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Next-Generation Buccal Drug Delivery: Cyclodextrin-Based Films for Improved Therapeutic Performance of Carvedilol

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ABSTRACT

Carvedilol, a non-selective β-adrenergic blocker with additional α_1-blocking activity, is widely used in the management of hypertension and chronic heart failure; however, its clinical performance is limited by poor aqueous solubility and extensive first-pass metabolism, resulting in low and variable oral bioavailability. In recent years, buccal drug delivery has emerged as a promising alternative route capable of bypassing hepatic metabolism while enabling rapid and controlled systemic absorption. Concurrently, cyclodextrins have gained significant attention as multifunctional excipients due to their ability to form inclusion complexes with hydrophobic drugs, thereby enhancing solubility, stability, and permeability.This review critically examines the integration of cyclodextrin complexation with mucoadhesive buccal film technology as a synergistic strategy to improve the biopharmaceutical performance of carvedilol. Key aspects discussed include the physicochemical and pharmacokinetic limitations of carvedilol, structural and functional characteristics of cyclodextrins, and the mechanistic basis of drug-cyclodextrin inclusion complex formation. Furthermore, the review highlights formulation strategies involving polymer selection, plasticizers, and permeation enhancers, along with preparation techniques such as solvent casting. Comprehensive evaluation parameters, including physicochemical characterization, mechanical strength, mucoadhesion, in vitro drug release, and ex vivo permeation studies, are also analyzed.Recent advances demonstrate that cyclodextrin-based buccal films significantly enhance drug dissolution, permeation, and bioavailability while offering improved patient compliance and reduced dosing frequency. Despite promising outcomes, challenges related to large-scale manufacturing, stability, and regulatory approval remain. Overall, this review underscores the potential of cyclodextrin-engineered buccal films as an innovative and clinically relevant platform for the delivery of poorly soluble cardiovascular drugs, with carvedilol serving as a representative model.

Keywords: Carvedilol; Cyclodextrin; Buccal films; Mucoadhesive drug delivery; Bioavailability enhancement

1. INTRODUCTION

1.1 Global Burden of Cardiovascular Diseases

Cardiovascular diseases (CVDs) continue to represent the foremost cause of mortality globally, accounting for approximately 17.9 million deaths annually and imposing a substantial socioeconomic burden on healthcare systems [1]. The prevalence of hypertension, ischemic heart disease, and chronic heart failure has increased significantly due to aging populations, sedentary lifestyles, and metabolic disorders such as diabetes and obesity [2,3]. In low- and middle-income countries, including India, the burden is further exacerbated by limited access to early diagnosis and long-term therapeutic management [4].

Despite advancements in pharmacotherapy, effective management of CVDs remains challenging due to issues related to drug pharmacokinetics, suboptimal bioavailability, and poor patient adherence to chronic medication regimens [5]. Many cardiovascular drugs require long-term administration, and fluctuations in plasma drug concentrations can result in therapeutic inefficacy or adverse effects [6]. Consequently, there is a growing emphasis on optimizing drug delivery systems to ensure consistent therapeutic outcomes and improved patient compliance.

1.2 Limitations of Conventional Drug Delivery Systems

Oral drug delivery is the most commonly employed route due to its convenience, patient acceptability, and cost-effectiveness; however, it is associated with several inherent limitations, particularly for drugs with unfavorable biopharmaceutical properties [7]. One of the major challenges is poor aqueous solubility, which limits dissolution and, subsequently, absorption of drugs classified

under the Biopharmaceutics Classification System (BCS) Class II [8]. Additionally, extensive first-pass metabolism in the liver significantly reduces systemic bioavailability of many therapeutic agents, including β-blockers such as carvedilol [9].

Gastrointestinal variability, including pH fluctuations, enzymatic degradation, and food–drug interactions, further contributes to inconsistent drug absorption [10]. Moreover, drugs with short half-lives often require frequent dosing, which may reduce patient adherence and increase the risk of dose-related adverse effects [11]. These limitations collectively hinder therapeutic efficacy and highlight the need for alternative delivery strategies capable of bypassing gastrointestinal barriers and hepatic metabolism.

1.3 Need for Transmucosal and Advanced Delivery Platforms

Transmucosal drug delivery systems have emerged as a promising alternative to conventional routes by enabling direct absorption of drugs into systemic circulation through mucosal tissues [12]. Among these, the buccal route offers distinct advantages, including a highly vascularized epithelium, relatively low enzymatic activity, and ease of accessibility [13]. Importantly, buccal drug delivery bypasses hepatic first-pass metabolism, thereby enhancing systemic bioavailability and reducing inter-individual variability in drug response [14].

Recent advances in formulation science have facilitated the development of innovative dosage forms such as buccal films, patches, and gels, which allow controlled and sustained drug release [15]. Buccal films, in particular, have gained significant attention due to their thin, flexible nature, ease of administration, and improved patient compliance [16]. These systems can be engineered to provide both immediate and prolonged drug release, making them suitable for the management of chronic conditions such as cardiovascular diseases [17].

Furthermore, the integration of advanced excipients and drug delivery technologies has enabled the modulation of drug solubility, permeability, and stability, thereby enhancing overall therapeutic performance [18]. Such approaches are essential for addressing the limitations associated with poorly soluble and extensively metabolized drugs.

1.4 Rationale for Cyclodextrin-Based Buccal Films of Carvedilol

Carvedilol is a third-generation non-selective β-adrenergic receptor antagonist with additional α_1-blocking activity, widely used in the treatment of hypertension and chronic heart failure [19]. Despite its clinical efficacy, carvedilol exhibits poor aqueous solubility and undergoes extensive first-pass metabolism, resulting in low and variable oral bioavailability (approximately 25–35%) [20]. These limitations necessitate the development of alternative delivery systems to improve its pharmacokinetic profile and therapeutic performance.

Cyclodextrins, cyclic oligosaccharides with a hydrophilic exterior and hydrophobic cavity, have been extensively explored as solubility-enhancing agents through inclusion complex formation with poorly soluble drugs [21]. The encapsulation of drug molecules within the cyclodextrin cavity enhances aqueous solubility, dissolution rate, and chemical stability while potentially improving membrane permeability [22]. Among various derivatives, hydroxypropyl-β-cyclodextrin has demonstrated superior solubilization efficiency and safety profile [23].

The combination of cyclodextrin complexation with buccal film technology represents a synergistic strategy to overcome both solubility and bioavailability limitations [24]. While cyclodextrins enhance drug dissolution, buccal films facilitate direct systemic absorption, bypassing hepatic metabolism and ensuring consistent plasma drug levels [25]. Additionally, the mucoadhesive nature of buccal films prolongs residence time at the site of absorption, further improving drug uptake [26].

