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International Journal of Pharmaceutical Chemistry and Analysis

Journal homepage: https://ijpca.org/

Review Article

Natural polymer for buccal drug delivery: Challenges, innovations and future directions

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Abstract

Natural polymers are one of the important ingredients because of their non-toxicity, biocompatibility, and biodegradability have made them attractive options for creating buccal drug delivery systems. In recent years, buccal drug delivery systems have drawn a lot of attention because they can administer drugs in a regulated and targeted manner, by avoiding the first-pass metabolism and lead to increasing bioavailability. Natural polymers are used in the preparation of in buccal drug delivery systems which have benefits in recent developments are the main topics of this review paper. The main topic focus on this review is mechanism of buccal absorption, formulation parameters especially natural polymers, recents developments along with the future aspects.

Keywords: Buccal drug delivery, Natural polymers, Chitosan, Alginate, Controlled release, Nanotechnology

Received: 10-08-2025; **Accepted:** 19-09-2025; **Available Online:** 10-11-2025

1. Introduction

The buccal mucosa is an attractive route for drug administration which is highly vascularized and permeable region.

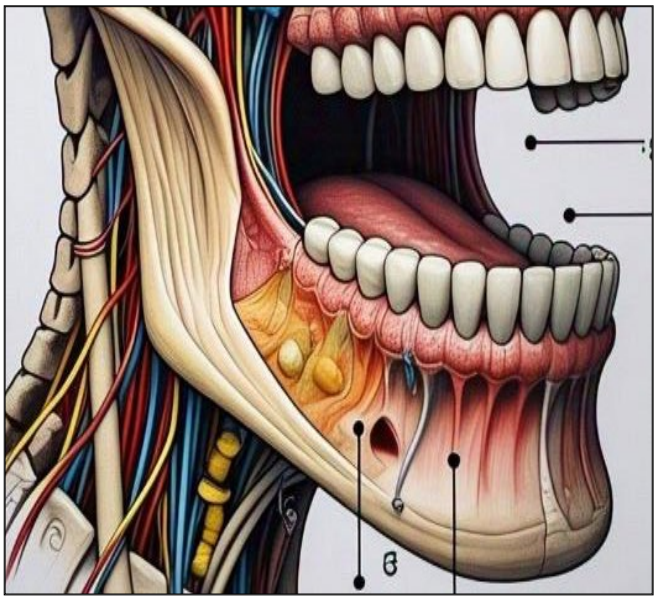

Figure 1: Drug in buccal cavity release of drug in buccal

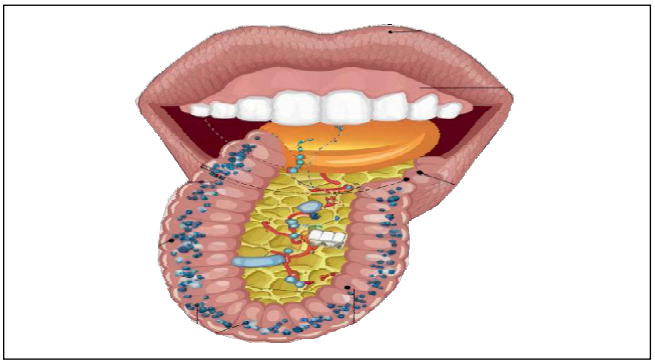

Figure 2: Cavity to systemic circulation

Buccal drug delivery systems (BDDS) have several advantages that includes ease of drug administration, prevent gastrointestinal degradation, and enhance patient compliance.[1] Due to the unique properties of natural polymers, such as chitosan, alginate, gelatine, and pectin, they are highly explored for their potential in BDDS.[2] This review provide an extensive overview of natural buccal drug delivery systems. Mainly focusing on their formulation, mechanisms, and applications. **(Figure 1), (Figure 2**)

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https://doi.org/10.18231/j.ijpca.89960.1762764274

2. Advantages

1. **Elemination of first-pass metabolism:** Drugs administered through buccal route reduce metabolic degradation and enhance bioavailability, bypassing the liver.[3]
2. **Enhanced patient compliance**: Painless administration improves the patient to stick on.[4]
3. **Quick on set of action:** Ensures quick drug absorption, due to the high blood supply in buccal mucosa.[5]
4. **Sustained and controlled release:** Natural polymers bring out prolonged drug release.[6]

3. Natural Polymers in Buccal Drug Delivery

Due to the biocompatibility, biodegradability and mucoadhesive properties, natural polymers are mostly used in BDDS. Most commonly used natural polymers are:

