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Development and evaluation of mucoadhesive buccal films for the sustained release of diclofenac sodium: An innovative approach for pain management

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Abstract

The research explores the development and evaluation of mucoadhesive buccal films for the sustained release of diclofenac sodium, a widely used non-steroidal anti-inflammatory drug (NSAID) for pain relief. Mucoadhesive buccal films are an innovative drug delivery system designed to adhere to the mucous membrane in the oral cavity, enabling the controlled release of drugs directly into the bloodstream, bypassing first-pass metabolism and improving therapeutic outcomes. These films provide sustained release, localized action, and improved compliance, making them more convenient for patients. Mucus membranes, which are moist surfaces lining body cavities, are the main components of mucus gels. The wetting theory applies to mucoadhesion, which involves the release of mucus from the mucosal surface into the bloodstream. The study aims to develop a more efficient and effective method for the controlled release of diclofenac sodium, a potent anti-inflammatory and analgesic drug.

Keywords: Mucoadhesive buccal films; Diclofenac sodium; Sustained drug release; Pain management; Bioadhesion; Non-steroidal anti-inflammatory drug (NSAID)

1. Introduction

Buccal drug delivery has gained attention due to its convenience, non-invasive nature, and ability to provide localized or systemic drug effects. Mucoadhesive buccal films are composed of biocompatible polymers that adhere to the buccal mucosa, allowing the drug to permeate through the mucous membrane. By using mucoadhesive films, the systemic absorption of drugs is enhanced, and the need for frequent dosing is reduced, improving patient compliance. Diclofenac sodium, chosen for its potent anti-inflammatory and analgesic properties, can be delivered effectively through this system.

Oral administration of drugs can be inefficient due to first-pass metabolism, resulting in reduced bioavailability. Mucoadhesive buccal films are an innovative drug delivery system designed to adhere to the mucous membrane in the oral cavity. These films enable the controlled release of drugs directly into the bloodstream, bypassing first-pass metabolism and improving therapeutic outcomes. This research explores the development of mucoadhesive buccal films for the delivery of diclofenac sodium, a widely used non-steroidal anti-inflammatory drug (NSAID) for pain relief.

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1.1. Mucoadhesive Buccal Film

A mucoadhesive buccal film is a type of pharmaceutical dosage form designed to adhere to the mucosal lining of the buccal cavity (the inner cheek area).

Here's a breakdown of its key aspects

- Mucoadhesive: The film is formulated with materials that can to the mucosal
- surface, allowing it to adhere stay in place and release its active ingredients over an extended period.
- Buccal: Refers to the buccal cavity or cheek area of the mouth. The film is applied to this area for drug delivery.
- Film: The dosage form is typically thin, flexible, and designed to dissolve or disintegrate gradually, releasing the drug into the mucosal tissues.

1.2. Purpose and Benefits

- Sustained Release: Provides a controlled release of medication over a longer duration compared to other dosage forms.
- Localized Action: Can deliver drugs directly to the site of action, which may be beneficial for local effects or to reduce systemic side effects.
- Improved Compliance: Often more convenient for patients as it avoids the need for swallowing pills or frequent dosing.[1-5]

Therapeutic Applications Of Muucoadhesive Buccal Films [6-88]

