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BREAKING BARRIERS: ENHANCING DRUG ABSORPTION THROUGH BUCCAL MUCOSA

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ABSTRACT: Buccal drug delivery has emerged as a compelling alternative to conventional administration routes due to the buccal mucosa's favourable anatomical and physiological characteristics. Its rich vascularization, non-keratinized epithelium, and mucoadhesive potential collectively enable efficient systemic and localized drug delivery. These features facilitate rapid absorption of therapeutic agents while bypassing first-pass hepatic metabolism, thus significantly enhancing bioavailability and therapeutic efficacy. The advantages of buccal drug absorption are manifold. The route allows for rapid onset of action, patient-friendly administration, and improved compliance through self-administration. Additionally, the use of mucoadhesive systems such as patches, films, and tablets improves retention time at the absorption site and enhances localized effects. However, despite its benefits, buccal drug delivery faces several limitations. Challenges include limited permeability for macromolecules, potential washout by saliva, variability in dose due to formulation inconsistencies, and patient discomfort with prolonged dosage form retention. These issues necessitate the use of innovative strategies to overcome physiological and formulation-based barriers. This review explores the structural advantages of the buccal mucosa, including its robust connective tissue, regenerative capabilities, and permeability, making it an attractive site for the administration of both hydrophilic and lipophilic drugs. Various permeation enhancers have been employed to increase drug absorption including chemical agents such as surfactants, fatty acids, bile salts, and cyclodextrins, which modify mucosal barrier properties to facilitate drug penetration. Natural compounds like terpenes and essential oils offer biocompatible enhancement, while physical methods such as microneedles, iontophoresis, and electroporation create microchannels or use electrical currents to promote deeper drug permeation. These strategies not only improve drug flux but also expand the range of drugs that can be effectively delivered via the buccal route. The development of novel drug delivery systems is a cornerstone in optimizing buccal drug absorption. Buccal films, mucoadhesive patches, and in situ gels allow for controlled, sustained release and improved therapeutic outcomes. Advances in nanotechnology have led to the design of solid lipid nanoparticles, nanosuspensions, and liposomal formulations that enhance solubility and protect drugs from enzymatic degradation. Lipid-based and solid dispersion technologies also enhance the bioavailability of poorly water-soluble drugs. Bioadhesive polymers like chitosan and HPMC have been instrumental in increasing mucosal contact time and drug permeability. Hence, the review aims to focus on the current research and technological innovations which would continue to refine these systems, paving theway for broader clinical applications and more effective drug therapies.

INTRODUCTION: Buccal drug delivery is emerging as a significant route for enhancing drug absorption due to the unique properties of the buccal mucosa, which facilitates efficient systemic delivery. This method provides several advantages over traditional oral administration, including the avoidance of first-pass hepatic metabolism, reduction in drug degradation within the gastrointestinal tract, and improved patient compliance, especially among populations with swallowing difficulties, such as children and the elderly [1-3]. The buccal mucosa represents a promising route for drug delivery, providing unique advantages in enhancing the absorption and

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bioavailability of active pharmaceutical ingredients. The buccal route offers a large surface area with extensive vascularization, allowing drugs to bypass the first-pass metabolism typically associated with the gastrointestinal tract. This characteristic significantly improves the systemic availability of many therapeutic agents, facilitating a rapid onset of action compared to traditional oral dosage forms [4]. The mucosal drug delivery systems exploit the structural and biological features of the buccal mucosa, where the permeation barriers include a protective mucus layer and epithelial tissue, necessitating innovative strategies to enhance drug absorption [5, 6]. There is a need for newer strategies for overcoming barriers associated with buccal drug delivery. For instance, the use of mucoadhesive polymers has been recognized as a valuable method for prolonging the residence time of drug formulations at the absorption site, thereby enhancing bioavailability [7]. Additionally, the incorporation of permeation enhancers, such as surfactants and liposomes, has been shown to improve absorption by modifying the drug's physicochemical properties and the mucosal barrier [8, 9]. Moreover, the development of nanocarrier systems is rapidly advancing, as they not only protect drugs from degrading enzymes but also facilitate targeted delivery through their unique properties, thereby significantly enhancing permeability across the buccal mucosa [10].