Recent studies have demonstrated that cyclodextrin-based buccal systems can significantly enhance the dissolution, permeability, and therapeutic efficacy of poorly soluble drugs [27–29]. Therefore, the development of cyclodextrin-complexed buccal films of carvedilol represents a promising next-generation drug delivery approach aimed at improving bioavailability, reducing dosing frequency, and enhancing patient compliance [30].

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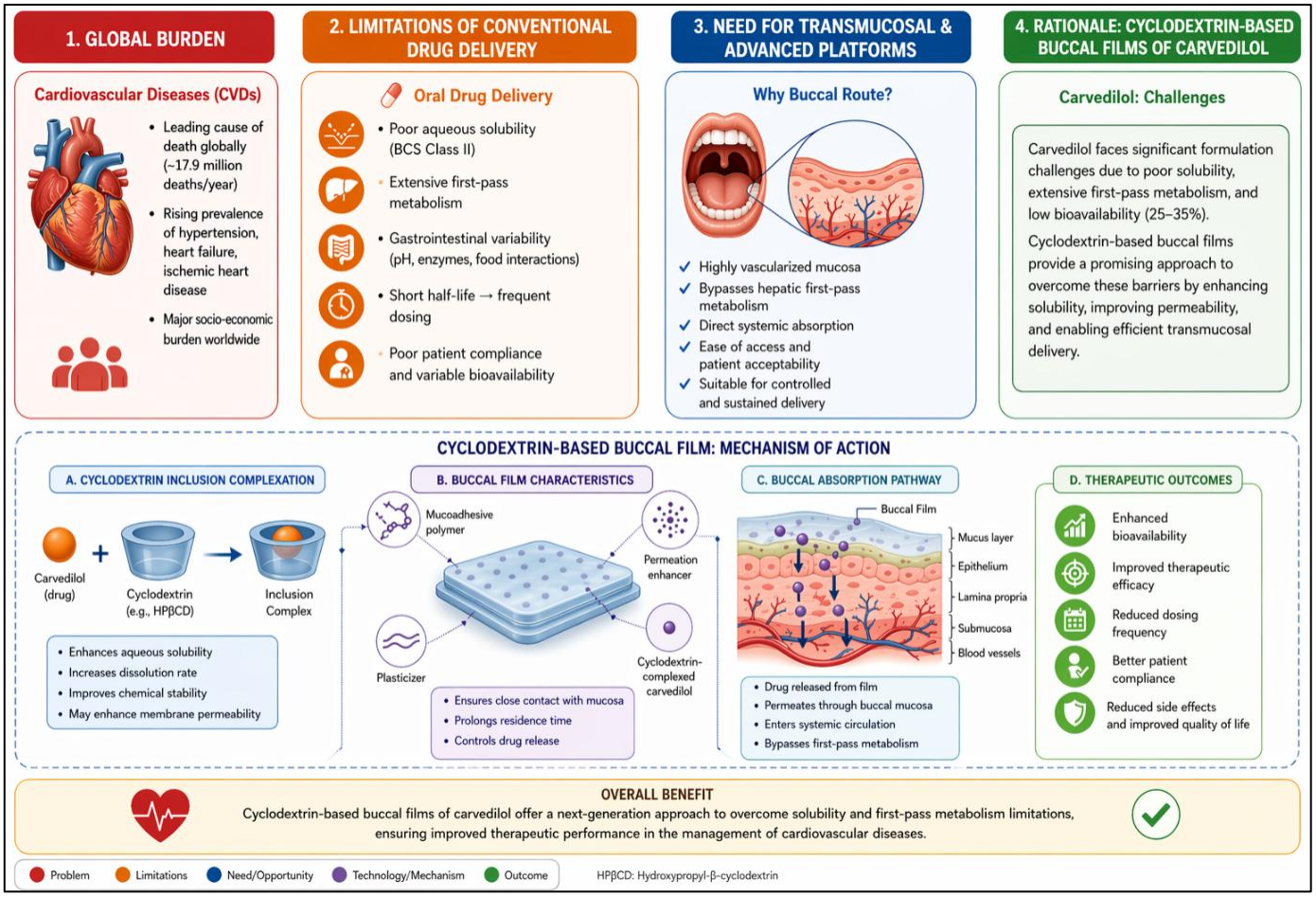

Figure 1: Schematic Representation of Cyclodextrin-Based Buccal Film Delivery System for Carvedilol: Rationale, Mechanism, and Therapeutic Outcomes

2. Biopharmaceutical Constraints of Carvedilol

2.1 Physicochemical Properties and BCS Classification

Carvedilol is a non-selective β-adrenergic blocker with additional α1-blocking activity, widely used in the management of hypertension and heart failure. From a biopharmaceutical perspective, carvedilol exhibits poor aqueous solubility coupled with relatively high lipophilicity, which significantly influences its oral absorption profile [31]. The drug possesses a high partition coefficient (log P ~3.5-4.0), indicating substantial membrane permeability but limited dissolution in gastrointestinal fluids [32].

The ionization behavior of carvedilol, governed by its pKa (~7.8), results in pH-dependent solubility, with relatively better solubility in acidic environments and poor solubility at intestinal pH [33]. This property leads to dissolution-limited absorption, especially in the small intestine where most drug absorption occurs.

Based on these characteristics, carvedilol is classified under the Biopharmaceutics Classification System (BCS) as a Class II drug, characterized by low solubility and high permeability [34]. Consequently, the rate-limiting step in its absorption is dissolution rather than permeability. This necessitates formulation strategies aimed at enhancing solubility and dissolution rate to improve systemic bioavailability [35].

2.2 Pharmacokinetic Limitations

Despite favorable permeability, carvedilol demonstrates low and variable oral bioavailability (approximately 25–35%), primarily due to extensive first-pass hepatic metabolism [36]. The drug undergoes significant metabolism in the liver via the cytochrome P450 enzyme system, particularly CYP2D6 and CYP2C9, leading to substantial presystemic elimination [37].

This extensive metabolism contributes to high inter-individual variability in pharmacokinetic parameters, influenced by genetic polymorphism in metabolizing enzymes [38]. Additionally, carvedilol exhibits high plasma protein binding (>95%), which may further affect its free drug concentration and therapeutic efficacy [39].

The elimination half-life of carvedilol ranges from 6 to 10 hours, necessitating multiple dosing in conventional formulations to maintain therapeutic plasma levels [40]. Furthermore, variability in gastrointestinal conditions such as pH, motility, and presence of food can significantly impact drug absorption, adding another layer of unpredictability to its pharmacokinetic profile [41].

2.3 Clinical Challenges in Therapy

The biopharmaceutical and pharmacokinetic limitations of carvedilol translate into several clinical challenges. The low and variable bioavailability often results in inconsistent therapeutic outcomes, requiring careful dose titration in patients [42].