1. **Chitosan:** It is derived from chitin, that exhibits good mucoadhesive properties and improves drug permeation.[7]
2. **Alginate:** It is suitable for controlled drug release due to the formation of gels in the presence of calcium ions.[8]
3. **Gelatin:** It is biocompatible and protein derived from collagen. And is used in the preparation of films and gels for BDDS.[9]
4. **Pectin:** It is a cell wall derived polysaccharide used because of its gelling and mucoadhesive properties.[10]

4. Mechanisms of Drug Absorption in Buccal Delivery

Drug absorption through the buccal mucosa occurs via passive diffusion, facilitated diffusion, or active transport.[11] The permeability of the buccal epithelium depends on factors such as molecular weight, lipophilicity, and the presence of permeation enhancers.[12] Natural polymers can act as permeation enhancers by disrupting the tight junctions between epithelial cells, thereby improving drug absorption. Chitosan, a natural polyaminosaccharide which is non toxic, biocompatible and biodegradable polymer have good mucoadhesive properties and improved absorption by disrupting the tight junctions between epithelial cells.[13]

4.1. Principal routes of drug permeation

4.1.1. Transcellular route (Intracellular)

1. Drug passes through the cells (lipophilic pathway).
2. It favours lipophilic and small molecules.

4.1.2. Paracellular route (Intercellular)

1. Drug diffuses between the cells.
2. It actually through tight junctions.
3. It favors hydrophilic and small molecules.

5. How Natural Polymers Aid Buccal Permeation

5.1. Natural polymers enhance buccal drug absorption

5.1.1. Mucoadhesion mechanism

1. Interactions between functional groups in the polymer (eg:-COOH, OH, -NH2) and mucin glycoproteins.
2. Hydrogen bonding, Van der Waal's forces, and electrostatic interactions.

Example: Chitosan

5.1.2. Permeation enhancement mechanisms

1. Chitosan can open tight junctions by interacting with the cell membrane, temporarily loosening intercellular connections.
2. Some gums and pectins may interact with calcium ions and modulate cell-cell adhesion.

5.1.3. Enzyme inhibition

Salivary and epithelial enzymes can degrade certain drugs (eg: peptides, proteins). Some natural polymers inhibit enzymes or protect drugs through encapsulation.

Example: Chitosan derivatives can inhibit proteases.

Summery of various polymers used in BBDS are listed in **Table 1**.[14–21]

Table 1: Summary of natural polymers used in Bio-Dental Drug Delivery Systems (BDDS)

Polymer	Natural source	Functions in buccal delivery
Chitosan	Crustacean shells	Mucoadhesion, permeation enhancer,enzyme inhibition
Alginate	Brown algae	Mucoadhesion, controlled release
Pectin	Citrus peels	Mucoadhesion, controlled release
Guar gum	Guar plant seeds	Mucoadhesion, swelling
Xanthan gum	Bacterial fermentation	Mucoadhesion, swelling

6. Formulation Strategies for Natural Buccal Drug Delivery Systems

1. **Buccal films:** Thin, flexible films made from natural polymers that adhere to the buccal mucosa and provide controlled drug release.[22]
2. **Buccal tablets:** Compressed tablets that dissolve or erode in the buccal cavity, releasing the drug gradually.[23]
3. **Buccal gels:** Semi-solid formulations that can be applied directly to the buccal mucosa for localized or systemic drug delivery.[24]
4. **Buccal patches:** Multi-layered patches that provide sustained drug release and improved patient comfort.[25]

7. Challenges and Limitations

Despite their advantages, natural buccal drug delivery systems face several challenges:

1. **Limited drug loading capacity**: Natural polymers may have limited capacity to encapsulate high drug doses.[26]

2. **Stability issues:** Natural polymers are susceptible to microbial contamination and degradation.[27]
3. **Variability in drug release:** The drug release profile may vary depending on the polymer used and the formulation method.[28]
4. **Regulatory hurdles:** Ensuring the safety and efficacy of natural polymer-based formulations requires extensive clinical trials.[29]

Examples of drug/formulations for buccal drug delivery that are impacted by the given challenges:

1. Itraconazole or posaconazole-poorly soluble drugs
2. High dose medications
3. Peptides and proteins
4. Insulin

Potential solutions for challenges in buccal drug delivery system:

1. **Prodrug approach:** Lipophilic prodrugs are made for increasing the permeability in buccal mucosa before they are converted to active drug in the body.
2. **Ion pairing:** Done by increasing the lipophilicity of drug by forming ion pairs. Which is done by drug and suitable counter-ion that increase permeability.
3. **Nanocarriers:** The drug is encapsulated in nanocarriers to prevent it from degradation, increase drug stability and improve permeation.
4. **Inhibitors:** The drug is formulated with enzyme inhibitors that protect it from degradation.
5. **pH modifiers:** pH modifiers are added to the formulation for optimum pH to prevent the degradation of pH sensitive drug.
6. **Polymeric marices:** Drug can be protected from degradation by using stable polymeric matrices.
7. **Mucoadhesive polymer:** They increase residence time in buccal mucosa. This ensure that drug is released in sustained and consistent manner.
8. **Innovative manufacturing technique:** Using slot-die coating form uniform film. This release drug consistently.