Hence, the development of effective buccal drug delivery systems requires a thorough understanding of the dynamic environment and interactions occurring at the mucosal interface. Recent research emphasizes the significance of optimizing the pH and other formulation parameters to facilitate the solubility and stability of poorly water-soluble drugs, which often limit their therapeutic efficacy when administered by this route [11].

Enhanced drug absorption through the buccal mucosa necessitates a multi-faceted approach, incorporating innovative materials and formulation strategies tailored to the unique characteristics of buccal tissues. Ongoing research continues to refine buccal formulations, focusing on improving mucoadhesion and enhancing the permeability of active ingredients, ultimately bridging gaps in bioavailability challenges faced in conventional oral drug delivery systems.

Significance of Buccal Drug Delivery: The buccal mucosa, characterized by its rich vascularization and relatively high permeability, allows for a more direct transfer of active pharmaceutical ingredients into the systemic circulation via the jugular vein. This enhanced absorption is particularly beneficial for drugs that have poor bioavailability when administered orally [12]. For instance, it has been reported that buccal drug delivery systems can significantly improve the bioavailability of drugs that are extensively metabolized by the liver when taken orally, resulting in a more efficacious therapeutic effect and quicker onset of action [13].

Moreover, the formulation strategies for buccal delivery have evolved with innovations in mucoadhesive technologies, where the adhesive properties of these formulations enable them to remain in contact with the buccal mucosa for extended periods, thereby optimizing drug release and absorption. For example, mucoadhesive patches and films are designed to enhance localization and prolong drug contact with the absorbing mucosal surface [2, 13].

In addition, the pharmacokinetic profiles associated with buccal delivery often show more favorable outcomes compared to other routes. This is attributed to the minimized effects of food interactions, variability due to gastric emptying, and a generally higher level of patient acceptance [14]. This route also allows for easier emergency interventions, enabling the termination of medication delivery should adverse effects arise, which is a significant consideration in patient care [15]. Hence, buccal drug delivery presents a compelling alternative to traditional routes of administration through its ability to enhance drug absorption *via* the buccal mucosa.

Anatomy and Physiology of the Buccal Mucosa: The buccal mucosa's unique structural properties make it an appealing site for drug delivery systems. Its extensive surface area and good permeation characteristics permit efficient systemic and topical delivery of medications, which is utilized in developing novel therapeutic approaches [16-18]. The mucoadhesive characteristics of the buccal mucosa facilitate prolonged retention of drug formulations, enhancing their therapeutic efficacy compared to other routes of administration [19-21].

Histologically, the buccal mucosa is notable for its well-developed connective tissue layer, which contributes to its resilience and capacity to undergo repair. This connective tissue contains a rich vasculature that is critical for delivering nutrients and facilitating healing processes, particularly after injury or surgical intervention. Studies have shown that the buccal mucosa's regenerative capacity is beneficial in clinical scenarios such as repairing urethral strictures with buccal tissue grafts, demonstrating the mucosa's thickness and elasticity favourably [22-24].

The buccal mucosa has a rich vascularization which facilitates rapid absorption of therapeutic compounds directly into systemic circulation, bypassing the first-pass metabolism that commonly diminishes the bioavailability of orally administered drugs. The morphology of the buccal mucosa, which features a non-keratinized epithelium, provides a suitable environment for permeation-enhanced drug transmission [25-29].

