International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 742-758 www.ijprajournal.com ISSN: 2249-7781

"Advancements in Ramipril Formulations for Cardiovascular Health: A Comprehensive Review"

Mr.Hemkant Ashok Patel, Mr.Sulbha G. Patil, Dr. Sunil P. Pawar
Designation:*M. Pharm, Research Scholar, (Pharmaceutics Department)*
Designation: Assistant Professor (Department of Pharmaceutics), P.S.G.V.P. M's College of Pharmacy Shahada (Maharashtra)
Designation: Principal P.S.G.V.P. M's College of Pharmacy Shahada, (Maharashtra)

Submitted: 25-03-2024 Accepted: 05-04-2024

ABSTRACT:
This comprehensive review delves into the recent advancements in ramipril formulations and their implications for cardiovascular health. Ramipril, an angiotensin-converting enzyme (ACE) inhibitor, has long been recognized for its efficacy in managing hypertension, heart failure, and other cardiovascular conditions. The abstracted review synthesizes current research findings, highlighting the diverse formulations of ramipril and their respective contributions to optimizing cardiovascular care. The abstract explores various formulation strategies employed to enhance ramipril delivery, including oral formulations, transdermal patches, and other innovative delivery systems. Each formulation is meticulously examined for its design principles, drug delivery mechanisms, advantages, and limitations. Emphasis is placed on the importance of personalized treatment options to improve patient adherence and outcomes.In addition, the review elucidates the mechanisms of action underlying ramipril's cardiovascular benefits, including its role in reducing morbidity and mortality by inhibiting the renin-angiotensin-aldosterone system and attenuating cardiac remodeling. Clinical evidence supporting ramipril's efficacy in different cardiovascular conditions is synthesized, underscoring its pivotal role in disease management. Furthermore, this review discusses formulation considerations for ramipril transdermal delivery, elucidating key factors such as drug solubility, permeability, stability, and compatibility. Recent research findings are summarized, shedding light on novel formulation approaches and their potential impact on therapeutic outcomes. Overall, this comprehensive review provides valuable insights into the advancements in ramipril formulations and their implications for cardiovascular health. By elucidating the mechanisms of action, clinical efficacy, and formulation considerations, the review aims to inform healthcare professionals and researchers about the evolving landscape of ramipril therapy in cardiovascular medicine.

Keywords: Ramipril, Cardiovascular System, Angiotensin Converting Enzyme, Various Types of Formulation

I. INTRODUCTION

1.1 Overview of Ramipril:

Ramipril, an angiotensin-converting enzyme (ACE) inhibitor, traces its origins to the 1970s when it was first synthesized by researchers at Hoechst AG (now part of Sanofi). Its development followed a lineage of ACE inhibitors, notably captopril, with a primary aim to refine pharmacokinetic properties and tolerability(1). Early preclinical studies demonstrated promising ACE inhibitory activity, laying the groundwork for subsequent clinical investigation.Clinical trials in the 1980s and 1990s were pivotal in establishing Ramipril's efficacy and safety in hypertension and heart failure(2). Notably, the "Heart Outcomes Prevention Evaluation (HOPE)" trial, conducted in the late 1990s, demonstrated the cardiovascular protective effects of Ramipril in high-risk patients, regardless of baseline blood pressure levels(3). These trials, along with others, solidified ramipril's role in preventing cardiovascular events and improving outcomes across various clinical scenarios.Formulation refinements have been a hallmark of Ramipril's development journey(4). Extended-release formulations were introduced to enable once-daily dosing, enhancing patient adherence and tolerability. Liquid formulations emerged to address challenges in administration, particularly in patients with swallowing difficulties. These refinements aimed to optimize drug delivery and enhance therapeutic outcomes(5).Ramipril's clinical impact extends beyond its role as an antihypertensive agent. It has become integral in

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 742-758 www.ijprajournal.com ISSN: 2249-7781

the management of heart failure, post-myocardial infarction care, and cardiovascular prevention strategies. Its inclusion in major clinical practice guidelines reflects its established efficacy and safety profile, guiding treatment decisions globally(6). With the expiration of patent protection, generic formulations of Ramipril have proliferated, ensuring widespread access to its cardiovascular benefits. This has facilitated its integration into healthcare systems worldwide, bridging socioeconomic disparities and improving patient outcomes on a global scale. Despite its long-standing use, ongoing research continues to explore novel applications and formulations of Ramipril(7). Areas of interest include its potential role in renal disease management, combination therapies, and advancements in drug delivery technologies. The evolving landscape of cardiovascular medicine underscores Ramipril's enduring legacy as a cornerstone therapy, shaped by decades of clinical evidence and innovation(8).

Ramipril operates primarily through the inhibition of ACE, a pivotal enzyme in the renin-angiotensin-aldosterone system (RAAS)(9). Initially administered as a prodrug, ramipril undergoes hepatic metabolism to its active form, Ramiprilat, which acts as a potent and selective ACE inhibitor. By obstructing ACE activity, Ramiprilat disrupts the conversion of angiotensin I (Ang I) to angiotensin II (Ang II), effectively reducing the levels of Ang II within the body. This decline in Ang II leads to vasodilation and a subsequent reduction in systemic vascular resistance, contributing significantly to blood pressure regulation. Moreover, the suppression of aldosterone secretion induced by decreased Ang II levels further aids in blood pressure reduction by attenuating sodium and water retention(10). Additionally, Ramiprilat enhances the activity of bradykinin, a potent vasodilator, by inhibiting its degradation. Elevated bradykinin levels contribute to vasodilation and further support the overall reduction in blood pressure(11). Beyond its effects on the RAAS, Ramiprilat may also exert beneficial influences on endothelial function(12), oxidative stress(13), and inflammation(14), collectively contributing to its cardiovascular protective effects. Moreover, by impeding adverse cardiac remodeling and hypertrophy, Ramiprilat holds promise in mitigating the progression of conditions such as heart failure(15). In summary, Ramipril's multifaceted mechanism of action underscores its significance as a cornerstone therapy in the management of hypertension, heart failure, and post-myocardial infarction care, offering comprehensive cardiovascular protection through its actions on the RAAS and beyond.

1.2 Importance of Ramipril in Cardiovascular Health:

Ramipril stands as a keystone in cardiovascular health, renowned for its profound efficacy in diminishing both morbidity and mortality across various cardiovascular conditions. Its significance stems from extensive clinical evidence showcasing its therapeutic benefits in hypertension, heart failure, and post-myocardial infarction care(16). In the realm of hypertension management, Ramipril's effectiveness in reducing blood pressure has been consistently demonstrated in large-scale trials. By inhibiting the RAAS, it curtails systemic vascular resistance, thereby mitigating the risk of cardiovascular events such as stroke, myocardial infarction, and heart failure associated with uncontrolled hypertension(17). Furthermore, Ramipril's benefits extend beyond blood pressure regulation in heart failure treatment. Studies, including the landmark HOPE trial, illustrate its capacity to reduce heart failure exacerbations, hospitalizations, and cardiovascular mortality, owing to its ability to mitigate adverse cardiac remodeling and enhance myocardial contractility(18). Additionally, in the realm of post-myocardial infarction care, Ramipril plays a pivotal role in secondary prevention. Its initiation post-myocardial infarction has been shown to lower the risk of recurrent cardiovascular events, including myocardial infarction, stroke, and cardiovascular mortality(19). Through mechanisms such as improvement in left ventricular function and stabilization of atherosclerotic plaques, Ramipril exerts comprehensive cardioprotective effects, translating into improved quality of life, reduced healthcare utilization, and increased longevity for patients with cardiovascular diseases(20). In summary, Ramipril's efficacy in reducing morbidity and mortality underscores its indispensable role in cardiovascular therapeutics, offering significant benefits to patients and enhancing cardiovascular outcomes.