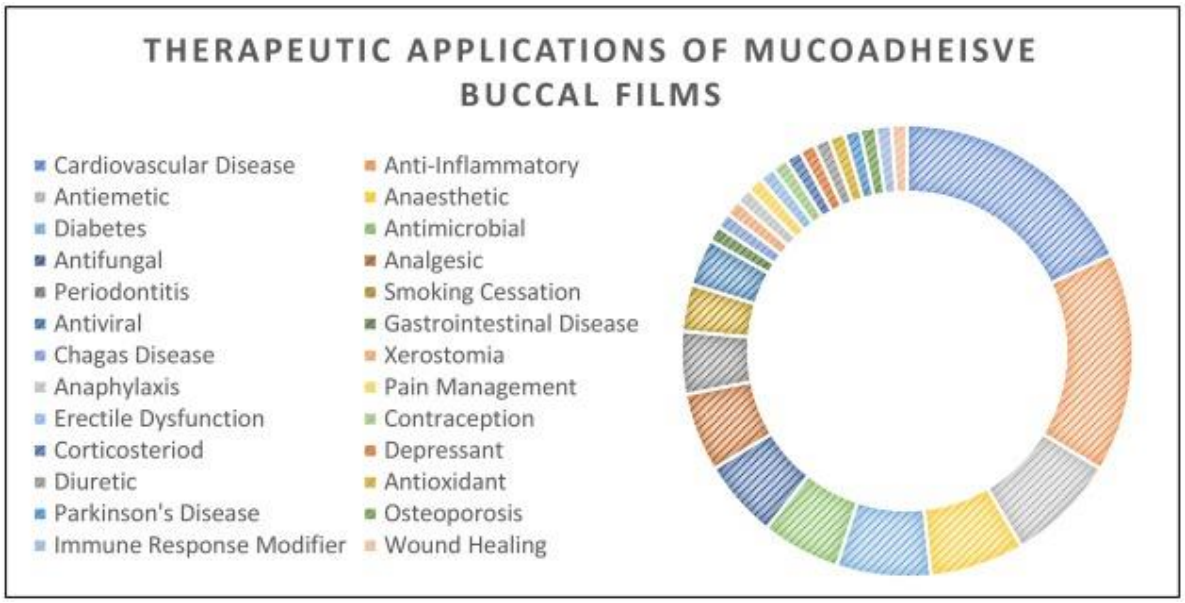

Figure 1 Therapeutic Applications Of Muucoadhesive Buccal Films

1.3. Mucus Membranes

Mucus membranes (mucosae) are the moist surfaces lining the walls of various body cavities such as the gastrointestinal and respiratory tracts. They consist of a connective tissue layer (the lamina propria) above which is an epithelial layer, the surface of which is made moist usually by the presence of a mucus layer. The epithelia may be either single layered (e.g. the stomach, small and large intestines and bronchi) or multilayered/stratified (e.g. in the esophagus, vagina and cornea). The former contain goblet cells which secrete mucus directly onto the epithelial surfaces; the latter contain, or are adjacent to tissue.

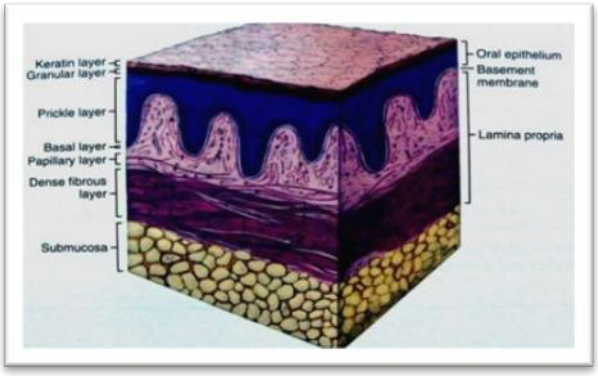

Figure 2 Oral Mucosal Membrane

containing, specialized glands such as salivary glands that secrete mucus onto the epithelial surface. Mucus is present either as a gel layer adherent to the mucosal surface or as a luminal soluble or suspended form. The major components of all mucus gels are mucin glycoproteins, lipids, inorganic salts and water, the latter accounting for more than 95% of their weight, making them a highly hydrated system.[89] The major functions of mucus are that of protection and lub

2. Mucoadhession Theories

Mucoadhesion is a complex process and numerous theories have been proposed to explain the mechanisms involved. These theories include mechanical interlocking, electrostatic, diffusion interpenetration, adsorption and fracture processes.

2.1. Wetting Theory

The wetting theory applies to liquid systems which present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle, the greater is the affinity [Figure 3]. The contact angle should be equal or close to zero to provide adequate spreadability. The spreadability coefficient, S_{AB}, can be calculated from the difference between the surface energies γ_B and γ_A and the interfacial energy γ_{AB}, as indicated in the equation given below.[89] This theory explains the importance of contact angle and reduction of surface and interfacial energies to achieve good amount of mucoadhesion.

$$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB}$$

2.2. Diffusion Theory

Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond . It is believed that the adhesion force increases with the degree of penetration of the polymer chains. This penetration rate depends on the diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility and contact time. According to the literature, the depth of interpenetration required to produce an efficient bioadhesive bond lies in the range 0.2–0.5 μm. This interpenetration depth of polymer and mucin chains can be estimated by the following equation:[89]

$$l = (tD_b)^{1/2}$$

where t is the contact time and D_b is the diffusion coefficient of the mucoadhesive material in the mucus. The adhesion strength for a polymer is reached when the depth of penetration is approximately equivalent to the polymer chain size. In order for diffusion to occur, it is important that the components involved have good mutual solubility, that is, both

the bioadhesive and the mucus have similar chemical structures. The greater the structural similarity, the better is the mucoadhesive bond.[89]

2.3. Fracture Theory

This is perhaps the most used theory in studies on the mechanical measurement of mucoadhesion. It analyzes the force required to separate two surfaces after adhesion is established. This force, s_m, is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, F_m, and the total surface area, A_0, involved in the adhesive interaction