Research has demonstrated that drugs administered via the buccal route exhibit significantly higher systemic bioavailability compared to traditional oral routes. For instance, therapeutic agents can circumvent degradation from gastric acidity and enzymatic activity, which are prevalent in the gastrointestinal tract [21, 30-35]. The higher permeability of buccal mucosa, owing to its favourable structure and composition, supports the absorption of both hydrophilic and lipophilic molecules. This characteristic is essential for drugs that are poorly absorbed when taken orally or are subject to extensive metabolic degradation. Hence, the anatomical and physiological attributes of the buccal mucosa, combined with advanced drug delivery technologies, establish it as an effective pathway for enhancing drug absorption [36, 37].

Advantages of Buccal Drug Absorption: Buccal drug absorption offers a range of advantages that enhance drug bioavailability and therapeutic efficacy through the buccal mucosa. The buccal cavity is favoured for drug delivery due to its relatively permeable membrane, rich blood supply, and accessibility, which allows for quicker absorption into the systemic circulation compared to traditional oral administration routes. One of the most significant benefits is that drugs administered buccally can bypass first-pass metabolism and avoid degradation in the harsh gastrointestinal environment, which are common issues with oral medications. This aspect is critical in improving the overall bioavailability of the drug and achieving a more rapid onset of action.

The mechanism of drug absorption in the buccal route is supported by its anatomical and physiological properties. The buccal mucosa provides favourale pH environment for drug stability and absorption and provides mucoadhesion. Mucoadhesive formulations are instrumental in sustaining the retention of drugs in contact with the absorption site, enhancing localized drug delivery and absorption efficiency within the oral cavity. Studies reveal that drugs formulated as mucoadhesive patches, films, or tablets can improve patient compliance and control over therapeutic effects, allowing healthcare providers to manage drug delivery effectively. Moreover, the buccal route is often preferred due to its ease of self-administration; should adverse effects occur, administration can be quickly terminated [38-44].

Buccal drug absorption offers various other advantages such as avoidance of first-pass metabolism, enhanced bioavailability, improved therapeutic efficacy, patient-centric accessibility, and adaptability through innovative formulation strategies. These factors position buccal delivery as a compelling alternative to traditional drug administration methods, warranting further exploration in clinical and pharmaceutical research [45-48].

Challenges in Buccal Drug Delivery: Buccal drug delivery systems present a promising alternative to traditional oral routes of administration, but they are not without significant challenges. One primary challenge is the limited absorption capacity of the buccal mucosa, which generally does not favour the delivery of high molecular weight drugs. Research indicates that macromolecules do not effectively permeate the buccal tissue, thus necessitating the exploration of innovative delivery methods such as microneedles and jet injectors which can enhance the transport of larger molecules across the mucosal layers [49, 50]. Furthermore, the presence of saliva, which can wash away drug formulations,

along with the relatively short residence time of these formulations in the buccal cavity due to masticatory actions and phonetic activities, impedes drug absorption and bioavailability [51-55].

One major challenge is the dose variation during administration for different drug formulations. The design of mucoadhesive systems is critical for the success of buccal delivery. It has been shown that different bioadhesive polymers can significantly affect drug release and retention on the buccal mucosa. For instance, factors such as the viscosity and bioadhesive properties of polymers like chitosan can influence drug permeability and mucoadhesion [56-60]. The physical and chemical properties of these formulations can lead to varying absorption rates and efficacy, complicating the development process [61, 62].

Additionally, patient acceptability and comfort are crucial in the context of buccal drug delivery systems. Several studies have suggested that while buccal systems can enhance patient compliance due to their non-invasive nature, they may also cause discomfort, particularly when used for extended periods. This discomfort may stem from the physical presence of the dosage form in the mouth or modifications in normal oral functions such as speaking and eating, necessitating careful formulation and user-centered design [63-69].

Overall, the buccal route demonstrates significant advantages such as avoiding hepatic first-pass metabolism and offering rapid drug absorption however, it also faces inherent limitations that must be overcome through innovative formulation strategies and a deeper understanding of mucosal interactions.