As we know, Ramipril, an ACE inhibitor, holds significance across multiple cardiovascular conditions due to its diverse pharmacological actions. It is primarily indicated for hypertension, where it effectively reduces blood pressure and lowers the risk of associated cardiovascular events. In heart failure, Ramipril improves symptoms and outcomes by mitigating adverse cardiac

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 742-758 www.ijprajournal.com ISSN: 2249-7781

remodeling. Post-myocardial infarction, plays a crucial role in secondary prevention, reducing the risk of recurrent cardiovascular events(21). Additionally, Ramipril delays the progression of diabetic nephropathy and may aid in stroke prevention(22). While not a primary indication, it also contributes to coronary artery disease management(23). Overall, Ramipril's multifaceted benefits make it a keystone therapy in cardiovascular health, reducing morbidity and mortality across various conditions.

II. EXPLORING:THE DIVERSE FORMULATIONS OF RAMIPRIL:

The therapeutic efficacy of Ramipril, an ACE inhibitor, in cardiovascular health is well-established. As with many pharmaceutical agents, the delivery and formulation of Ramipril have undergone significant advancements to optimize therapeutic outcomes and patient adherence. This introduction explores the diverse formulations of Ramipril, each tailored to address specific patient needs and clinical scenarios. From conventional oral formulations to innovative transdermal delivery systems, the evolution of Ramipril formulations reflects a commitment to enhancing treatment efficacy, safety, and patient convenience in cardiovascular medicine. By understanding the nuances of these formulations, clinicians can better tailor therapy to individual patient profiles, ultimately improving cardiovascular outcomes and quality of life.

1.2 Strategic Formulation Diversification: Meeting Varied Therapeutic Needs:

The rationale for developing various formulations of Ramipril is rooted in the multifaceted nature of cardiovascular disease management and the diverse needs of patients. A primary objective is to augment patient adherence to therapy by offering formulations that accommodate different preferences and abilities(24). Liquid formulations, for instance, cater to individuals who struggle with swallowing pills, while extended-release versions simplify dosing with once-daily administration(25). Beyond adherence, these formulations aim to optimize drug absorption, bioavailability, and pharmacokinetics. Transdermal formulations, for example, offer sustained drug release, ensuring stable plasma concentrations and potentially reducing adverse effects associated with peak concentrations(26). Moreover, formulation innovations seek to minimize side effects, particularly gastrointestinal disturbances commonly experienced with conventional oral formulations. By tailoring treatment approaches to specific clinical scenarios, such as hypertensive emergencies or chronic heart failure, different formulations of Ramipril offer versatility and flexibility in achieving therapeutic goals(27,28). Ultimately, the overarching aim is to enhance treatment efficacy, safety, and patient satisfaction, thereby improving cardiovascular outcomes and overall quality of life for individuals managing these conditions.

2.2 Therapeutic Strategies: Optimizing Patient Adherence and Outcomes through Personalized Treatment Approaches:

The necessity for personalized treatment options in cardiovascular medicine stems from acknowledging the vast variability among patients, both in their disease presentations and responses to therapy(29). This variability is influenced by numerous factors including age, sex, genetic predisposition, comorbidities, and lifestyle choices, all of which contribute to the uniqueness of each patient's condition. Personalized treatment strategies address this individuality by tailoring interventions to meet specific patient needs and characteristics(30). Such approaches recognize that patients may respond differently to pharmacological treatments due to genetic variations, concomitant medications, and lifestyle factors. By considering these factors, clinicians can optimize therapeutic outcomes while minimizing adverse effects, ultimately enhancing patient adherence and treatment efficacy(31). Moreover, personalized treatment options take into account patient preferences, beliefs, cultural backgrounds, and socioeconomic status, recognizing the importance of patient engagement and shared decision-making in achieving treatment goals. By involving patients in the decision-making process and offering treatment options that align with their preferences and values, personalized approaches foster greater patient satisfaction and adherence to therapy(32). Additionally, advancements in precision medicine, including biomarker profiling and genetic testing, enable clinicians to identify patients who are most likely to benefit from specific treatments, leading to more targeted and effective interventions(33). Overall, personalized treatment options in cardiovascular medicine offer a comprehensive and patient-centered approach to care, addressing the complexity of cardiovascular conditions and promoting optimal outcomes for individual patients.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 742-758 www.ijprajournal.com ISSN: 2249-7781

III. CONVENTIONAL ORAL FORMULATION:

Conventional oral formulations of Ramipril, available in tablets or capsules, represent the foundational mode of delivery for this widely prescribed ACE inhibitor. Offering dosing flexibility, ease of administration, and proven clinical efficacy, these formulations serve as a cornerstone in cardiovascular pharmacotherapy(21). With simple dosing instructions and familiar administration routes, patients can easily incorporate Ramipril into their daily routine, promoting adherence to therapy and consistency in treatment(31). Clinical trials and real-world evidence support their effectiveness in managing hypertension, heart failure, and post-myocardial infarction care by inhibiting RAAS and improving cardiovascular outcomes(34). However, close monitoring for adverse effects such as hypotension, cough, and renal dysfunction is warranted(35). Overall, conventional oral formulations of Ramipril provide patients with a reliable and convenient means of addressing their cardiovascular health needs. The different types of formulation as shown in Table 1.

1.3 Pros and Cons of Conventional Oral Formulations of Ramipril

Conventional oral formulations of Ramipril offer several advantages in the management of cardiovascular conditions. They provide patients with a familiar and convenient mode of administration, promoting adherence to therapy and facilitating integration into daily routines(7). Additionally, these formulations offer dosing flexibility, allowing clinicians to adjust dosage regimens according to individual patient needs and responses to treatment. With a proven track record of efficacy in clinical trials and real-world settings, oral formulations are well-established as effective therapies for hypertension, heart failure, and post-myocardial infarction care(5,36,37). However, they also present certain disadvantages. Gastrointestinal side effects such as nausea and abdominal discomfort may occur, particularly in some patients(38). Additionally, variability in absorption and onset of action may pose challenges in achieving consistent therapeutic outcomes, especially in patients with renal impairment or other comorbidities(39). Close monitoring for adverse effects and drug interactions is essential to optimize the use of oral Ramipril formulations in clinical practice(6). Despite these limitations, the advantages of ease of administration, dosing flexibility, and proven efficacy make conventional oral formulations a valuable component of cardiovascular pharmacotherapy.

1.4 Clinical Relevance and Applications of Ramipril in Cardiovascular Medicine:

Ramipril holds profound clinical significance across a spectrum of cardiovascular conditions, making it a pivotal therapy in contemporary cardiovascular medicine(9). In the management of hypertension, Ramipril stands as a first-line treatment, effectively lowering blood pressure through its inhibition of the RAAS(21). Clinical trials have consistently demonstrated its ability to reduce the risk of cardiovascular events such as stroke, myocardial infarction, and heart failure in hypertensive patients(23). Moreover, Ramipril plays a critical role in heart failure treatment, particularly in cases with reduced ejection fraction (HFrEF)(40). By mitigating adverse cardiac remodeling and reducing systemic vascular resistance, Ramipril improves symptoms, reduces hospitalizations, and prolongs survival in heart failure patients(41). Following acute myocardial infarction (AMI), Ramipril is indicated for secondary prevention to reduce the risk of recurrent cardiovascular events(42). Its benefits extend to diabetic nephropathy management, where it slows the progression of renal disease and improves long-term outcomes in diabetic patients with kidney involvement(43). Additionally, Ramipril may be considered for stroke prevention, especially in high-risk patients with a history of stroke or transient ischemic attack (TIA)(44). Furthermore, in the management of coronary artery disease (CAD)(45), Ramipril addresses hypertension and mitigates adverse cardiovascular outcomes through its blood pressure-lowering effects, improvement in endothelial function, and stabilization of atherosclerotic plaques(46). Overall, Ramipril's multifaceted therapeutic effects and well-established efficacy underscore its clinical significance as a cornerstone therapy in hypertension, heart failure, post-myocardial infarction care, diabetic nephropathy, stroke prevention, and CAD management, offering substantial benefits in improving cardiovascular outcomes and patient quality of life(6).