Since the fracture theory is concerned only with the force required to separate the parts, it does not take into account the interpenetration or diffusion of polymer chains. Consequently, it is appropriate for use in the calculations for rigid or semi-rigid bioadhesive materials, in which the polymer chains do not penetrate into the mucus layer. [89,90]

2.4. The Electronic Theory

This theory describes adhesion occurring by means of electron transfer between the mucus and the mucoadhesive system, arising through differences in their electronic structures. The electron transfer between the mucus and the mucoadhesive results in the formation of double layer of electrical charges at the mucus and mucoadhesive interface. The net result of such a process is the formation of attractive forces within this double layer.[91]

2.5. The Adsorption Theory

In this instance, adhesion is the result of various surface interactions (primary and secondary bonding) between the adhesive polymer and mucus substrate. Primary bonds due to chemisorptions result in adhesion due to ionic, covalent and metallic bonding, which is generally undesirable due to their permanency.[92] Secondary bonds arise mainly due to van der Waals forces, hydrophobic interactions and hydrogen bonding. Whilst these interactions require less energy to "break", they are the most prominent form of surface interaction in mucoadhesion processes as they have the advantage of being semi-permanent bonds.[93]

All these numerous theories should be considered as supplementary processes involved in the different stages of the mucus/substrate interaction, rather than individual and alternative theories. Each and every theory is equally important to describe the mucoadhesion process. There is a possibility that there will be initial wetting of the mucin, and then diffusion of the polymer into mucin layer, thus causing the fracture in the layers to effect the adhesion or electronic transfer or simple adsorption phenomenon that finally leads to the perfect mucoadhesion. The mechanism by which a mucoadhesive bond is formed will depend on the nature of the mucus membrane and mucoadhesive material, the type of formulation, the attachment process and the subsequent environment of the bond. It is apparent that a single mechanism for mucoadhesion proposed in many texts is unlikely for all the different occasions when adhesion occurs.

3. Sites For Mucoadhesive Drug Delivery Systems

Mucoadhesive drug delivery systems can be applied to various sites, each offering distinct advantages and challenges. The buccal cavity, with its easy access and avoidance of first-pass metabolism, is ideal for systemic and local treatments. Polymers such as cyanoacrylates and chitosan are commonly used, though saliva can wash away the drug. The sublingual mucosa, being more permeable, facilitates rapid drug release but requires controlled formulations for effective delivery. The nasal cavity, with its larger surface area, is suited for both systemic and local delivery, but the presence of mucociliary activity shortens the residence time of drugs. For ocular delivery, mucoadhesive polymers like thiolated poly(acrylic acid) and poloxamer help combat rapid removal due to tears and blinking. The vaginal and rectal lumens, useful for bypassing hepatic metabolism, use polymers such as mucin and gelatin but face challenges with system migration. Lastly, the gastrointestinal tract offers improved absorption and avoidance of first-pass metabolism using polymers like chitosan and alginate, though it contends with acid instability and first-pass effects. Each site provides unique benefits but also presents specific obstacles for effective drug delivery.

3.1. Diclofenac Sodium

Diclofenac Sodium is a nonsteroidal anti-inflammatory drug (NSAID) used to reduce inflammation, pain, and fever. Here's an overview of its mechanism of action (MOA):