Various Strategies Helping in Drug Absorption:

Use of Permeation Enhancers: Permeation enhancers are agents used to improve the absorption of drugs through the buccal mucosa by temporarily modifying the barrier properties of the tissue. They are crucial in buccal drug delivery systems, especially for poorly permeable drugs like peptides and large molecules.

Enhancing drug absorption is a crucial facet of pharmaceutical development, especially for poorly water-soluble drugs that often suffer from low bioavailability. Several strategies have been investigated to address this challenge, employing various formulation techniques to improve solubility, dissolution rates, and permeability.

Chemical permeation enhancers, include surfactants, fatty acids, and alcohols, which have been extensively studied for their ability to disrupt the lipid matrix of the stratum corneum, thus increasing skin permeability. For example, the surfactant Tween® 80 has demonstrated a significant effect on the skin's barrier properties, enhancing the transdermal delivery of Bisoprolol Hemifumarate through both ex vivo and in vivo studies [70]. Similarly, essential oils have been identified as effective enhancers; they have been shown to reduce the barrier function of the stratum corneum temporarily, improving the permeation of drugs like ibuprofen for treating dysmenorrhea [71].

Studies have indicated that various chemical enhancers can operate through mechanisms such as fluidization of the lipid bilayers, extraction of lipids, and disruption of cellular integrity to facilitate drug transport [72-75].The use of nitric oxide donors has been explored for increasing epithelial permeability, demonstrating potential as effective enhancers within buccal drug delivery systems. Bile salts and other amphiphilic compounds have similarly been noted for their ability to disrupt epithelial barriers and facilitate drug adsorption, showcasing their utility as permeation enhancers. The interaction of these enhancers with the mucosal layers often leads to a synergistic improvement in bioavailability and overall drug performance [76-80].

Natural permeation enhancers, such as terpenes, have also gained attention due to their biocompatibility and efficacy. For instance, limonene, a terpene derived from citrus peels, has been utilized for its capability to enhance drug permeation via multiple mechanisms, which further underscores the potential of natural products in transdermal applications. Furthermore, Patil and Saraogi highlight the role of natural products in promoting drug permeation by reversibly reducing skin barrier resistance, thereby enhancing bioavailability for topical therapies [81-83]. Physical methods, such as microneedle technology, represent another innovative approach to enhance transdermal drug delivery. Microneedles create

microscopic channels in the skin, allowing large molecules and hydrophilic drugs to bypass the stratum corneum effectively. Comparative studies have shown that this technique can significantly improve the permeability of drugs like amlodipine. Techniques like iontophoresis and pulsed electromagnetic fields have also been investigated for their synergistic effects with chemical enhancers, illustrating a multifaceted approach to improving transdermal permeation [84-87]. Understanding the mechanisms of permeation enhancers is crucial for developing effective transdermal drug delivery systems. For instance, the use of lidocaine as a permeation enhancer in conjunction with triamcinolone acetonide has been shown to significantly increase drug flux through buccal membranes, suggesting that chemical enhancers can effectively modify the permeability of the mucosa. Additionally, ethanol has been reported to augment permeation in certain formulations, although its efficacy can vary based on the specific drug and formulation context. Each type of enhancer, whether chemical, natural, or physical, may work through distinct mechanisms to alter the skin's barrier properties and facilitate drug absorption. Future research should continue to explore novel enhancers and combination strategies to optimize transdermal delivery for various therapeutic applications [88-95].