Frequent dosing associated with its relatively short half-life can lead to poor patient compliance, particularly in chronic conditions such as hypertension and heart failure [43]. Additionally, fluctuations in plasma drug concentration may increase the risk of dose-related adverse effects, including hypotension, dizziness, and fatigue [44].

Another significant concern is the potential for drug–drug interactions, particularly with medications that influence CYP450 enzymes, which can alter carvedilol metabolism and therapeutic response [45]. Moreover, variability in patient response due to genetic and physiological differences complicates treatment optimization [46].

These challenges highlight the necessity for advanced drug delivery systems that can enhance bioavailability, reduce dosing frequency, and provide more consistent therapeutic outcomes, thereby improving overall patient compliance and treatment efficacy [47].

3. Buccal Drug Delivery: Fundamentals and Advances

3.1 Anatomy and Physiology of Buccal Mucosa

The buccal mucosa, lining the inner cheek, is an attractive site for transmucosal drug delivery due to its rich vascularization and relatively permeable epithelial structure [48]. It consists of a non-keratinized stratified squamous epithelium, typically 500-800 µm thick, supported by a lamina propria and submucosa [49]. Unlike keratinized tissues (e.g., gingiva), the buccal mucosa exhibits higher permeability, facilitating drug absorption into systemic circulation.

The presence of a mucus layer, primarily composed of mucin glycoproteins, plays a dual role-acting as a protective barrier while also providing a substrate for mucoadhesion, which is crucial for dosage form retention [50]. Salivary secretion (~0.5–2 L/day) can influence drug dissolution and residence time, thereby affecting drug absorption kinetics [51].

Additionally, the buccal region avoids first-pass hepatic metabolism, as absorbed drugs directly enter systemic circulation via the jugular vein, making it particularly advantageous for drugs with extensive presystemic elimination [52].

3.2 Drug Transport Mechanisms (Transcellular vs Paracellular)

Drug permeation across the buccal mucosa occurs primarily via two pathways: transcellular (intracellular) and paracellular (intercellular) routes [53].

The transcellular pathway involves drug diffusion through epithelial cells and is generally favored by lipophilic molecules, as it requires partitioning into and traversing the lipid bilayer of cell membranes [54]. This route is predominant for drugs like carvedilol, which exhibit high lipophilicity.

In contrast, the paracellular pathway involves transport through intercellular spaces and tight junctions. This route is typically limited to hydrophilic drugs and small molecules, but its contribution is restricted due to the presence of tight junctions that act as permeability barriers [55].

The efficiency of drug transport is influenced by factors such as molecular weight, lipophilicity, ionization state, and formulation characteristics [56]. Advanced formulation strategies, including the use of permeation enhancers and mucoadhesive polymers, can modulate these pathways to improve drug absorption [57].

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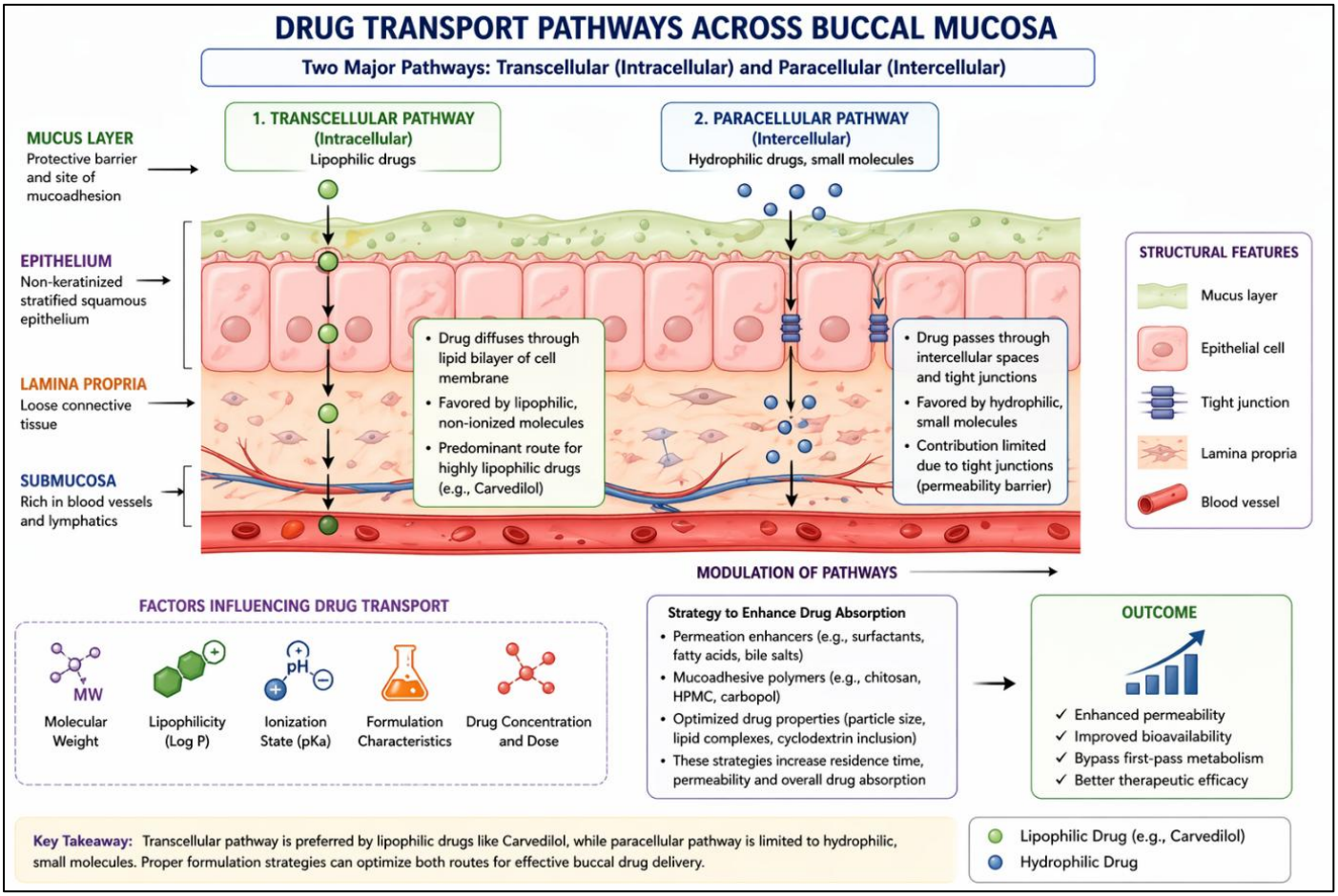

Figure 2: Drug Transport Pathways

3.3 Advantages Over Oral and Parenteral Routes

Buccal drug delivery offers several advantages over conventional oral and parenteral routes. One of the most significant benefits is the avoidance of first-pass metabolism, leading to enhanced bioavailability for drugs with extensive hepatic degradation [58].