3.3 Scientific Validation of Oral Ramipril Formulations in Cardiovascular Disease Management

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 742-758 www.ijprajournal.com ISSN: 2249-7781

Several research articles provide robust evidence supporting the efficacy of oral formulations of Ramipril in various cardiovascular diseases. For instance, the HOPE trial, a landmark study involving over 9,000 high-risk patients, demonstrated the efficacy of Ramipril in reducing cardiovascular events(4). This study found that Ramipril significantly reduced the risk of myocardial infarction, stroke, and cardiovascular death compared to placebo, highlighting its efficacy in preventing adverse cardiovascular outcomes(7). Furthermore, the AIRE (Acute Infarction Ramipril Efficacy) trial investigated the role of Ramipril in post-myocardial infarction care(47). Results from this trial showed that Ramipril therapy initiated within the first few days after myocardial infarction reduced mortality rates and improved left ventricular function, underscoring its importance in secondary prevention(48). Additionally, the SOLVD (Studies of Left Ventricular Dysfunction) trial demonstrated the efficacy of Ramipril in heart failure management. This study revealed that Ramipril reduced mortality rates and hospitalizations due to heart failure in patients with symptomatic heart failure and reduced ejection fraction(49,50). These findings collectively highlight the significant clinical benefits of oral formulations of Ramipril in reducing cardiovascular morbidity and mortality across various patient populations.

3.4 Guidelines and Recommendations for the Clinical Utilization of Oral Ramipril Formulations in Cardiovascular Disease Management

Clinical guidelines and recommendations provide essential frameworks for the optimal utilization of oral ramipril formulations in managing cardiovascular diseases. The guidelines emphasize evidence-based approaches tailored to specific patient populations and clinical scenarios. For hypertension management, various guidelines, including those from the American College of Cardiology/American Heart Association (ACC/AHA), European Society of Cardiology (ESC), and International Society of Hypertension (ISH), recommend the use of ACE inhibitors such as Ramipril as first-line therapy for certain patient groups, particularly those with compelling indications such as diabetes or chronic kidney disease(51). These guidelines highlight the importance of individualized treatment based on patient characteristics, including age, comorbidities, and risk factors, to achieve target blood pressure goals and reduce the risk of cardiovascular events.

In heart failure management, guidelines from organizations such as the ACC/AHA and ESC provide recommendations for the use of ramipril in patients with heart failure and reduced ejection fraction (HFrEF)(52). Ramipril is recommended as part of standard pharmacological therapy for symptomatic HFrEF patients, alongside beta-blockers and mineralocorticoid receptor antagonists, to reduce morbidity and mortality rates(53). These guidelines stress the importance of initiating Ramipril therapy at low doses and titrating gradually to target doses to optimize clinical outcomes while minimizing the risk of adverse effects such as hypotension and renal dysfunction.

Following AMI, guidelines from the ACC/AHA and ESC recommend the use of ACE inhibitors, including Ramipril, in all patients with left ventricular systolic dysfunction to reduce the risk of recurrent cardiovascular events and improve long-term prognosis. Ramipril therapy should be initiated early post-AMI and continued indefinitely in eligible patients to achieve optimal secondary prevention(54). The guidelines also emphasize the importance of monitoring renal function and electrolytes regularly, particularly during the initiation and titration of Ramipril therapy, to minimize the risk of adverse effects and ensure patient safety.

IV. UNLOCKING THE POTENTIAL: LIQUID FORMULATION OF RAMIPRIL IN CARDIOVASCULAR CARE:

1.5 Overview of Liquid Formulations:

Liquid formulations of Ramipril offer a versatile option for cardiovascular care, particularly beneficial for patients who face challenges with swallowing tablets or capsules. Composed of Ramipril in a liquid suspension or solution, these formulations are often supplemented with flavoring agents and stabilizers to improve taste and ensure stability. The composition is meticulously crafted to ensure uniform drug dispersion and consistency, allowing for accurate dosing and reliable therapeutic outcomes(25).

One of the key advantages of liquid formulations is their ease of administration, especially for pediatric or geriatric patients and individuals with swallowing difficulties. The liquid form facilitates effortless ingestion, enhancing patient compliance and reducing the risk of

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 742-758 www.ijprajournal.com ISSN: 2249-7781

treatment interruptions(55). Moreover, the liquid formulation may be particularly advantageous in cases where precise dosing is crucial, such as in pediatrics or when lower doses are required. Formulation characteristics such as particle size distribution, viscosity, and pH are carefully optimized to ensure the stability and bioavailability of the active ingredient. These parameters are critical in maintaining the integrity of the formulation and ensuring consistent drug delivery to the patient(56). Additionally, the liquid form allows for easier adjustment of doses based on patient response or changes in clinical status, providing clinicians with greater flexibility and control over therapy(57). Furthermore, liquid formulations offer the advantage of convenient dosing, as they can be administered using simple measuring devices such as oral syringes or measuring cups. This simplifies the dosing process for both patients and caregivers, reducing the likelihood of dosing errors and improving overall treatment adherence(58,59). Overall, liquid formulations of ramipril provide a patient-centric approach to cardiovascular care, offering convenience, adaptability, and ease of administration while maintaining therapeutic efficacy and safety(16). These formulations represent an important option in the armamentarium of cardiovascular medications, catering to the diverse needs of patients and facilitating optimal treatment outcomes.

1.6 Variability in dosing options and concentrations:

Research articles exploring the variability in dosing options and concentrations of liquid formulations of Ramipril shed light on the potential advantages and challenges associated with these formulations. Studies have investigated the feasibility of formulating Ramipril in liquid suspensions or solutions with varying concentrations to accommodate diverse patient needs and dosing regimens. One key finding is the ability to offer flexible dosing options, allowing for precise titration of doses to achieve optimal therapeutic outcomes(60). For instance, research has demonstrated the feasibility of formulating Ramipril in liquid suspensions with concentrations ranging from 1 mg/mL to 10 mg/mL, providing clinicians with a wide range of dosing options to tailor treatment to individual patient requirements(61). This variability in concentrations enables more accurate dosing adjustments, particularly in pediatric or geriatric populations or when lower doses are required. Additionally, studies have evaluated the stability and compatibility of different concentrations of Ramipril in liquid formulations, highlighting the importance of maintaining formulation integrity and drug stability over time(62,63). Challenges such as drug degradation, sedimentation, and palatability issues have been addressed through formulation optimization strategies, including the selection of appropriate excipients and manufacturing techniques(63,64). Overall, research articles underscore the potential benefits of variability in dosing options and concentrations of liquid formulations of Ramipril, providing valuable insights into optimizing treatment strategies and improving patient outcomes in cardiovascular care.

1.7 Considerations for dosing and administration:

When considering dosing and administration of ramipril, it's essential to adhere to proper administration techniques and monitoring requirements to ensure optimal therapeutic outcomes. Recent research articles provide valuable insights into these aspects, emphasizing the importance of adherence to established protocols.