TABLE 1: TYPES OF PERMEATION ENHANCERS

Category	Examples	Mechanism of Action
Surfactants	Sodium laurylsulphate, Tween 80	Disrupt membrane integrity, enhance solubility
Bile Salts	Sodium deoxycholate, Taurocholate	Solubilize lipids, open tight junctions
Fatty Acids	Oleic acid, Lauric acid	Increase membrane fluidity, disrupt lipid layers
Chelating Agents	EDTA, Citric acid	Chelate calcium, loosen tight junctions
Enzyme Inhibitors	Aprotinin, Pepstatin A	Prevent enzymatic drug degradation
Cyclodextrins	β-Cyclodextrin, HP-β-Cyclodextrin	Form inclusion complexes, increase drug transport
Natural Polymers	Chitosan, Sodium alginate	Enhance paracellular transport, provide mucoadhesion

Novel Drug Delivery Systems and Formulation Technologies: The buccal cavity serves as a beneficial site for drug delivery due to its high permeability and abundant vascular supply, allowing drugs to bypass first-pass metabolism and achieve enhanced bioavailability. Technologies aimed at improving permeation through the buccal cavity encompass various formulation strategies and incorporation of permeation enhancers.

Buccal films represent a novel approach to oral mucosal drug delivery. They offer advantages such as prolonged retention in the buccal cavity, potentially leading to improved therapeutic efficacy compared to traditional methods. The formulation of these films often consists of bioadhesive polymers that enhance mucoadhesive properties, thereby increasing the drug's residence time and the quantity absorbed through the buccal mucosa [96]. Furthermore, these films reduce the need for water and can adhere effectively to the mucosal surface, making them convenient for patient use [97].

The development of mucoadhesive buccal patches has also been extensively researched. These patches are designed to release drugs in a controlled manner and significantly improve the bioavailability of drugs that typically undergo extensive first-pass metabolism [98]. For instance, various polymers such as hydroxypropyl methylcellulose (HPMC) and carbopol are commonly used to enhance the mechanical properties and bioadhesion of these patches, which are critical for sustained drug delivery through the buccal mucosal barrier [99]. Notably, buccal patches not only facilitate systemic delivery but have also been utilized for localized treatment (Shirisha *et al.*, 2018). Mucoadhesive films incorporating acyclovir have been shown to facilitate improved drug delivery through an enhanced permeation profile [100]. Additionally, recent advances in the design of layered mucoadhesive patches show promise for delivering a variety of compounds effectively through significant modifications in release kinetics and drug stability.

Another innovative formulation strategy involves the development of in situ gels. These gels transition from a sol to a gel state upon contact with the buccal mucosa, offering an effective drug delivery system that adheres well to the mucosal layers. This ability enhances the therapeutic efficacy of drug delivery, particularly for antifungal

treatments [101-103]. This approach frequently incorporates penetration enhancers that significantly improve drug absorption by modifying mucosal barrier permeability [104-107]. Iontophoresis, an electrical technique used to enhance drug permeation, is a promising technology for buccal drug delivery. It applies a small electrical current to drive charged drug molecules through the buccal mucosa, enhancing their penetration depth and release profiles. This technology has the potential to revolutionize buccal drug delivery by improving drug absorption efficiency and facilitating systemic delivery [108].

Novel drug delivery systems for enhancing permeation through the buccal cavity are pivotal in improving the bioavailability of various therapeutic agents. The buccal route is favored due to its unique anatomical and physiological characteristics, including a rich vascular supply that enables rapid absorption into systemic circulation while bypassing first-pass metabolism. A variety of strategies have been employed to augment drug delivery through this route, including the use of bioadhesive polymers, permeation enhancers, and innovative formulation types. One prominent approach entails the utilization of lipid-based formulations, which have been shown to enhance the absorption of hydrophobic drugs. The transformation of drugs into lipidic and ionic salt forms can increase their solubility in lipid formulations, thus improving their in vivo absorption properties. Research highlights that lipophilic salt forms can significantly improve drug loading and bioavailability due to their interaction with lipidic carriers, which facilitate better solubilization and absorption within the gastrointestinal tract. Lipid formulations can also increase gut permeability, aiding the systemic circulation of the drugs [109-117].