8. Current Research Limitations

Limited absorption area and physiological barriers:

1. **Small surface area:** The buccal mucosa have very limited surface area around 50 to 170 centimetre square compared to GIT.
2. **Low permeability:** The buccal mucosa act as a barrier for large,hydrophilic or ionized molecules
3. **Salivary flow and swallowing:** Continuous salivary secretion leads to the washout of drug from absorption site. There by reducing the contact time leads to reducing the bioavailability.

9. Formulation approaches

9.1. Achieving optimal mucoadhesion

1. **Permeation enhancement:** The permeation enhancers of some have limited efficacy and cause local irritation not suitable for long term use.
2. Stability: maintaining stability of formulation is difficult due to the concern of ph.
   a. Patient compliance
   b. Taste and irritation
   c. Discomfort
   d. Gaps in current research
3. **Long term efficacy and safety:** Long term efficacy of buccal formulations regarding safety and efficacy are having concern particularly of mucosal irritation
4. **Personalized medicine:** the impact of varying genetics, oral health, age, that affect the buccal absorption and development of personalized buccal drug delivery system.
5. **Targeted delivery:** more research is needed in case of target cell types and pathological conditions
6. **Bio macromolecule delivery:** delivering peptide and protein via buccal route have significant challenge. Research regarding the nanocarriers is ongoing.[30,31]

10. Recent Advancements

Recent research has focused on wide variety of formulating or combining the natural and synthetic polymers thereby develop a hybrid systems. These hybrid systems overcome the limitations of natural polymers.[32]

For example, chitosan-based nanoparticles have been widely used for targeted drug delivery to the buccal mucosa.[33] Moreover, the use of nanotechnology and 3D printing has opened new advancements for the development of advanced buccal drug delivery systems.[34]

11. Future Perspectives

The future of natural buccal drug delivery systems progress in the development of smart and stimuli-responsive formulations. The major benefit of these formulations are, that can release drugs in a controlled manner based on physiological conditions.[35] The advanced technologies such as nano technology and artificial intelligence always together with the integration of natural polymers holds great promise for the development of next-generation BDDS.[36]

Stimuli-responsive drug delivery systems is the release of drug by the specific physiological or external triggering factors. In buccal drug delivery, drug is administered through the mucosal membrane of cheek by using stimuli response systems lead to rapid systemic absorption and localized site of action.

Some of the stimuli responsive systems for buccal drug delivery system with example given in **Table 2**.

Table 2: Some of the stimuli responsive systems for buccal drug delivery system with example.[37,38,39]

Stimuli	Trigger source	Example
pH	Disease-related pH changes	Antifungal release for oral candidiasis
Enzyme	Salivary enzymes	MMP-triggered chemotherapeutic delivery in oral cancer
Temperature	Local heat due to inflammation	Thermoresponsive gel for NSAID delivery
Mechanical	Chewing, saliva flow, movement	Responsive mucoadhesive patches for sustained delivery

Buccal formulations are more complicated due to variation in drug permeability, release kinetics and taste issues.

So AI can assist to

1. Predicting the formulation parameter using AI models
2. Optimization of drug release profile
3. Al can predict the chemical structure to mask the bitter taste.

AI tools are used to optimise the formulation design with a predicted pharmacokinetics.[40]

3D printing used for formulation of high-quality products with different drug release profiles.[41]

12. Conclusion

Natural buccal drug delivery systems often provide the enhancing drug bioavailability and patient compliance. Buccal drug delivery system have greater impact with the natural polymers, having unique properties, polymers play a crucial role in the development of these systems. However, the need of further research is addressed as an important parameter. the challenges associated with their use and the variety of exploring the potential are discussed.

13. Source of Funding

None.

14. Conflict of Interest

None.

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Cite this article: Hafeefa PT, Thahsina PH, Sreeshma M, Varsha T. Natural polymer for buccal drug delivery: challenges, innovations and future directions. *Int J Pharm Chem Anal.* 2025;12(3)*:*152–156.