3.2. Mechanism Of Action (MOA)

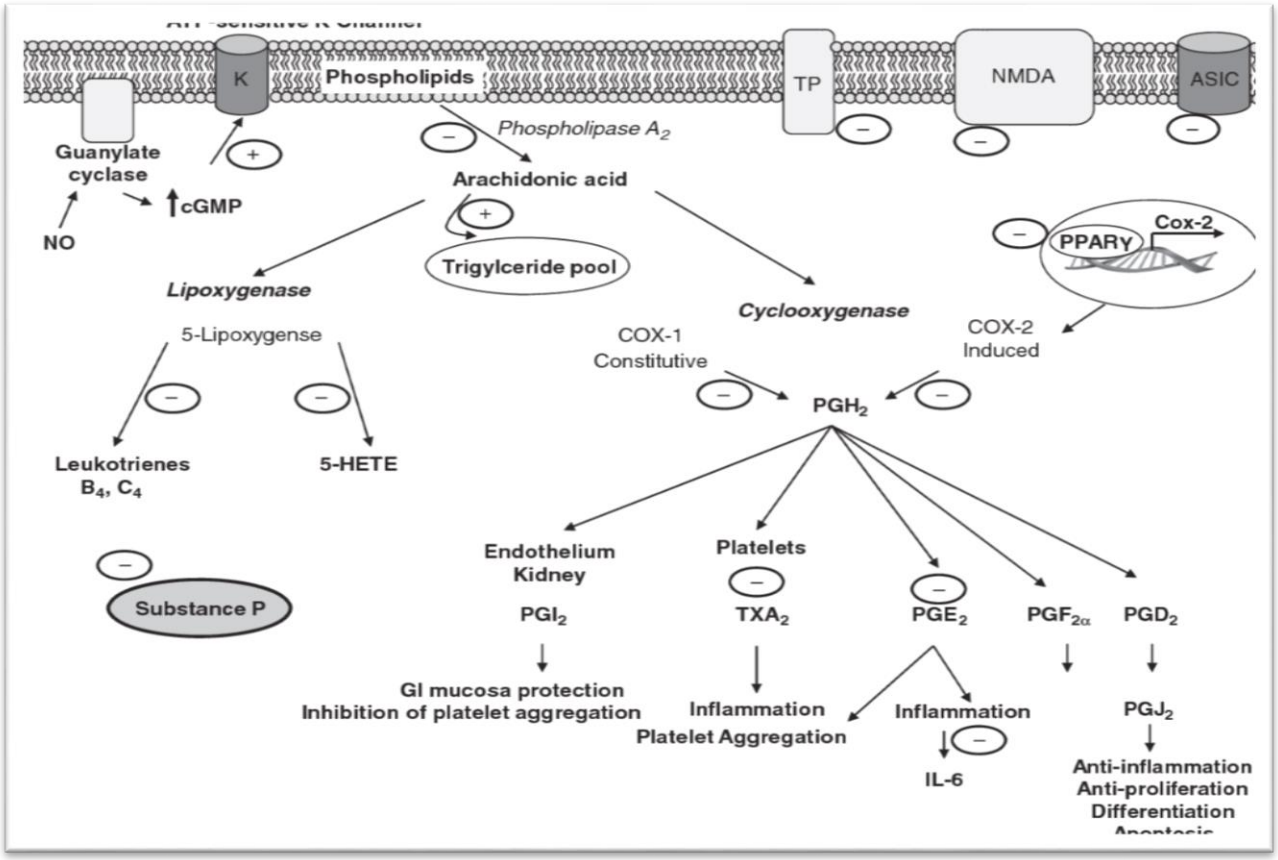

Figure 3 Mechanism of Action Of Diclofenac

3.2.1. Inhibition of Cyclooxygenase (COX) Enzymes

Diclofenac sodium primarily works by inhibiting cyclooxygenase enzymes (COX-1 and COX-2). COX enzymes are responsible for the conversion of arachidonic acid to prostaglandins, which are mediators of inflammation, pain, and fever.

By blocking COX-1 and COX-2, diclofenac decreases the production of prostaglandins, leading to reduced inflammation, pain, and fever.

3.2.2. Reduction of Prostaglandin Synthesis:

Prostaglandins play a significant role in the inflammatory response, pain perception, and fever. By inhibiting their synthesis, diclofenac helps alleviate symptoms associated with these conditions.

3.3. Additional Mechanisms

There is some evidence suggesting diclofenac may have additional mechanisms of action, such as stabilizing lysosomal membranes and reducing oxidative stress.

3.4. Mechanism Of Action Mucoadhesive Buccal Films

The mechanism of action for mucoadhesive buccal films of Diclofenac Sodium involves several stages: adherence to the buccal mucosa, drug release, drug absorption, and systemic distribution. Below is a detailed flow chart representing the process of drug delivery from the buccal films and their mechanism of action.