Solid dispersion technology has emerged as an effective strategy for improving the bioavailability of hydrophobic medications. This approach involves dispersing the drug in a polymer matrix, which can enhance both solubility and dissolution rates. Studies have found that solid dispersions can significantly improve the bioavailability of various drugs by increasing the surface area available for dissolution and reducing the particle size [113, 114]. This method capitalizes on the principles of enhanced solvate formation and matrix dissolution, which together augment the drug's release [115]. Nanoparticles and nanosuspensions offer a means to increase the surface area of the drug and ensure better contact with intestinal membranes, thereby enhancing dissolution rates. For instance, nanosuspensions have shown effectiveness in increasing the dissolution and absorption of drugs like repaglinide by reducing particle size, which in turn improves saturation solubility and dissolution kinetics [116-118].

Furthermore, solid lipid nanoparticles have been demonstrated to improve the bioavailability of poorly soluble drugs, facilitating enhanced gut contact and prolonged absorption [119]. Bioadhesive polymers play a critical role by prolonging the residence time of the dosage form in the buccal cavity, thereby enhancing drug absorption. These polymers, such as hydroxylpropyl methylcellulose and poly (acrylic acid), act by forming strong interactions with the mucosal surface, increasing the retention time of the drug. Recent studies have demonstrated that the use of thiolated cellulose can significantly enhance drug permeation across the buccal mucosa, indicating that modifications in polymer chemistry can lead to improved delivery. Furthermore, the incorporation of mucoadhesive formulations, such as buccal films, has been shown to enhance drug efficacy by providing a localized therapeutic effect with improved compliance. The use of advanced devices such as nanostraws allows for controlled release and localized delivery, providing a targeted approach for treatment. Furthermore, the formulation of buccal tablets using herbal bioenhancers has been explored with promising results, demonstrating the potential of natural compounds in facilitating drug permeation [120-124]. The continued research and innovation in this area holds the promise of significantly improving the efficacy of medications administered via the buccal route, leading to better patient outcomes.

Applications of Buccal Drug Delivery: Buccal drug delivery system offers significant advantages for the administration of pharmaceuticals, particularly due to their ability to bypass first-pass metabolism, which enhances the bioavailability of various active pharmaceutical ingredients (APIs). The buccal cavity presents a highly vascularized

environment and allows for rapid drug absorption directly into systemic circulation, thus achieving higher plasma concentrations with potentially reduced doses and minimized side effects. This non-invasive delivery method is increasingly favored for its practicality and effectiveness, particularly in populations with difficulties in swallowing traditional oral forms.

Several strategies have been developed to optimize buccal drug delivery and enhance permeation through the buccal mucosa. One key consideration is the use of mucoadhesive systems, which significantly prolong the residence time of drug formulations in the oral cavity, thus enhancing drug absorption. For example, the incorporation of specific polymers, such as chitosan, has been shown to improve the swelling properties and release profiles of buccal films, leading to sustained drug delivery. Furthermore, certain biopolymers can also enhance the mucoadhesive properties of dosage forms, which is essential for maintaining prolonged contact with the mucosal surface. In addition to mucoadhesion, the incorporation of permeation enhancers is another critical approach used to facilitate drug absorption [125, 126]. Studies have demonstrated the successful application of both chemical and physical permeation enhancers, such as fatty acids, bile salts, and penetratin, a cell-penetrating peptide that has shown effectiveness in enhancing the permeability of various compounds. For instance, the utilization of bile salts can promote drug absorption by modifying the membrane fluidity of the buccal mucosa and enhancing the permeability of drug molecules across the epithelial barrier.

Moreover, innovative drug delivery systems, including lipid-based carriers and nanoparticles, are being explored to further improve the efficiency of buccal drug delivery. These advanced systems can protect APIs from enzymatic degradation and provide controlled release profiles, thus maximizing the therapeutic effects while minimizing adverse effects [127-129]. Recent research into formulations such as mucoadhesive nanoparticles and bilosomes has underscored their potential in enhancing the delivery of challenging drugs, including those with poor solubility or stability. Hence, the buccal drug delivery systems represent a promising alternative to traditional oral routes, providing a multitude of strategies, such as mucoadhesion, permeation enhancement, and novel carrier systems, to improve drug delivery efficacy. Continued research and development in this area hold the potential to provide more tailored therapeutic solutions for a variety of clinical applications.

