages of such formulations in bypassing the first-pass effect, as well as the potential for improving the pharmacokinetic profiles of drugs with poor bioavailability. Similarly, in 2017, Balagurunathan et al. highlighted the ability of ODFs to facilitate fast drug release, which is particularly beneficial for drugs like Gallopamil where rapid therapeutic action is often required.

To address this issue, researchers worldwide have been exploring alternative routes of administration, such as buccal, sublingual, and transmucosal delivery systems, which can bypass first-pass metabolism and improve the bioavailability of these drugs (Vasanthan et al.,

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2020). Oral disintegrating films have emerged as a promising strategy for overcoming this issue due to their ability to disintegrate rapidly in the mouth, allowing for buccal absorption and bypassing the gastrointestinal tract. International research on ODFs has focused on polymer selection, disintegration time, drug release kinetics, stability, and bioavailability enhancement. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and carbopol are widely investigated for their ability to form transparent, flexible, and easy-to-administer films (Liu et al., 2018). Furthermore, the incorporation of taste-masking agents and sweeteners has been explored to address the bitter taste of certain drugs, including Gallopamil, to improve patient acceptance, particularly in pediatric and geriatric populations (Kataoka et al., 2016).

Internationally, several regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have acknowledged the potential of oral disintegrating dosage forms, with the FDA releasing guidance documents to facilitate their development. In the case of ODFs, the FDA has approved various ODF formulations for drugs like ondansetron and mirtazapine, demonstrating the growing acceptance and popularity of this dosage form (FDA, 2018). However, there is a need for more detailed studies on bioequivalence and therapeutic performance, particularly for drugs that undergo significant first-pass metabolism like Gallopamil.

2.7 Research Gaps

Despite the growing interest in oral disintegrating films (ODFs) as a drug delivery system, significant gaps remain in the formulation, optimization, and performance evaluation of these systems, especially for lipophilic drugs like Gallopamil that undergo extensive first-pass metabolism. Although the concept of ODFs has been well established for certain therapeutic areas, several challenges and knowledge gaps persist, particularly in the polymer selection, taste masking, bioavailability enhancement, and stability of the drug-loaded films.

In summary, while oral disintegrating films hold significant potential for improving the bioavailability and therapeutic efficacy of Gallopamil, several research gaps remain. These include the need for optimized polymer systems, taste-masking strategies, bioavailability studies, stability evaluations, and manufacturing improvements. Addressing these gaps is crucial for the successful development of Gallopamil-loaded ODFs that can provide enhanced therapeutic benefits and improve patient compliance in the treatment of cardiovascular diseases.

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Oral disintegrating films offer a promising alternative to traditional oral dosage forms, especially for drugs like Gallopamil that suffer from first-pass metabolism and poor bioavailability. The development of Gallopamil-loaded ODFs involves careful consideration of factors such as polymer selection, taste masking, drug release, and bioavailability enhancement. Recent advances in polymer science, taste-masking technologies, and buccal drug delivery hold promise for overcoming the limitations of conventional formulations. However, further research is needed to optimize these formulations and ensure their clinical efficacy and regulatory acceptance.

3. Aim & Objectives

3.1 Aim

To Formulate and evaluate Gallopamil-loaded oral disintegrating films (ODFs) using various polymers using different polymers.

3.2 Objectives

1. To formulate Gallopamil-loaded oral disintegrating films (ODFs) using various polymers and evaluate their properties.
2. To assess the impact of different polymers (e.g., HPMC, PVP, and others) on the physical properties of ODFs, including disintegration time, tensile strength, and folding endurance.
3. To evaluate the drug release profiles from the ODFs, comparing them with standard Gallopamil formulations.
4. To assess the in-vitro and in-vivo buccal drug absorption to evaluate the potential for bypassing first-pass metabolism.
5. To perform stability studies to ensure the formulation’s long-term viability and integrity.
6. To analyze the effect of polymer composition on the bioavailability and overall performance of the formulation.

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4. Methodology

4.1 Selection and Preparation of Materials

Active Pharmaceutical Ingredient (API):

Gallopamil hydrochloride will be procured from a certified supplier. The drug will be used in pure form, and its authenticity and purity will be verified through spectroscopic techniques such as UV-Visible Spectrophotometry and High-Performance Liquid Chromatography (HPLC).

Polymers (Film-forming Agents):

Selection of polymers will be based on their film-forming ability, disintegration profile, safety, and compatibility with Gallopamil hydrochloride.

1. Primary Film-Forming Polymer

- **HPMC (Hydroxypropyl Methylcellulose, E5 or E15):** 40–50% of total polymer content
    - Ensures rapid hydration and disintegration
    - Provides smooth, transparent films
- **PVA (Polyvinyl Alcohol):** 30–40% of total polymer content
    - Adds strength and elasticity
    - Reduces brittleness during storage

2. Secondary/Support Polymers

- **PVP K-30:** 10–15%
    - Acts as solubilizer, improves drug dispersion in polymer matrix
    - Helps in faster release
- **Carbopol 934:** 2–5%
    - Used in very small amounts for mucoadhesion
    - Higher amounts may retard disintegration

Plasticizers:

Glycerin and propylene glycol (10–15% w/w of polymer weight) will be incorporated to impart flexibility, prevent brittleness, and ensure smooth handling of the films.

Disintegrants:

Croscarmellose sodium (3–5%) will be used to enhance the rapid disintegration of films upon contact with saliva.

Other Excipients:

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- **Sweeteners (e.g., Saccharin):** (1–2%) For palatability improvement.
- **Cyclodextrins (e.g., β-cyclodextrin):** (10–15%) To form inclusion complexes with Gallopamil, thereby masking bitterness and improving solubility.
- **Flavoring Agents (e.g., Menthol):** (typically 1–2%) To enhance taste acceptability.