Additionally, buccal delivery provides rapid onset of action due to direct entry into systemic circulation, which is beneficial in acute therapeutic conditions [59]. The route is also non-invasive and patient-friendly, improving compliance, particularly in geriatric and pediatric populations [60].

Compared to parenteral administration, buccal systems eliminate the risks associated with injections, such as pain, infection, and need for trained personnel [61]. Furthermore, buccal formulations such as films and tablets allow for controlled and sustained drug release, improving therapeutic consistency [62].

These advantages make buccal delivery a promising alternative for drugs with poor oral bioavailability, such as carvedilol.

3.4 Limitations and Technological Barriers

Despite its advantages, buccal drug delivery is associated with several limitations and formulation challenges. The relatively small absorption surface area compared to the gastrointestinal tract restricts the total drug dose that can be delivered [63].

Continuous salivary flow and involuntary swallowing can lead to drug loss and reduced residence time, affecting overall bioavailability [64]. Additionally, the mucus barrier and enzymatic activity within the oral cavity may hinder drug permeation and stability [65].

Formulation challenges include achieving adequate mucoadhesion, maintaining mechanical strength of dosage forms, and ensuring patient acceptability in terms of taste and mouthfeel [66]. Moreover, variability in mucosal permeability among individuals can lead to inconsistent drug absorption [67].

Technological barriers such as limited permeation enhancers with proven safety profiles and challenges in large-scale manufacturing further complicate the development of buccal delivery systems [68].

4. Buccal Films as Next-Generation Dosage Forms

4.1 Classification (Fast-Dissolving vs Mucoadhesive Systems)

Buccal films have emerged as advanced drug delivery systems designed to improve therapeutic outcomes through rapid onset or sustained drug release, depending on formulation design [69]. These systems are broadly classified into fast-dissolving films and mucoadhesive films based on their functional characteristics.

Fast-dissolving buccal films are intended to disintegrate quickly upon contact with saliva, releasing the drug for rapid absorption through the buccal mucosa. These systems are particularly advantageous for conditions requiring immediate therapeutic action and for patient populations with swallowing difficulties [70].

In contrast, mucoadhesive buccal films are designed to adhere to the mucosal surface for extended periods, allowing controlled and sustained drug release [71]. These films utilize bioadhesive polymers such as chitosan, carbopol, and hydroxypropyl methylcellulose (HPMC) to enhance residence time and improve drug absorption [72].

The selection between these systems depends on the therapeutic objective, drug properties, and required pharmacokinetic profile, making buccal films a versatile platform for both immediate and controlled drug delivery [73].

4.2 Design Considerations for Systemic Delivery

The successful development of buccal films for systemic delivery requires careful consideration of multiple formulation and physiological parameters. One of the primary factors is the selection of suitable polymers, which must provide adequate mucoadhesion, flexibility, and mechanical strength [74].

The drug's physicochemical properties, including solubility, molecular weight, and lipophilicity, play a crucial role in determining its suitability for buccal delivery [75]. Incorporation of permeation enhancers such as surfactants, bile salts, and fatty acids can significantly improve drug transport across the buccal mucosa [76].

Additionally, film thickness, surface area, and drug loading must be optimized to ensure uniform drug distribution and consistent release kinetics [77]. The inclusion of plasticizers (e.g., glycerol, polyethylene glycol) enhances film flexibility and patient comfort [78].

Advanced strategies such as cyclodextrin inclusion complexes, nanoformulations, and multilayer films are increasingly being explored to overcome solubility and permeability limitations, thereby enhancing systemic drug delivery [79].

4.3 Patient-Centric Benefits and Compliance

One of the most significant advantages of buccal films is their patient-centric design, which directly contributes to improved treatment adherence. These dosage forms are non-invasive, easy to administer, and do not require water, making them particularly suitable for geriatric, pediatric, and dysphagic patients [80].

Buccal films also offer improved dosing accuracy and convenience, reducing the burden associated with frequent dosing in chronic therapies (81). The ability to achieve controlled drug release minimizes fluctuations in plasma drug levels, thereby reducing side effects and enhancing therapeutic efficacy [82].

Furthermore, buccal films can be designed with acceptable taste, texture, and mouthfeel, which significantly enhances patient acceptability [83]. The combination of improved bioavailability, ease of use, and enhanced therapeutic outcomes positions buccal films as a promising next-generation dosage form in modern drug delivery [84].

5. Cyclodextrins in Advanced Drug Delivery

5.1 Structural Chemistry and Types

Cyclodextrins (CDs) are cyclic oligosaccharides derived from starch through enzymatic degradation, consisting of α-(1,4)-linked D-glucopyranose units arranged in a truncated cone-shaped structure [85]. This unique molecular architecture results in a hydrophilic outer surface and a relatively hydrophobic central cavity, enabling cyclodextrins to form inclusion complexes with poorly water-soluble drugs.

The most common natural cyclodextrins include α-cyclodextrin (six glucose units), β-cyclodextrin (seven units), and γ-cyclodextrin (eight units), each differing in cavity size and complexation efficiency [86]. Among these, β-cyclodextrin is widely used due to its appropriate cavity size and cost-effectiveness. However, its limited aqueous solubility has led to the development of chemically modified derivatives such as hydroxypropyl-β-cyclodextrin (HPβCD) and sulfobutyl ether-β-cyclodextrin (SBEβCD) [87].

These derivatives exhibit enhanced solubility and improved safety profiles, making them suitable for various pharmaceutical applications, including oral, parenteral, and transmucosal drug delivery systems [88].

5.2 Inclusion Complexation Mechanism

The fundamental mechanism underlying cyclodextrin-based drug delivery is inclusion complexation, wherein a guest molecule (drug) is partially or completely entrapped within the hydrophobic cavity of the cyclodextrin [89]. This process is primarily driven by non-covalent interactions, including van der Waals forces, hydrophobic interactions, and hydrogen bonding [90].

The formation of inclusion complexes depends on factors such as molecular size compatibility, drug polarity, and environmental conditions (e.g., pH and temperature) [91]. The drug molecule typically enters the cyclodextrin cavity in a dynamic equilibrium process, forming a reversible complex that can dissociate upon dilution or interaction with biological membranes [92].

This reversible binding is essential, as it facilitates drug release at the site of absorption, thereby enhancing bioavailability without altering pharmacological activity [93].

5.3 Role in Solubility, Stability, and Permeability Enhancement

Cyclodextrins play a significant role in improving the biopharmaceutical performance of poorly soluble drugs such as carvedilol. Through inclusion complex formation, cyclodextrins enhance aqueous solubility and dissolution rate, which are critical limitations for BCS Class II drugs [94].

In addition to solubility enhancement, cyclodextrins improve chemical and physical stability by protecting drugs from degradation pathways such as hydrolysis, oxidation, and photodegradation [95]. This stabilization is particularly important for labile drug molecules in physiological environments.