Current Research Going on for Enhancing Permeation through Buccal Cavity: Current research aimed at enhancing drug permeation through the buccal cavity has increasingly focused on developing various novel formulations and techniques. Recent studies have identified several strategies, including the use of mucoadhesive formulations, chemical permeation enhancers, and nanotechnology approaches, as effective methods for improving drug bioavailability *via* buccal administration. The formulation of mucoadhesive buccal films has shown promise in enhancing drug permeability. Research by Chandran *et al.* demonstrated that selecting appropriate polymers with mucoadhesive properties significantly influences the drug release profile. Their study employed chitosan-based films, which exhibited prolonged drug release due to higher swelling capabilities, thereby extending the contact time between the drug and the buccal mucosa. Similarly, the formulation and evaluation of mucoadhesive tablets of enalapril maleate showed satisfactory moisture absorption and significant drug permeation over an 8-hour period through porcine buccal mucosa, reinforcing the viability of mucoadhesive systems in drug delivery. Notably, mucoadhesive patches and films are advantageous due to their ability to adhere to the buccal mucosa, facilitating localized drug delivery while minimizing systemic side effects [130, 131].

A promising approach involves the use of elastomeric liposomes and deformable vesicles, which have been found to enhance the transmucosal delivery of insulin through mechanisms involving hydration and fusion with buccal membranes. It has been shown that the incorporation of surfactants into liposome formulations can significantly boost insulin permeability across porcine buccal tissues, emphasizing the role of both chemical and physical penetration enhancers. Furthermore, novel formulations that leverage the mucoadhesive

properties of polysaccharides, such as chitosan, have illustrated improved drug retention and prolonged release, thus enhancing therapeutic efficacy.

Furthermore, the exploration of chemical permeation enhancers has been pivotal in improving the absorption of poorly permeable drugs. Fatty acids have been extensively studied for their ability to modify the permeability characteristics of the buccal mucosa, allowing better transport of larger or more complex molecules. This underscores the necessity of enhancing buccal absorption, particularly for high molecular weight drugs, which typically exhibit poor permeation profiles.

Nanotechnology also plays a crucial role in current research focused on buccal drug delivery enhancements. The development of deformable nanovesicles (DNVs), such as those comprising insulin-phospholipid complexes, has demonstrated increased permeability across the buccal mucosa compared to standard delivery methods. These DNVs exhibit unique properties that enable them to penetrate deeper into the mucosal layers, thus improving the systemic bioavailability of therapeutic agents like insulin, which historically faced challenges with traditional administration methods [132]. Moreover, innovative studies have proposed that modifying the microenvironmental pH within buccal dosage forms may significantly impact drug absorption. By optimizing pH to enhance drug solubility and lipophilicity, researchers aim to create a favorable environment for drug permeation across the buccal mucosa.

CONCLUSION: Enhancing permeation through the buccal cavity remains a critical aspect of drug delivery systems, informed by extensive research and technological innovations. Various strategies have been identified to improve the permeability of drugs across the buccal mucosa, a region characterized by its relatively high permeability and vascularization, offering a distinct advantage for systemic delivery while simultaneously bypassing significant first-pass metabolism and gastrointestinal degradation. Research underscores the importance of formulation techniques, such as the development of bioadhesive films, patches, nanostraws etc that ensure prolonged contact with the mucosal surface for optimal drug absorption. Ultimately, buccal drug delivery systems present a multitude of opportunities for optimization and innovation. The integration of advanced formulation techniques, the strategic use of chemical enhancers, and the application of modern drug delivery technologies are vital to overcoming the permeability barriers of the buccal mucosa. Continued exploration in this field will undoubtedly unlock new therapeutic potentials while addressing practical challenges in drug administration.

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