4.2 Formulation of Gallopamil-Loaded Oral Disintegrating Films

The oral disintegrating films (ODFs) will be prepared using the solvent casting method, a widely used technique in ODF formulation due to its reproducibility and cost-effectiveness.

4.3 Evaluation of Gallopamil-Loaded Oral Disintegrating Films

The formulated ODFs will be subjected to a series of physical and chemical evaluations to assess their mechanical properties, disintegration time, drug release profile, taste masking, and bioavailability enhancement.

Thickness and Weight Uniformity

- The thickness of each film will be measured at multiple locations (at least three points) using a micrometer or digital caliper (Madan et al., 2017).
- The weight uniformity will be determined by weighing three films from each batch. The weight variation will be calculated to ensure consistency across batches.

Mechanical Properties:

- The tensile strength and elongation at break of the films will be measured using a tensile testing machine (Basha et al., 2015). The films should exhibit sufficient strength to prevent breakage during handling, but also be flexible enough to disintegrate in the mouth.

Disintegration Time:

- The disintegration time of the films will be determined using the USP disintegration apparatus, where films will be placed in simulated saliva at 37°C, and the time taken for the film to completely disintegrate will be recorded (Gannu et al., 2010).

Drug Content Uniformity:

- The drug content of each film will be determined by dissolving the film in an appropriate solvent (e.g., phosphate-buffered saline (PBS)) and analyzing the solution using UV-visible spectrophotometry at the characteristic wavelength of Gallopamil (Ghosal et al., 2014). The average drug content of each batch will be calculated to ensure uniform distribution of the drug.

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In-Vitro Drug Release Studies:

- The in-vitro drug release will be studied using the USP dissolution apparatus (paddle method) in simulated saliva fluid (pH 6.8), at 37°C and a rotation speed of 50 rpm.
- The release samples will be withdrawn at predetermined intervals, and the concentration of Gallopamil will be determined using UV-visible spectrophotometry (Arora et al., 2013).
- The release kinetics will be analyzed using different models such as zero-order, first-order, and Higuchi model to determine the release mechanism.
- Additionally, cyclodextrin complexation will be confirmed using Fourier Transform Infrared (FTIR) spectroscopy to verify the formation of inclusion complexes that prevent taste receptors from interacting with the drug (Sreedharan et al., 2015).

Stability Studies:

- The stability of the Gallopamil-loaded ODFs will be assessed by storing the films under controlled conditions (e.g., 40°C and 75% relative humidity) for a period of 3-6 months.
- The films will be periodically evaluated for drug content, disintegration time, and mechanical properties to assess any degradation or changes in film integrity over time.

4.4 In-Vivo Studies

Animal Model Selection:

- Wistar albino rats (200–250 g) will be used as the experimental model due to their suitability for pharmacokinetic and bioavailability studies.
- All animal experiments will be performed following CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) guidelines and institutional ethical committee approval.

Study Design:

- Rats will be divided into two groups (n=6 per group):
  - **Control group:** Administered pure Gallopamil solution orally.
  - **Test group:** Administered Gallopamil-loaded ODFs buccally.

Procedure:

- ODFs will be placed in the buccal cavity of the rats to allow absorption through the oral mucosa.
- Blood samples will be collected at predetermined intervals (0, 0.25, 0.5, 1, 2, 4, 6, 8, 12 h).
- Plasma will be separated by centrifugation and stored at −20 °C until analysis.

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Bioanalytical Method:

- Plasma concentrations of Gallopamil will be quantified using a validated HPLC method with UV detection.
- Pharmacokinetic parameters including C_{max}, T_{max}, AUC (0–t), and elimination half-life (t½) will be calculated using non-compartmental analysis.

4.5 Data Analysis

All data obtained from the evaluation tests will be analyzed using appropriate statistical methods. The results will be presented as mean ± standard deviation (SD). Statistical significance will be determined using one-way ANOVA followed by the Tukey test for pairwise comparison. A p-value less than 0.05 will be considered statistically significant.

5. Plan of Work

Phase 1: Preparation and Characterization of Raw Materials (Month 1-6)

1. Literature Review
2. Procurement of Raw Materials
3. Characterization of Gallopamil
4. Polymers and Excipients Analysis

Phase 2: Formulation Development (Month 6 - Month 12)

1. Formulation Design
2. Preparation of Drug-Polymer Mixture
3. Casting and Drying
4. Cutting and Packaging

Phase 3: Physical and Chemical Characterization (Month 3 - Month 18)

1. Thickness and Weight Uniformity
2. Mechanical Properties
3. Disintegration Time
4. Drug Content Uniformity

Phase 4: In-Vitro Drug Release and Taste Masking Studies (Month 18 - Month 24)

1. In-Vitro Drug Release
2. Taste Masking Evaluation

Phase 5 (Months 18–24): In-Vivo Pharmacokinetic Studies

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1. Animal experimentation
2. Plasma analysis and pharmacokinetic modeling

Phase 6: Stability Studies (Month 18 - Month 24)

Phase 7: Data Analysis and Report Writing (Month 24-36)

1. Data Analysis:
2. Preparation of Research Report
3. Prepare manuscripts for publication in scientific journals.

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6. Expected Outcomes

The study will identify the best combination of polymers for developing Gallopamil-loaded ODFs with rapid disintegration, good mechanical strength, and controlled drug release. This formulation will be designed to enhance the bioavailability of Gallopamil by providing faster absorption and bypassing the first-pass effect. The ODFs will be easy to take, portable, and discreet, which will likely improve patient adherence to the prescribed regimen. The research will provide a foundation for potential clinical studies and eventual regulatory approval for a new dosage form of Gallopamil.

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