Cyclodextrins can also enhance membrane permeability by increasing the apparent drug solubility at the absorption site and facilitating drug partitioning across biological membranes [96]. Furthermore, they may reduce local irritation and toxicity by minimizing direct drug–membrane interactions [97].

These properties make cyclodextrins valuable excipients in advanced drug delivery systems, particularly for buccal, nasal, and transdermal applications [98].

5.4 Safety and Regulatory Considerations

The safety profile of cyclodextrins has been extensively studied, and several derivatives are classified as Generally Recognized as Safe (GRAS) for pharmaceutical use under defined conditions [99]. However, safety depends on the type of cyclodextrin, route of administration, and dosage.

For example, β-cyclodextrin has limited suitability for parenteral administration due to potential nephrotoxicity at high doses, whereas modified derivatives such as HPβCD and SBEβCD demonstrate improved safety and broader applicability [100].

Regulatory authorities such as the U.S. Food and Drug Administration and the European Medicines Agency provide specific guidelines regarding the acceptable use and limits of cyclodextrins in pharmaceutical formulations [101].

Toxicological evaluation-including assessment of renal toxicity, hemolysis, and local irritation-is essential during formulation development to ensure safety [102]. Overall, when appropriately selected and used within recommended limits, cyclodextrins are considered safe and effective excipients in modern drug delivery systems [103].

6. Cyclodextrin-Carvedilol Complexation

6.1 Phase Solubility Analysis and Stability Constants

Phase solubility analysis is a fundamental technique used to evaluate the complexation behavior between Carvedilol and cyclodextrins. According to the Higuchi-Connors model, the solubility profile of a drug in the presence of increasing cyclodextrin concentration provides insight into the stoichiometry and stability of the inclusion complex [104].

Typically, carvedilol exhibits an A L-type phase solubility diagram, indicating a linear increase in drug solubility with increasing cyclodextrin concentration, suggestive of a 1:1 drug-cyclodextrin complex (105). The apparent stability constant ($K_{1:1}$) is calculated from the slope of the phase solubility plot and reflects the strength of interaction between the drug and cyclodextrin [106].

An optimal stability constant is critical-values that are too low indicate weak complexation, whereas excessively high values may hinder drug release from the complex at the absorption site [107]. Therefore, achieving a balance between complex stability and drug release is essential for effective formulation development [108].

6.2 Methods of Complex Preparation

Several methods have been developed for the preparation of cyclodextrin–carvedilol inclusion complexes, each influencing the physicochemical properties and performance of the final product.

The physical mixing method is the simplest approach, involving blending of drug and cyclodextrin powders; however, it often results in limited complexation efficiency [109]. In contrast, the kneading method enhances interaction by triturating the drug and cyclodextrin with a minimal amount of solvent, leading to improved complex formation [110].

The co-precipitation method involves dissolving both components in a suitable solvent system followed by precipitation, yielding more uniform complexes with better inclusion efficiency [111]. Advanced techniques such as freeze-drying (lyophilization) and spray drying are widely used to produce highly amorphous complexes with superior solubility and dissolution characteristics [112].

More recently, solvent evaporation, supercritical fluid technology, and microwave-assisted methods have been explored to enhance complexation efficiency and scalability [113]. The choice of preparation method significantly affects the degree of inclusion, crystallinity, and dissolution behavior of the resulting complex [114].

6.3 Impact on Dissolution and Bioavailability

Cyclodextrin complexation has a profound impact on the dissolution behavior and oral bioavailability of carvedilol. Due to its poor aqueous solubility, carvedilol exhibits dissolution-limited absorption; however, inclusion complex formation significantly enhances its apparent solubility and dissolution rate [115].

The improved dissolution profile leads to a higher concentration gradient at the absorption site, facilitating enhanced drug permeation across biological membranes [116]. Additionally, cyclodextrins maintain the drug in a molecularly dispersed state, reducing aggregation and improving wettability [117].

Preclinical and clinical studies have demonstrated that cyclodextrin-based formulations of carvedilol result in increased bioavailability, reduced variability, and improved therapeutic efficacy compared to conventional formulations [118]. Furthermore, when combined with advanced delivery systems such as buccal films, these complexes can bypass first-pass metabolism, further enhancing systemic drug exposure [119].

Overall, cyclodextrin–carvedilol complexation represents a promising strategy to overcome the biopharmaceutical limitations of carvedilol and improve its clinical performance [120].

7. Integrated Strategy: Cyclodextrin-Based Buccal Films

7.1 Mechanistic Synergy (Solubility + Permeability + Retention)

The integration of cyclodextrin inclusion complexes with mucoadhesive buccal films represents a multifunctional delivery platform that simultaneously addresses key biopharmaceutical barriers of Carvedilol, namely poor solubility, limited permeability, and short residence time [121].

Cyclodextrins enhance the aqueous solubility and dissolution rate of carvedilol by forming inclusion complexes, thereby increasing the concentration of drug available at the absorption interface [122]. This elevated local concentration establishes a favorable concentration gradient, which drives passive diffusion across the buccal epithelium [123].

Simultaneously, the mucoadhesive buccal film matrix-composed of polymers such as HPMC, carbopol, or chitosan-ensures prolonged contact with the mucosal surface, thereby enhancing residence time and drug absorption window [124]. The combined effect results in improved permeation efficiency, as the drug is maintained in a solubilized state while being continuously presented to the absorption site [125].

Moreover, cyclodextrins can modulate membrane interactions and reduce drug crystallization, while the film provides controlled hydration and release kinetics, creating a synergistic system that optimizes drug delivery performance [126].

7.2 Enhancement of Systemic Drug Delivery

Cyclodextrin-based buccal films significantly improve the systemic delivery profile of carvedilol by overcoming the limitations associated with conventional oral dosage forms. One of the most critical advantages is the avoidance of first-pass hepatic metabolism, which otherwise reduces the bioavailability of carvedilol when administered orally [127].

By facilitating direct absorption into the systemic circulation via the buccal mucosa, this system leads to enhanced bioavailability and reduced inter-individual variability [128]. The improved dissolution and sustained release characteristics further contribute to stable plasma drug concentrations, minimizing peak–trough fluctuations commonly observed with immediate-release oral formulations [129].

Additionally, the incorporation of cyclodextrins ensures that the drug remains in a molecularly dispersed and bioavailable form, while the buccal film matrix controls the rate of drug release, thereby optimizing pharmacokinetic parameters such as Cmax, Tmax, and AUC [130].

These combined effects translate into improved therapeutic efficacy, faster onset of action, and reduced dosing frequency, making this system highly suitable for chronic cardiovascular therapy [131].