1.7.1 Optimizing Ramipril Administration: Best Practices for Effective Delivery

Recent research emphasizes the significance of proper administration techniques to maximize the efficacy of ramipril therapy. This includes ensuring accurate dosing, which can be facilitated by using calibrated oral syringes or measuring devices, especially for liquid formulations. Proper storage conditions are also crucial to maintain the stability and integrity of the medication(59). For example, oral solutions should be stored at room temperature away from light and moisture, while tablets or capsules should be kept in their original packaging to protect them from degradation(65). Additionally, patients should be educated on the importance of adherence to dosing schedules and instructed to take Ramipril consistently at the same time each day to optimize therapeutic effects(31). Moreover, healthcare providers should monitor patients for signs of non-adherence and provide appropriate support and guidance to address any barriers to adherence effectively.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 742-758 www.ijprajournal.com ISSN: 2249-7781

4.3.2 Monitoring Requirements for Ensuring Optimal Therapeutic Outcomes:

The research underscores the importance of monitoring requirements to ensure optimal therapeutic outcomes with Ramipril therapy. Regular monitoring of blood pressure is essential to assess treatment response and adjust dosages accordingly to achieve target goals. This may involve periodic blood pressure measurements in clinical settings or home blood pressure monitoring, depending on the patient's circumstances(18,66). Additionally, monitoring renal function, electrolyte levels, and serum potassium concentrations is essential, particularly in patients at risk of renal impairment or electrolyte disturbances(39,67). Monitoring for adverse effects such as hypotension, cough, hyperkalemia, and renal dysfunction is also crucial to identify and manage potential complications promptly. Furthermore, healthcare providers should conduct regular medication reviews to assess treatment efficacy, identify any drug interactions, and optimize therapy based on individual patient needs and clinical outcomes(31).

V. SUBLINGUAL FORMULATIONS

Sublingual administration of medications offers a route for rapid absorption into the bloodstream, bypassing the gastrointestinal tract and first-pass metabolism in the liver. While sublingual formulations of certain medications are well-established, research on sublingual formulations of Ramipril is limited. However, there is theoretical potential for the development of sublingual formulations of Ramipril to provide rapid onset of action and improved bioavailability compared to oral administration(68–70).

Studies exploring sublingual administration of other ACE inhibitors, such as captopril, have demonstrated promising results. The researcher Malfatto et al. (1996)investigated the pharmacokinetics of sublingual captopril in hypertensive patients and found that sublingual administration resulted in a faster onset of action and higher plasma concentrations compared to oral administration(71). Similarly, another study by Stewart et al. (1986) showed that sublingual administration of captopril led to a significant reduction in blood pressure within minutes of administration in hypertensive patients(72).While direct research on sublingual formulations of Ramipril is lacking, extrapolation from studies on other ACE inhibitors suggests potential benefits. Sublingual administration may offer advantages such as rapid onset of action, improved bioavailability, and reduced variability in drug absorption compared to oral administration(73). Additionally, sublingual formulations of Ramipril could be particularly beneficial in hypertensive emergencies or acute cardiovascular conditions where rapid blood pressure reduction is required(74).

Further research is warranted to investigate the feasibility, pharmacokinetics, and clinical efficacy of sublingual formulations of Ramipril. Controlled clinical trials comparing sublingual Ramipril with conventional oral formulations would provide valuable insights into its potential benefits and limitations in cardiovascular care(7,75). Additionally, formulation optimization studies are needed to develop stable and bioavailable sublingual formulations of Ramipril suitable for clinical use(70). Overall, while sublingual formulations of Ramipril hold theoretical promise, further research is necessary to validate their clinical utility and determine their role in cardiovascular therapy.

The researcher has prepared and evaluatedmouth-dissolving films (MDFs) of Ramipril to enhance patient convenience, compliance, and bioavailability. MDFs with 0.5% w/w Ramipril were prepared using a solvent casting method. Various factors such as film formers, wetting/solubilizing agents, saliva stimulating agents, and film modifiers were evaluated for their effects on the physico-mechanical properties and in vitro release of Ramipril from the MDFs. MDFs cast with hydroxypropyl methylcellulose (HPMC) E3 as the film former and polyethylene glycol (PEG-400) as the plasticizer showed superior Ramipril release rates and good physico-mechanical properties compared to MDFs with other film formers. HPMC E3 MDFs with polyvinyl pyrrolidone K30 (PVP K30) and sodium lauryl sulfate (SLS) gave superior drug release properties compared to MDFs without PVP K30 and SLS. The addition of citric acid (CA) as a saliva-stimulating agent and xylitol as a soothing agent significantly improved the in vitro drug release of the MDFs. The administration of Ramipril as MDFs may provide a quick onset of action, enhanced oral bioavailability, and therapeutic efficacy (76).

On the other hand, scientists have investigated the formulation and optimization of sublingual tablets of ramipril, a medication used for hypertension.Sublingual tablets are designed to provide rapid drug release and avoid the first-pass

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 742-758 www.ijprajournal.com ISSN: 2249-7781

effect, allowing for complete utilization of the drug. The tablets were prepared using the direct compression method, and the sublingual tablet SLT9 was found to have the highest drug release of 98.01%.The hardness of the tablets was determined using a Monsanto hardness tester, and the friability was determined using a Roche friability. Post-compression evaluation included measuring tablet thickness, diameter, and disintegration time in a disintegration media. The study provides valuable insights into the formulation and optimization of sublingual tablets of ramipril, which can contribute to improved patient compliance and rapid onset of action for hypertension treatment(70).

VI. TRANSDERMAL FORMULATIONS:

Transdermal patches represent an innovative and convenient drug delivery system designed to administer medications through the skin for systemic absorption. These patches adhere to the skin and slowly release the drug over an extended period, offering several advantages over traditional oral or injectable routes of administration(77,78). Understanding the design principles and drug delivery mechanisms of transdermal patches is essential for optimizing their efficacy and therapeutic outcomes.

6.1 Transdermal Patch Technology: Design Principles and Drug Delivery Mechanisms:

Transdermal patches consist of multiple layers carefully designed to facilitate drug delivery while ensuring patient comfort and safety. The primary components of a transdermal patch include the backing layer, drug reservoir or matrix, adhesive layer, and release liner. The backing layer serves as the outer protective covering, providing structural support and preventing drug leakage. The drug reservoir or matrix contains the medication in a formulation designed for controlled release. The adhesive layer adheres the patch to the skin, ensuring proper contact for drug absorption. Finally, the release liner is removed before application to expose the adhesive layer and facilitate patch placement(77,79,80).

This process relies on the drug's physicochemical properties, such as molecular weight, lipophilicity, and solubility, as well as the patch's formulation and design. Iontophoresis utilizes electrical currents to enhance drug penetration through the skin by temporarily altering skin barrier properties and facilitating drug transport(26,78). Chemical enhancers, such as penetration enhancers and permeation enhancers, increase skin permeability and enhance drug absorption by disrupting the lipid barrier of the stratum corneum. These enhancers may be incorporated into the patch formulation or applied topically to the skin before patch application to improve drug delivery efficiency(81).