7.3 Comparative Advantage Over Conventional Systems

Cyclodextrin-based buccal films offer several advantages over traditional drug delivery systems, including oral tablets, capsules, and parenteral formulations. Unlike oral dosage forms, this approach bypasses gastrointestinal degradation and first-pass metabolism, leading to improved bioavailability [132].

Compared to parenteral administration, buccal films are non-invasive, pain-free, and do not require skilled personnel, significantly enhancing patient convenience and compliance [133]. Furthermore, the system provides controlled and targeted drug delivery, reducing systemic side effects and improving safety profiles [134].

The combination of cyclodextrin complexation and buccal film technology also enables dose reduction, improved formulation stability, and enhanced patient acceptability due to better taste masking and ease of administration [135].

Overall, this integrated strategy represents a next-generation drug delivery approach, offering superior performance compared to conventional systems, particularly for drugs with challenging biopharmaceutical properties like carvedilol [136].

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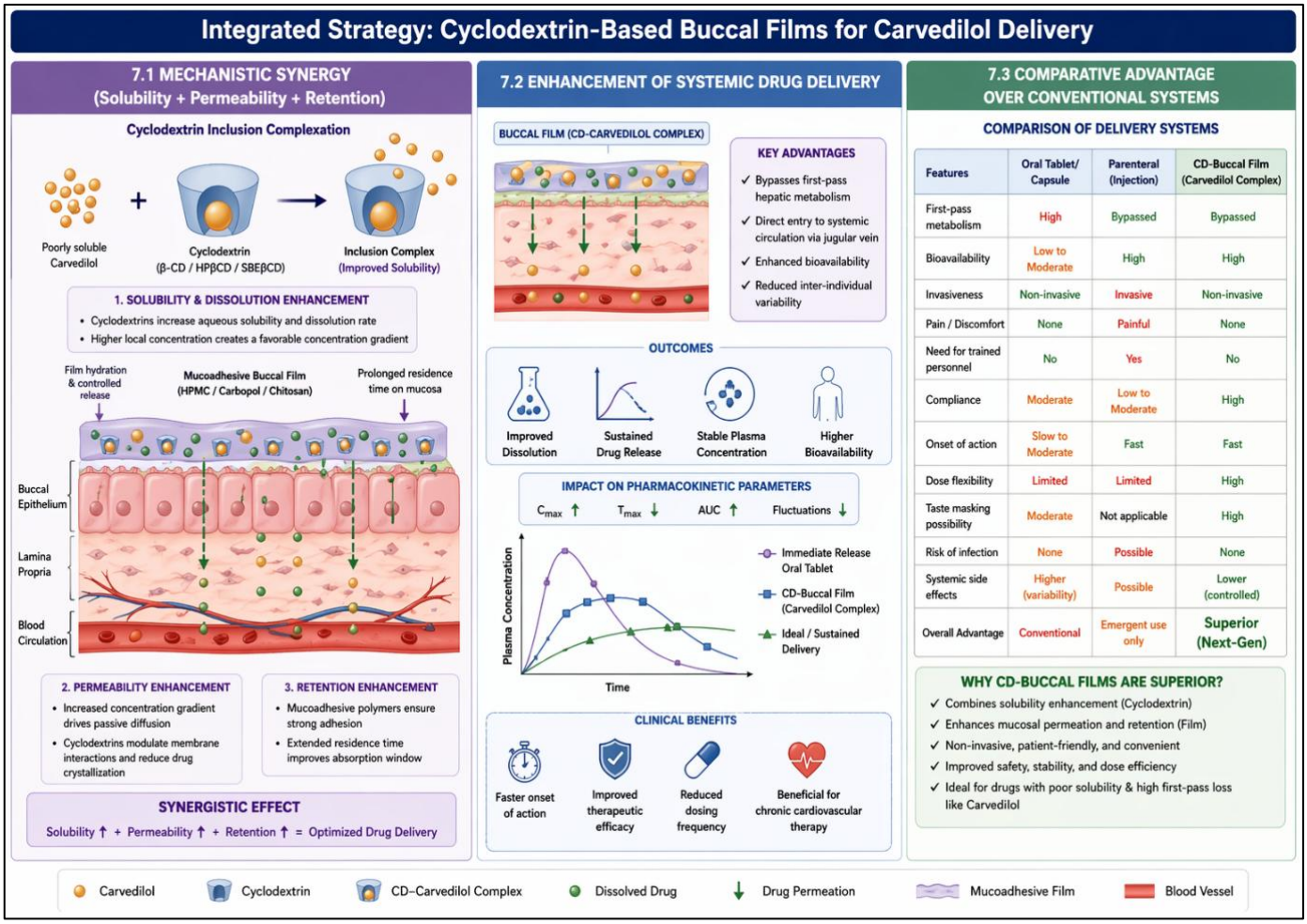

Figure 3: Synergistic Drug Delivery Approach: Cyclodextrin Complexation and Buccal Film Technology for Carvedilol

8. Formulation Engineering of Buccal Films

8.1 Polymer Selection and Functional Roles

The performance of buccal films is fundamentally governed by the choice of polymer, which dictates mucoadhesion, mechanical integrity, hydration behavior, and drug release kinetics [137]. Commonly employed polymers include hydroxypropyl methylcellulose (HPMC), carbopol, chitosan, sodium alginate, and polyvinyl alcohol (PVA), each offering distinct functional attributes [138].

Mucoadhesive polymers such as carbopol and chitosan interact with mucin via hydrogen bonding, electrostatic interactions, and chain interpenetration, thereby enhancing residence time at the site of application [139]. Hydrophilic polymers like HPMC facilitate rapid hydration and swelling, promoting controlled drug release and improved patient comfort [140].

Polymer selection must also consider biocompatibility, non-toxicity, film-forming ability, and compatibility with the drug and excipients [141]. The use of polymer blends is often preferred to achieve an optimal balance between mechanical strength and mucoadhesive performance [142].

8.2 Plasticizers and Film Modifiers

Plasticizers are essential components in buccal film formulations, as they enhance flexibility, elasticity, and mechanical strength by reducing intermolecular forces within the polymer matrix [143]. Common plasticizers include glycerol, propylene glycol, polyethylene glycol (PEG), and triethyl citrate [144].

The concentration of plasticizer plays a critical role; insufficient amounts may lead to brittle films, whereas excessive levels can result in over-softening, stickiness, and reduced tensile strength [145].

In addition to plasticizers, film modifiers such as sweeteners, flavoring agents, and surfactants are incorporated to improve organoleptic properties and patient acceptability [146]. Surfactants may also enhance drug solubilization and uniform distribution within the film matrix [147].

8.3 Permeation Enhancers and Their Mechanisms

Permeation enhancers are incorporated to improve drug transport across the buccal mucosa, particularly for drugs with limited permeability [148]. These agents function through various mechanisms, including modulation of lipid bilayer fluidity, opening of tight junctions, and interaction with membrane proteins [149].

Common permeation enhancers include fatty acids (oleic acid), bile salts, surfactants, and polymers such as chitosan, which can transiently alter mucosal barrier properties [150].

The selection of permeation enhancers requires careful consideration of efficacy versus safety, as excessive disruption of mucosal integrity may lead to irritation or toxicity [151]. Therefore, optimizing concentration and exposure time is critical to ensure reversible and safe enhancement of permeability [152].

8.4 Manufacturing Techniques (Solvent Casting, Hot-Melt Extrusion)

The manufacturing method plays a critical role in determining the physicochemical properties and overall performance of buccal films. The solvent casting method is the most widely used technique, involving the dissolution of polymers and the drug in a suitable solvent, followed by casting and solvent evaporation to form a uniform film [153]. This method offers several advantages, including simplicity, uniform drug distribution, and ease of scale-up; however, concerns related to residual solvents must be carefully addressed [154].

In contrast, hot-melt extrusion (HME) is a solvent-free technique that involves the melting and mixing of the drug and polymer under controlled temperature and pressure conditions [155]. HME provides advantages such as improved drug dispersion, enhanced stability, and suitability for continuous manufacturing processes [156].

Furthermore, advanced techniques such as electrospinning and 3D printing are emerging as innovative approaches for the fabrication of buccal films with tailored physicochemical and drug release properties [157].

8.5 Critical Quality Attributes (CQAs)

Critical Quality Attributes (CQAs) are essential parameters that ensure the quality, safety, and efficacy of buccal film formulations [158]. These include film thickness, uniformity of weight, drug content uniformity, surface pH, folding endurance, tensile strength, and elongation at break [159].

In vitro performance characteristics such as disintegration time, swelling index, mucoadhesive strength, and drug release profile are also crucial for evaluating formulation performance [160].

Advanced analytical techniques are employed to characterize buccal films, including Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and scanning electron microscopy (SEM) to assess compatibility, thermal behavior, and surface morphology [161].

A systematic approach based on Quality by Design (QbD) principles is increasingly adopted to optimize formulation variables and ensure consistent product quality [162].

9. Characterization and Evaluation Techniques

9.1 Physicochemical and Mechanical Properties

Comprehensive characterization of buccal films begins with evaluation of physicochemical attributes that govern performance and patient acceptability. Key parameters include film thickness, weight variation, surface pH, drug content uniformity, and moisture content (163). Surface pH is particularly important to ensure compatibility with buccal mucosa and to minimize irritation (164).

Mechanical properties such as tensile strength, elongation at break, and folding endurance are critical for assessing film robustness and handling characteristics (165). These properties are influenced by polymer composition and plasticizer concentration, and they determine the film's ability to withstand mechanical stress during application (166).

Uniform drug distribution within the film matrix is essential to ensure dose accuracy and reproducibility, which are key quality requirements for pharmaceutical formulations (167).

9.2 Mucoadhesion and Swelling Behavior

Mucoadhesion is a defining feature of buccal films, as it determines the residence time of the dosage form at the site of absorption. Mucoadhesive strength is typically evaluated using texture analyzers or modified balance methods, which measure the force required to detach the film from mucosal tissue (168).

Swelling behavior is another critical parameter, as hydration of the polymer matrix facilitates chain relaxation and interpenetration with mucin, enhancing adhesion (169). The swelling index is determined by measuring the weight gain of the film upon exposure to simulated salivary fluid (170).

An optimal balance between swelling and structural integrity is required; excessive swelling may lead to premature disintegration, while insufficient swelling can limit mucoadhesion and drug release (171).

9.3 Solid-State Characterization (FTIR, DSC, XRD)

Solid-state characterization techniques are essential for understanding drug–excipient interactions and physical state changes within buccal films.

Fourier-transform infrared spectroscopy (FTIR) is used to identify potential chemical interactions between the drug and formulation components by analyzing characteristic functional group vibrations (172).

Differential scanning calorimetry (DSC) provides information on thermal behavior, including melting point, crystallinity, and possible phase transitions, which can indicate successful drug incorporation or complexation (173).

X-ray diffraction (XRD) is employed to assess the crystalline or amorphous nature of the drug within the film matrix. A reduction in crystallinity or conversion to an amorphous state is often associated with improved solubility and dissolution (174).

Together, these techniques provide critical insights into the structural and physicochemical integrity of the formulation (175).

9.4 In Vitro Drug Release Studies

In vitro drug release studies are conducted to evaluate the release profile and kinetics of the drug from buccal films. These studies are typically performed using USP dissolution apparatus or modified diffusion cells, employing simulated salivary fluid as the dissolution medium (176).

Samples are collected at predetermined intervals and analyzed using suitable analytical techniques such as UV–visible spectroscopy or HPLC (177). The release data are fitted to kinetic models (e.g., zero-order, first-order, Higuchi, and Korsmeyer–Peppas models) to elucidate the mechanism of drug release (178).

These studies are essential for predicting in vivo performance and ensuring consistency in drug delivery (179).

9.5 Ex Vivo and In Vivo Correlation

Ex vivo studies are performed using animal buccal mucosa (e.g., porcine or bovine tissue) to evaluate drug permeation and mucoadhesion under conditions that closely mimic physiological environments (180). These studies provide valuable data on permeability coefficients and flux, which are critical for assessing formulation efficiency (181).

In vivo studies, conducted in suitable animal models or human subjects, are used to evaluate pharmacokinetic parameters such as Cmax, Tmax, and AUC, thereby confirming the systemic performance of the buccal film (182).

Establishing a correlation between in vitro and in vivo data, commonly referred to as in vitro–in vivo correlation (IVIVC), is crucial for predicting clinical performance and supporting regulatory approval (183). A strong IVIVC enables optimization of formulation variables and reduces the need for extensive in vivo studies (184).