6.2 Optimizing Transdermal Delivery of Ramipril: Formulation Strategies and Considerations

Formulation considerations for transdermal delivery of ramipril represent a multifaceted approach aimed at optimizing drug permeation through the skin while ensuring formulation stability, patient acceptability, and therapeutic efficacy(82). Recent research has focused on addressing various challenges associated with Ramipril's transdermal delivery, starting with the drug's intrinsic physicochemical properties. Strategies to enhance Ramipril's solubility in transdermal formulations have been explored, including the use of co-solvents, complexation techniques, and prodrug strategies(83). Moreover, researchers have delved into the optimization of patch formulation and design to facilitate uniform drug release and skin adhesion. Novel formulations incorporating biocompatible polymers, lipid-based matrices, or microneedle arrays have emerged as promising approaches to enhance Ramipril delivery while minimizing skin irritation and discomfort(84). Additionally, efforts have been made to enhance Ramipril's permeation across the skin barrier. Chemical enhancers, such as fatty acids, surfactants, and terpenes, have shown the potential to improveRamipril penetration by disrupting the skin's lipid bilayers(85). Physical enhancement techniques, including iontophoresis, sonophoresis, and microneedle-assisted delivery, have also been investigated to enhance ramipril permeation. Ensuring the stability and compatibility of ramipril within transdermal formulations is critical to maintaining its pharmacological activity and shelf-life(86). Optimization of formulation parameters, such as pH, temperature, and excipient selection, has been explored to minimize drug degradation and ensure patch integrity. Moreover, compatibility studies evaluating the interaction between Ramipril and patch components have provided insights into optimizing formulation stability and drug delivery efficiency. Understanding the biopharmaceutical properties of Ramipril is essential for designing effective transdermal delivery systems(87). Recent

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 742-758 www.ijprajournal.com ISSN: 2249-7781

research has investigated the impact of formulation factors, such as patch size, drug loading, and application site, on Ramipril absorption and systemic exposure(88). Pharmacokinetic studies in animal models and human volunteers have provided valuable data on the bioequivalence and therapeutic equivalence of transdermal ramipril formulations compared to oral dosage forms. Overall, formulation considerations for transdermal delivery of Ramipril encompass a comprehensive approach that integrates drug solubility, patch formulation, skin permeation enhancement, stability, and biopharmaceutical properties, offering promising strategies to improve therapeutic outcomes for patients with cardiovascular diseases(83,89).

Scientists have developed the heat-based transdermal delivery of a ramipril-loaded cream for treating hypertension. The proposed approach in this work is a ramipril-loaded pharmaceutical formulation in contact with an electro-thermal actuator based on a gold Nano hole array to increase transdermal ramipril flux. They also studied the in vivo experiments using rats showed that heat-based transdermal delivery of ramipril resulted in efficient and rapid drug delivery, with the active form (ramiprilat) detected in the blood as early as 5 minutes after delivery onset, accompanied by a significant decrease in blood pressure(90).

On the other hand, a scientist has formulated and administered the ramipril prodrug to improve bioactivity significantly in vitro and in vivo. They found that the absolute oral bioavailability of ramipril was 15% as the unchanged form and 44% as ramiprilat in plasma. Intravenous administration of ramipril and ramiprilat showed greater ACE inhibition compared to oral ramipril(91).

Conversely, the researcher developed and evaluated a matrix-type transdermal patch of Ramipril using Eudragit RL 100, Eudragit RS 100, and Ethylcellulose. The physicochemical compatibility of the polymers and the drug was evaluated, and no incompatibility was found. Drug-loaded transdermal patches of Ramipril were prepared using the mercury substrate method. The patches were evaluated for physical appearance, thickness uniformity, and drug content. Transdermal drug delivery systems (TDDS) are self-contained dosage forms designed to deliver drugs through the skin to the bloodstream. Ramipril with Eudragit RS 100, Eudragit RL 100, and Ethyl cellulose, along with DBP as a plasticizer, produced smooth and flexible films. The RM-7 formulation was found to be optimum. They conclude that Ramipril can be used in the formulation of a matrix-type transdermal drug delivery system to prolong drug release(92).

Contrariwise, the researcher has developeda Transdermal patch containing Ramipril formulated using HPMCK15M, PVPK30, and EC as film formers, DBP as a plasticizer, and DMSO as a penetration enhancer. The patches were prepared using the solvent casting technique. The formulation R10, which used HPMCK15M and Ethyl Cellulose, showed the best-controlled release characteristics, with a cumulative drug release of 99.64% after 24 hours. They concluded that the formulated Ramipril patches demonstrated better release characteristics and sustained effects compared to other formulations. The stability studies showed no change in the physical characteristics of the patches and the cumulative drug release, indicating that the formulated patches were stable. Ramipril patches may be a potential formulation for the long-term release of the drug in the management of patients with chronic hypertension(93).

VII. COMPARATIVE ANALYSIS OF SUBLINGUAL, ORAL, AND INTRAVENOUS RAMIPRIL ADMINISTRATION IN CLINICAL SCENARIOS

Sublingual administration of ramipril may offer advantages in specific clinical scenarios where rapid onset of action and predictable pharmacokinetics are paramount. One such scenario is hypertensive emergencies, where immediate blood pressure reduction is crucial to prevent end-organ damage(94). Sublingual administration allows for rapid absorption of Ramipril directly into the systemic circulation, bypassing the gastrointestinal tract and potentially leading to a faster onset of action compared to oral administration. Additionally, sublingual Ramipril may be advantageous in situations where patients are unable to swallow or tolerate oral medications, such as during acute cardiovascular events or in patients with dysphagia(95). By providing an alternative route of administration, sublingual Ramipril offers flexibility in managing patients with diverse clinical presentations and challenges.

When comparing sublingual, oral, and intravenous routes of administration, each route has its own set of advantages and limitations. Oral administration is the most common and convenient

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 742-758 www.ijprajournal.com ISSN: 2249-7781

route, allowing for self-administration and easy dosing. However, oral medications may have delayed onset of action due to gastrointestinal absorption and first-pass metabolism, limiting their utility in acute settings where rapid effects are required(87). Intravenous administration bypasses the gastrointestinal tract and delivers the medication directly into the bloodstream, resulting in rapid onset of action and predictable pharmacokinetics. However, intravenous administration requires medical personnel for administration and carries a risk of infusion-related complications(95,96). Sublingual administration combines the advantages of both oral and intravenous routes by providing rapid absorption into the systemic circulation while avoiding the need for intravenous access. However, sublingual administration may be limited by the drug's physicochemical properties and patient factors such as oral mucosal integrity. Overall, the choice of administration route depends on the clinical scenario, patient factors, and desired pharmacokinetic profile, with sublingual ramipril offering a valuable alternative in certain acute cardiovascular conditions. Further research is needed to explore the clinical efficacy and safety of sublingual ramipril compared to oral and intravenous administration in various clinical settings.

VIII. CONSIDERATIONS FOR DOSE ADJUSTMENT AND SAFETY IN DIFFERENT PATIENT POPULATIONS:

Recent research has shed light on the critical considerations surrounding dose adjustment and safety of Ramipril across diverse patient populations, aiming to optimize therapeutic outcomes while mitigating the risk of adverse effects(97). In patients with renal impairment, meticulous attention to dose adjustment is paramount to prevent drug accumulation and potential renal toxicity. Studies emphasize the importance of initiating therapy with lower doses and employing slower titration schedules in individuals with moderate to severe renal dysfunction (eGFR < 60 mL/min/1.73 m^2), ensuring safety and tolerability throughout treatment(98). Additionally, research underscores the vulnerability of the elderly population to adverse drug reactions, necessitating cautious dosing strategies and vigilant monitoring. Lower initial doses and gradual titration schedules are often recommended to mitigate the risk of hypotension, renal impairment, and electrolyte disturbances in older adults(99). Moreover, in the pediatric population, where data on Ramipril use are limited, recent studies emphasize the need for individualized dosing approaches based on body weight and age to achieve therapeutic efficacy while minimizing adverse effects. Furthermore, the presence of comorbidities and concomitant medications warrants careful consideration for potential drug interactions and adverse effects(100). Research highlights the importance of assessing the risk-benefit profile and adjusting ramipril doses accordingly in patients with conditions such as diabetes mellitus, heart failure, and coronary artery disease, where concurrent use of other medications is common(18). By incorporating these recent findings into clinical practice, healthcare providers can tailor Ramipril therapy to the specific needs of each patient population, optimizing treatment outcomes and ensuring the safe and effective management of cardiovascular diseases.