10. Recent Advances and Emerging Trends (2020-2025)

Table 1: Recent Advanves And Emerging Trends

Section	Technology / Approach	Key Features	Mechanism / Advantage	Applications	Recent Trends (2020–2025)
11.1 Nanostructured Buccal Films	Nanoparticle-loaded buccal films	Incorporation of polymeric or lipid nanoparticles into film matrix	Enhances drug solubility, protects drug from degradation	Poorly soluble drugs (e.g., carvedilol)	Increased use of SLNs, NLCs, polymeric nanoparticles
	Nanoemulsion-based films	Drug solubilized in nano-sized oil droplets	Improved permeation and rapid drug release	Lipophilic drugs	Focus on high bioavailability formulations
	Nanofiber films (electrospinning)	High surface area, porous structure	Rapid dissolution and enhanced absorption	Fast-acting formulations	Growth in electrospinning technology
11.2 Hybrid Systems (Nano + Film Technology)	Cyclodextrin–nanoparticle–film systems	Combination of inclusion complex + nanocarrier	Dual enhancement: solubility + permeability	BCS Class II drugs	Increasing multi-functional delivery systems
	Liposome-loaded buccal films	Vesicular carriers embedded in films	Improved drug stability and controlled release	Peptides, proteins	Rise in biopharmaceutical delivery
	Solid dispersion-based films	Drug dispersed in amorphous form within matrix	Enhanced dissolution and uniform distribution	Poorly soluble APIs	Adoption of amorphous drug delivery systems
11.3 Smart and Stimuli-Responsive Buccal Systems	pH-responsive films	Drug release triggered by pH changes	Targeted release in specific oral conditions	Oral infections, cancer	Development of target-specific delivery systems
	Enzyme-responsive systems	Drug release triggered by enzymatic activity	Site-specific and controlled release	Disease-specific therapy	Exploration of biological triggers
	Temperature-responsive films	Drug release influenced by temp. variation	Controlled release under physiological conditions	Personalized therapy	Emerging thermo-sensitive polymers
	Bioadhesive smart polymers	Adaptive adhesion and controlled drug release	Improved retention and responsiveness	Chronic therapy	Integration of intelligent biomaterials

12. Limitations and Research Gaps

12.1 Stability Issues

Despite promising performance, buccal film systems—particularly those incorporating cyclodextrin complexes and nanostructures—face notable stability challenges. Moisture sensitivity can alter mechanical properties (brittleness/softening) and accelerate drug degradation or crystallization, especially for hygroscopic polymers and plasticizer-rich matrices (185). Temperature fluctuations may induce phase separation, drug recrystallization, or loss of amorphous character, compromising dissolution advantages (186).

For cyclodextrin-based systems, complex dissociation during storage and competitive inclusion with excipients can reduce effectiveness over time (187). Ensuring long-term stability therefore requires optimized packaging (e.g., moisture-barrier laminates), controlled humidity storage, and robust stability-indicating analytical methods (188).

12.2 Limited Clinical Data

While preclinical and in vitro studies demonstrate clear advantages, there is still limited clinical evidence supporting the widespread therapeutic use of buccal films for systemic delivery (189). Most available data are derived from animal models or small-scale human studies, which may not fully capture variability in human physiology and patient populations (190).

Key gaps include:

- Lack of large-scale randomized clinical trials
- Insufficient pharmacokinetic–pharmacodynamic (PK–PD) correlation data
- Limited long-term safety and tolerability profiles

These limitations hinder regulatory approval and clinical translation, emphasizing the need for well-designed clinical investigations (191).

12.3 Formulation Scalability Challenges

Translating laboratory-scale buccal film formulations to industrial-scale manufacturing presents several technical and economic challenges. Achieving uniform drug distribution, consistent thickness, and reproducible mechanical properties at scale is complex, particularly for multi-component systems (192).

Processes like solvent casting may face issues related to residual solvents, drying uniformity, and batch variability, while advanced techniques such as hot-melt extrusion or electrospinning require specialized equipment and process optimization (193).

Additional challenges include:

- Maintaining content uniformity during continuous production
- Ensuring process validation and regulatory compliance
- Cost implications of advanced excipients and technologies

Addressing these barriers requires adoption of Quality by Design (QbD), process analytical technology (PAT), and scalable manufacturing platforms (194).

13. Future Perspectives

13.1 Personalized Medicine Approach

Future development of buccal film systems is expected to align with the paradigm of personalized medicine, wherein drug delivery is tailored to individual patient characteristics such as genetics, disease state, and pharmacokinetic variability. Buccal films offer

inherent flexibility in dose customization, enabling precise adjustment of drug loading and release profiles to meet patient-specific therapeutic needs.

Advances in patient-centric design, including age-appropriate formulations and adaptive dosing strategies, further support individualized therapy. Integration with pharmacogenomic data may enable optimization of drug selection and dosing, particularly for drugs exhibiting high inter-individual variability such as carvedilol.

13.2 AI-Driven Formulation Optimization

The application of artificial intelligence (AI) and machine learning (ML) in pharmaceutical formulation is emerging as a transformative approach to accelerate drug development. AI-driven models can analyze complex datasets to predict optimal polymer combinations, drug–excipient compatibility, and release kinetics, significantly reducing reliance on trial-and-error experimentation.

Machine learning algorithms are increasingly being utilized for design of experiments (DoE), process optimization, and quality prediction, enhancing efficiency and reproducibility in formulation development. In buccal film systems, AI can assist in optimizing parameters such as film thickness, drug loading, and permeation behavior, ultimately improving product performance and scalability.

13.3 Clinical Translation Roadmap

Despite significant progress in formulation design, successful clinical translation of buccal film systems requires a well-defined development and regulatory roadmap. This includes comprehensive preclinical evaluation, robust pharmacokinetic studies, and large-scale clinical trials to establish safety and efficacy.

Regulatory approval pathways demand adherence to guidelines set by agencies such as the U.S. Food and Drug Administration and the European Medicines Agency, including requirements for quality, safety, and performance validation.

In addition, implementation of Quality by Design (QbD) and Process Analytical Technology (PAT) frameworks will be critical to ensure consistent product quality during scale-up and commercialization. Collaboration between academia, industry, and regulatory bodies will further facilitate the translation of innovative buccal delivery systems from bench to bedside.

14. Conclusion

Buccal drug delivery has emerged as a promising and patient-centric alternative to conventional oral and parenteral routes, particularly for drugs limited by poor solubility and extensive first-pass metabolism. The integration of cyclodextrin inclusion complexation with mucoadhesive buccal film technology represents a rational and synergistic approach to overcome key biopharmaceutical challenges associated with Carvedilol.

Cyclodextrins enhance the aqueous solubility, stability, and apparent permeability of the drug, while buccal films provide prolonged residence time, controlled release, and direct systemic absorption via the buccal mucosa. This combined strategy results in improved bioavailability, reduced dosing frequency, and enhanced therapeutic efficacy, addressing both pharmacokinetic and patient compliance limitations.

Advances in formulation engineering-including nanostructured systems, hybrid delivery platforms, and smart polymers-have further expanded the potential of buccal films as next-generation drug delivery systems. In parallel, emerging tools such as artificial intelligence-driven formulation optimization and personalized medicine approaches are expected to refine design strategies and accelerate development timelines.

However, challenges related to stability, limited clinical validation, and large-scale manufacturing must be addressed to facilitate successful clinical translation and commercialization. Adoption of Quality by Design (QbD) principles, advanced manufacturing technologies, and robust regulatory frameworks will be critical in overcoming these barriers.

In conclusion, cyclodextrin-based buccal films offer a versatile, efficient, and innovative platform for systemic drug delivery. With continued research and technological advancement, this approach holds significant potential to transform the delivery of poorly soluble drugs and improve therapeutic outcomes in clinical practice.

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