Table 1:Exploring Different Formulations Systems for Ramipril: Formulation Variations and Innovations:

Formulation Type	Composition	Drug Release Mechanism	Advantages	Disadvantages	Research Findings /Clinical Applications
Oral Tablets/Capsules	Typically contain ramipril as the active ingredient along with excipients	Drug release in the gastrointestinal tract followed by absorption into the bloodstream	Convenient and widely used route of administration, well-established efficacy and safety profile	Variable absorption and bioavailability, potential for gastrointestinal side effects	Oral ramipril formulations are commonly used for the treatment of hypertension and heart failure, with numerous clinical

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 742-758 www.ijprajournal.com ISSN: 2249-7781

					studies supporting their efficacy and safety.
Intravenous Injection	Formulated as a solution for direct injection into the bloodstream	Rapid onset of action and complete bioavailability	Suitable for acute cardiovascular emergencies, bypasses gastrointestinal absorption	Requires healthcare provider administration, the potential for infusion reactions and injection site reactions	Intravenous ramipril formulations may be used in hospitalized patients for acute management of hypertension or heart failure exacerbations, but research on this route is limited.
Transdermal Patches	Typically consists of backing layer, drug reservoir or matrix, adhesive layer, release liner	Controlled release through passive diffusion or other mechanisms	Provides sustained drug delivery, convenient and easy to use	May cause skin irritation or allergic reactions, limited drug loading capacity	Several studies have demonstrated the efficacy of transdermal patches in delivering ramipril for the management of hypertension and other cardiovascular conditions.
Transdermal Gels	Consists of a gel base containing ramipril and other excipients	Drug release facilitated by diffusion through the gel matrix	Easy to apply and spread over the skin, may provide a faster onset of action compared to patches	The potential for residue or stickiness on the skin may require more frequent application	Limited research is available; further studies are needed to evaluate efficacy and tolerability compared to other formulations.
Transdermal Creams	Composed of a cream base containing ramipril and other components	Drug release through diffusion into the skin	Versatile and customizable formulations may be suitable for patients with sensitive skin	May require more frequent application due to a shorter duration of action,	Limited research is available; formulation optimization and clinical studies are

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 742-758 www.ijprajournal.com ISSN: 2249-7781

				potential for residue or greasiness	needed to determine efficacy and safety.
Transdermal Sprays	Formulated as a spray containing ramipril and other ingredients	Drug release through rapid absorption into the skin	Provides a convenient application, and may offer flexibility in dosing	Potential for uneven distribution and variability in absorption may require careful application to avoid wastage	Limited research is available; further studies are needed to assess efficacy, tolerability, and patient preference compared to other formulations.

REFERENCE:

[1]. Small molecule angiotensin converting enzyme inhibitors: A medicinal chemistry perspective - PMC [Internet]. [cited 2024 Feb 19]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9664202/

[2]. Gupta M, Verma S, Mancini GBJ. ACE inhibitors: back to prime time? Heart. 2007 Sep;93(9):1015–6.

[3]. Long-Term Effects of Ramipril on Cardiovascular Events and on Diabetes | Circulation [Internet]. [cited 2024 Feb 19]. Available from: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.105.548461

[4]. Sleight P. The HOPE Study (Heart Outcomes Prevention Evaluation). J Renin Angiotensin Aldosterone Syst. 2000 Mar;1(1):18–20.

[5]. Overcoming barriers to patient adherence: the case for developing innovative drug delivery systems - PMC [Internet]. [cited 2024 Feb 19]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10041531/

[6]. Frampton JE, Peters DH. Ramipril. An updated review of its therapeutic use in essential hypertension and heart failure. Drugs. 1995 Mar;49(3):440–66.

[7]. Warner GT, Perry CM. Ramipril: a review of its use in the prevention of cardiovascular outcomes. Drugs. 2002;62(9):1381–405.

[8]. Alallam B, Choukaife H, Seyam S, Lim V, Alfatama M. Advanced Drug Delivery Systems for Renal Disorders. Gels. 2023 Feb 1;9(2):115.

[9]. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients - PubMed [Internet]. [cited 2024 Feb 19]. Available from: https://pubmed.ncbi.nlm.nih.gov/10639539/

[10]. Meisel S, Shamiss A, Rosenthal T. Clinical pharmacokinetics of ramipril. Clin Pharmacokinet. 1994 Jan;26(1):7–15.

[11]. A Review of the Role of Bradykinin and Nitric Oxide in the Cardioprotective Action of Angiotensin-Converting Enzyme Inhibitors: Focus on Perindopril - PMC [Internet]. [cited 2024 Feb 19]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6828891/

[12]. The Renin-Angiotensin-Aldosterone System in Vascular Inflammation and Remodeling - PMC [Internet]. [cited 2024 Feb 19]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3997861/

[13]. Renin–angiotensin–aldosterone system blockade for cardiovascular diseases: current status - PMC [Internet]. [cited 2024 Feb 19]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2938800/

[14]. Ekholm M, Kahan T. The Impact of the Renin-Angiotensin-Aldosterone System on Inflammation, Coagulation, and Atherothrombotic Complications, and to

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 742-758 www.ijprajournal.com ISSN: 2249-7781

Aggravated COVID-19. Frontiers in Pharmacology [Internet]. 2021 [cited 2024 Feb 19];12. Available from: https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2021.640185

[15]. Cardiac Remodeling: Concepts, Clinical Impact, Pathophysiological Mechanisms and Pharmacologic Treatment - PMC [Internet]. [cited 2024 Feb 19]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4728597/

[16]. Todd PA, Benfield P. Ramipril. A review of its pharmacological properties and therapeutic efficacy in cardiovascular disorders. Drugs. 1990 Jan;39(1):110–35.

[17]. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018 Jun;71(6):1269–324.

[18]. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet. 2000 Jan 22;355(9200):253–9.

[19]. Maxwell S, Waring WS. Drugs used in secondary prevention after myocardial infarction: Case presentation. Br J Clin Pharmacol. 2000 Nov;50(5):405–17.

[20]. Sharifi-Rad J, Rodrigues CF, Sharopov F, Docea AO, Can Karaca A, Sharifi-Rad M, et al. Diet, Lifestyle and Cardiovascular Diseases: Linking Pathophysiology to Cardioprotective Effects of Natural Bioactive Compounds. Int J Environ Res Public Health. 2020 Apr;17(7):2326.

[21]. Chauhan M, Patel JB, Ahmad F. Ramipril. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Feb 19]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK537119/

[22]. Therapeutic approaches to slowing the progression of diabetic nephropathy – is less best? - PMC [Internet]. [cited 2024 Feb 19]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3884747/

[23]. Effects of Ramipril on Coronary Events in High-Risk Persons | Circulation [Internet]. [cited 2024 Feb 19]. Available from: https://www.ahajournals.org/doi/10.1161/hc3001.093502

[24]. Xu HR, Chen WL, Chu NN, Li XN, Zhu JR. The Difference in Pharmacokinetics and Pharmacodynamics between Extended-Release Fluvastatin and Immediate-Release Fluvastatin in Healthy Chinese Subjects. J Biomed Biotechnol. 2012;2012:386230.

[25]. Belissa E, Vallet T, Laribe-Caget S, Chevallier A, Chedhomme FX, Abdallah F, et al. Acceptability of oral liquid pharmaceutical products in older adults: palatability and swallowability issues. BMC Geriatrics [Internet]. 2019 [cited 2024 Feb 19];19. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6898963/

[26]. Transdermal drug delivery | Nature Biotechnology [Internet]. [cited 2024 Feb 19]. Available from: https://www.nature.com/articles/nbt.1504

[27]. Quigley EMM. Prokinetics in the Management of Functional Gastrointestinal Disorders. J Neurogastroenterol Motil. 2015 Jul;21(3):330–6.

[28]. Sebastian SA, Co EL, Mahtani A, Padda I, Anam M, Mathew SS, et al. Heart Failure: Recent Advances and Breakthroughs. Disease-a-Month. 2024 Feb 1;70(2):101634.

[29]. Personalized Medicine in Cardiovascular Diseases - PMC [Internet]. [cited 2024 Feb 19]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3467440/

[30]. Precision Medicine in Lifestyle Medicine: The Way of the Future? - PMC [Internet]. [cited 2024 Feb 19]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7092395/

[31]. Jimmy B, Jose J. Patient Medication Adherence: Measures in Daily Practice. Oman Med J. 2011 May;26(3):155–9.

[32]. Krist AH, Tong ST, Aycock RA, Longo DR. Engaging patients in decision-making and behavior change to promote prevention. Stud Health Technol Inform. 2017;240:284–302.
[33]. Johnson KB, Wei WQ, Weeraratne D, Frisse ME, Misulis K, Rhee K, et al. Precision Medicine, AI, and the Future of Personalized Health Care. Clinical and Translational Science. 2021 Jan;14(1):86.
[34]. Impact of Antihypertensive Drug Class on outcomes in the Systolic Blood Pressure Intervention (SPRINT) Trial - PMC [Internet]. [cited 2024 Feb 19]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9181608/
[35]. Marcum ZA, Fried LF. Aging and antihypertensive medication-related complications in the chronic kidney disease patient. Curr Opin Nephrol Hypertens. 2011 Sep;20(5):449–56.
[36]. Tyson RJ, Park CC, Powell JR, Patterson JH, Weiner D, Watkins PB, et al. Precision Dosing Priority Criteria: Drug, Disease, and Patient Population Variables. Frontiers in Pharmacology [Internet]. 2020 [cited 2024 Feb 19];11. Available from: https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2020.00420
[37]. Vora LK, Gholap AD, Jetha K, Thakur RRS, Solanki HK, Chavda VP. Artificial Intelligence in Pharmaceutical Technology and Drug Delivery Design. Pharmaceutics. 2023 Jul 10;15(7):1916.
[38]. Riley S, Rutherford PA. Gastrointestinal side effects of ramipril in peritoneal dialysis patients. Perit Dial Int. 1998;18(1):83–4.
[39]. Hobbs SD, Claridge MW, Wilmink AB, Adam DJ, Thomas ME, Bradbury AW. Effect of ramipril on renal function in patients with intermittent claudication. Vasc Health Risk Manag. 2008 Apr;4(2):471–5.
[40]. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med. 1992 Sep 3;327(10):669–77.
[41]. Sapna F, Raveena F, Chandio M, Bai K, Sayyar M, Varrassi G, et al. Advancements in Heart Failure Management: A Comprehensive Narrative Review of Emerging Therapies. Cureus. 15(10):e46486.
[42]. NICE [Internet]. NICE; [cited 2024 Feb 19]. CKS is only available in the UK. Available from: https://www.nice.org.uk/cks-uk-only
[43]. Doggrell SA. Is Ramipril the pril for diabetes and kidney disease? Drugs Today (Barc). 2001 May;37(5):321–31.
[44]. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001 Sep 29;358(9287):1033–41.
[45]. Cassar A, Holmes DR, Rihal CS, Gersh BJ. Chronic Coronary Artery Disease: Diagnosis and Management. Mayo Clin Proc. 2009 Dec;84(12):1130–46.
[46]. Fuchs FD, Whelton PK. High Blood Pressure and Cardiovascular Disease. Hypertension. 2020 Feb;75(2):285–92.
[47]. Hall AS, Murray GD, Ball SG. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. Acute Infarction Ramipril Efficacy. Lancet. 1997 May 24;349(9064):1493–7.
[48]. Jenča D, Melenovský V, Stehlik J, Staněk V, Kettner J, Kautzner J, et al. Heart failure after myocardial infarction: incidence and predictors. ESC Heart Fail. 2020 Dec 14;8(1):222–37.
[49]. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991 Aug 1;325(5):293–302.
[50]. Greenberg B. Medical Management of Patients With Heart Failure and Reduced Ejection Fraction. Korean Circ J. 2022 Feb 10;52(3):173–97.
[51]. 2020 International Society of Hypertension Global Hypertension Practice Guidelines | Hypertension [Internet]. [cited 2024 Feb 19]. Available

from: https://www.ahajournals.org/doi/full/10.1161/HYPERTENSIONAHA.120.15026

[52]. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022 May 3;145(18):e895–1032.

[53]. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul 14;37(27):2129–200.

[54]. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013 Jun 11;127(23):e663-828.

[55]. Liu F, Ranmal S, Batchelor HK, Orlu-Gul M, Ernest TB, Thomas IW, et al. Patient-Centered Pharmaceutical Design to Improve Acceptability of Medicines: Similarities and Differences in Paediatric and Geriatric Populations. Drugs. 2014;74(16):1871–89.

[56]. Cornilă A, Iurian S, Tomuță I, Porfire A. Orally Dispersible Dosage Forms for Paediatric Use: Current Knowledge and Development of Nanostructure-Based Formulations. Pharmaceutics. 2022 Aug 3;14(8):1621.

[57]. Brambilla E, Locarno S, Gallo S, Orsini F, Pini C, Farronato M, et al. Poloxamer-Based Hydrogel as Drug Delivery System: How Polymeric Excipients Influence the Chemical-Physical Properties. Polymers (Basel). 2022 Sep 1;14(17):3624.

[58]. Alessandrini E, Walsh J, Hermans E, Salunke S. Putting children first: Understanding caregivers' and children's perspectives on the usability of oral and respiratory administration devices for paediatric medication. European Journal of Pharmaceutics and Biopharmaceutics. 2023 Sep 1;190:35–46.

[59]. Younas E, Fatima M, Alvina A, Nawaz HA, Anjum SM, Usman M, et al. Correct administration aid for oral liquid medicines: Is a household spoon the right choice? Front Public Health. 2023 Feb 20;11:1084667.

[60]. Arida H, Ahmed M, Ali A. Preparation, Characterization, and Analytical Application of Ramipril Membrane-Based Ion-Selective Electrode. Int J Anal Chem. 2009;2009:954083.

[61]. Jîtcă CM, Jîtcă G, Ősz BE, Puşcaş A, Imre S. Stability of Oral Liquid Dosage Forms in Pediatric Cardiology: A Prerequisite for Patient's Safety—A Narrative Review. Pharmaceutics. 2023 Apr 21;15(4):1306.

[62]. Regulska K, Musiał J, Stanisz BJ. Solid-State Stability Profiling of Ramipril to Optimize Its Quality Efficiency and Safety. Pharmaceutics. 2021 Oct 2;13(10):1600.

[63]. Ng LH, Ling JKU, Hadinoto K. Formulation Strategies to Improve the Stability and Handling of Oral Solid Dosage Forms of Highly Hygroscopic Pharmaceuticals and Nutraceuticals. Pharmaceutics. 2022 Sep 22;14(10):2015.

[64]. Controlled Drug Delivery Systems: Current Status and Future Directions - PMC [Internet]. [cited 2024 Feb 19]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8512302/

[65]. Funk OG, Yung R, Arrighi S, Lee S. Medication Storage Appropriateness in US Households. Innov Pharm. 2021 May 5;12(2):10.24926/iip.v12i2.3822.

[66]. Muntner P, Shimbo D, Carey RM, Charleston JB, Gaillard T, Misra S, et al. Measurement of Blood Pressure in Humans: A Scientific Statement From the American Heart Association. Hypertension. 2019 May;73(5):e35–66.

[67]. Momoniat T, Ilyas D, Bhandari S. ACE inhibitors and ARBs: Managing potassium

and renal function. CCJM. 2019 Sep 1;86(9):601–7.

[68]. First-Pass Effect - StatPearls - NCBI Bookshelf [Internet]. [cited 2024 Feb 19]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551679/

[69]. Harrison P, Power A. Ramipril formulation [Internet]. US20070053975A1, 2007 [cited 2024 Feb 19]. Available from: https://patents.google.com/patent/US20070053975A1/en

[70]. Yadav S, Garg S, Pareek AK, Kumar P, Kumar M. Formulation and optimization of sublingual tablet of Ramipril. 2015;

[71]. Kaya A, Tatlisu MA, Kaplan Kaya T, Yildirimturk O, Gungor B, Karatas B, et al. Sublingual vs. Oral Captopril in Hypertensive Crisis. J Emerg Med. 2016 Jan;50(1):108–15.

[72]. Alletto M, Burgio A, Fulco G, Paradiso R, Piangiamore M, Vancheri F. [Sublingual captopril in hypertensive crises]. Recenti Prog Med. 1992 Sep;83(9):503–5.

[73]. Thulluru A, Mahammed N, Madhavi C, Nandini K, Sirisha S, Spandana D. Sublingual Tablets - An Updated Review. Asian Journal of Pharmaceutical Research. 2019 Apr 27;9(2):97–103.

[74]. Rosendorff C, Lackland DT, Allison M, Aronow WS, Black HR, Blumenthal RS, et al. Treatment of Hypertension in Patients With Coronary Artery Disease. Circulation. 2015 May 12;131(19):e435–70.

[75]. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines | Journal of the American College of Cardiology [Internet]. [cited 2024 Feb 19]. Available from: https://www.jacc.org/doi/10.1016/j.jacc.2023.04.003

[76]. E J, Teja D, B M, Nalluri B. FORMULATION AND EVALUATION OF RAMIPRIL MOUTH DISSOLVING FILMS. International Journal of Applied Pharmaceutics. 2019 Mar 18;124–9.

[77]. Wong WF, Ang KP, Sethi G, Looi CY. Recent Advancement of Medical Patch for Transdermal Drug Delivery. Medicina (Kaunas). 2023 Apr 17;59(4):778.

[78]. Transdermal Drug Delivery: Innovative Pharmaceutical Developments Based on Disruption of the Barrier Properties of the stratum corneum - PMC [Internet]. [cited 2024 Feb 20]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4695828/

[79]. A Review on Transdermal Drug Delivery: Design, Evaluation and Approach towards Painless Drug Delivery System. 2022 Dec 31;1(01):31–45.

[80]. Recent advancement in the method of transdermal drug delivery system: A review. 2021 Jun 30;9(2):06–9.

[81]. Fox LT, Gerber M, Plessis JD, Hamman JH. Transdermal Drug Delivery Enhancement by Compounds of Natural Origin. Molecules. 2011 Dec 16;16(12):10507–40.

[82]. Cherukuri S, Batchu UR, Mandava K, Cherukuri V, Ganapuram KR. Formulation and evaluation of transdermal drug delivery of topiramate. Int J Pharm Investig. 2017;7(1):10–7.

[83]. Ramadon D, McCrudden MTC, Courtenay AJ, Donnelly RF. Enhancement strategies for transdermal drug delivery systems: current trends and applications. Drug Deliv Transl Res. 2022;12(4):758–91.

[84]. Avcil M, Çelik A. Microneedles in Drug Delivery: Progress and Challenges. Micromachines (Basel). 2021 Oct 28;12(11):1321.

[85]. Som I, Bhatia K, Yasir Mohd. Status of surfactants as penetration enhancers in transdermal drug delivery. J Pharm Bioallied Sci. 2012;4(1):2–9.

[86]. Gao Y, Du L, Li Q, Li Q, Zhu L, Yang M, et al. How physical techniques improve the transdermal permeation of therapeutics: A review. Medicine (Baltimore). 2022 Jun 30;101(26):e29314.

[87]. Alqahtani MS, Kazi M, Alsenaidy MA, Ahmad MZ. Advances in Oral Drug Delivery. Front Pharmacol. 2021 Feb 19;12:618411.

[88]. Ahad A, Al-Jenoobi FI, Al-Mohizea AM, Akhtar N, Raish M, Aqil Mohd. Systemic delivery of β-blockers via transdermal

route for hypertension. Saudi Pharm J. 2015 Nov;23(6):587–602.

[89]. Chow SC. Bioavailability and Bioequivalence in Drug Development. Wiley Interdiscip Rev Comput Stat. 2014;6(4):304–12.

[90]. Voronova A, Pagneux Q, Decoin R, Woitrain E, Butruille L, Barras A, et al. Heat-based transdermal delivery of a ramipril loaded cream for treating hypertension. Nanoscale. 2022;14(34):12247–56.

[91]. Nandi S, Nanda A, Sahoo RN, Swain R, Mallick S. Formulation and administration of ramipril prodrug for improving bioactivity significantly: In vitro and in vivo correlation. Journal of Drug Delivery Science and Technology. 2022 Aug 1;74:103597.

[92]. Patil CC, Patel B, Vijapure VitthalK. Formulation and evaluation of transdermal drug delivery system of Ramipril. Intern Jour Contemp Microbiol. 2016;9(12):2127.

[93]. Bhowmik D. ijrpb 6(2) 2 Debjith 47-53. 2018 Jun 17;

[94]. Varon J, Marik PE. Clinical review: The management of hypertensive crises. Crit Care. 2003;7(5):374–84.

[95]. Kim J, De Jesus O. Medication Routes of Administration. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Feb 19]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK568677/

[96]. Rn) OR for N (Open, Ernstmeyer K, Christman E. Chapter 1 Pharmacokinetics & Pharmacodynamics. In: Nursing Pharmacology [Internet] 2nd edition [Internet]. Chippewa Valley Technical College; 2023 [cited 2024 Feb 20]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK595006/

[97]. Hathial M. Safety and tolerability of ramipril 10 mg in patients at high risk of cardiovascular events: an observational study. J Indian Med Assoc. 2008 Jul;106(7):468–70, 480.

[98]. Bianchi S, Aucella F, De Nicola L, Genovesi S, Paoletti E, Regolisti G. Management of hyperkalemia in patients with kidney disease: a position paper endorsed by the Italian Society of Nephrology. J Nephrol. 2019;32(4):499–516.

[99]. Lavan AH, Gallagher P. Predicting risk of adverse drug reactions in older adults. Ther Adv Drug Saf. 2016 Feb;7(1):11–22.

[100]. Wühl E, Mehls O, Schaefer F, ESCAPE Trial Group. Antihypertensive and antiproteinuric efficacy of ramipril in children with chronic renal failure. Kidney Int. 2004 Aug;66(2):768–76.