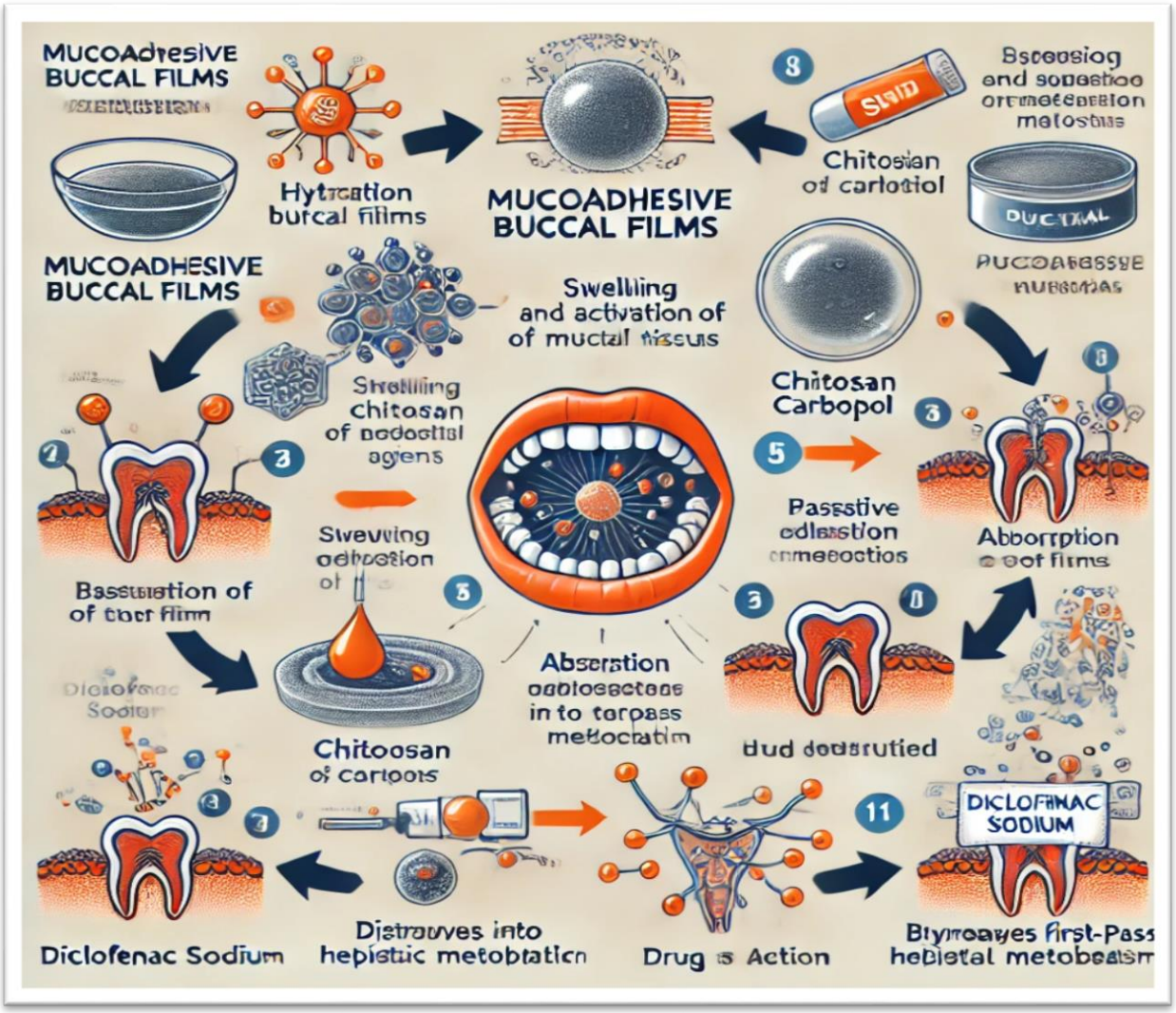

Figure 4 Mucoadhesive Buccal Films for the Sustained Release of Diclofenac Sodium

3.5. Stepwise Explanation

Mucoadhesive Buccal Film Application:

The buccal film is applied to the mucous membrane in the oral cavity (cheek or gum area).

- Hydration by Saliva:
- Upon contact with the buccal mucosa, saliva in the oral cavity hydrates the film. This process begins the activation of mucoadhesive components.
- Activation of Mucoadhesive Agents:
- The hydration causes Chitosan or Carbopol (mucoadhesive agents) to swell and adhere to the wet mucosal surface by forming hydrogen bonds or van der Waals forces with the mucous layer.
- Adhesion to Buccal Mucosa:
- The buccal film sticks to the mucosal layer and remains in place due to its mucoadhesive properties.
- Erosion or Dissolution of Film
- The buccal film gradually dissolves or erodes over time, ensuring controlled release of Diclofenac Sodium.
- Sustained Drug Release:
- Diclofenac Sodium is released slowly from the film, following a sustained-release profile. The release depends on the swelling of polymers and the dissolution of the drug within the film matrix.
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- Diffusion Across Buccal Mucosa:
- The released Diclofenac Sodium diffuses through the mucous membrane via passive diffusion and is absorbed into the capillaries in the underlying tissues.
- Absorption into Systemic Circulation:
- The drug enters the bloodstream directly via the buccal vasculature, bypassing first-pass metabolism in the liver.
- Systemic Distribution:
- Once in the bloodstream, the drug is distributed throughout the body to exert its therapeutic effects at the target sites.
- Therapeutic Action (Pain Relief):
- Diclofenac Sodium acts by inhibiting cyclooxygenase (COX) enzymes, reducing prostaglandin synthesis, and providing anti-inflammatory and analgesic effects, leading to pain relief.

4. Materials and methods

4.1. Materials

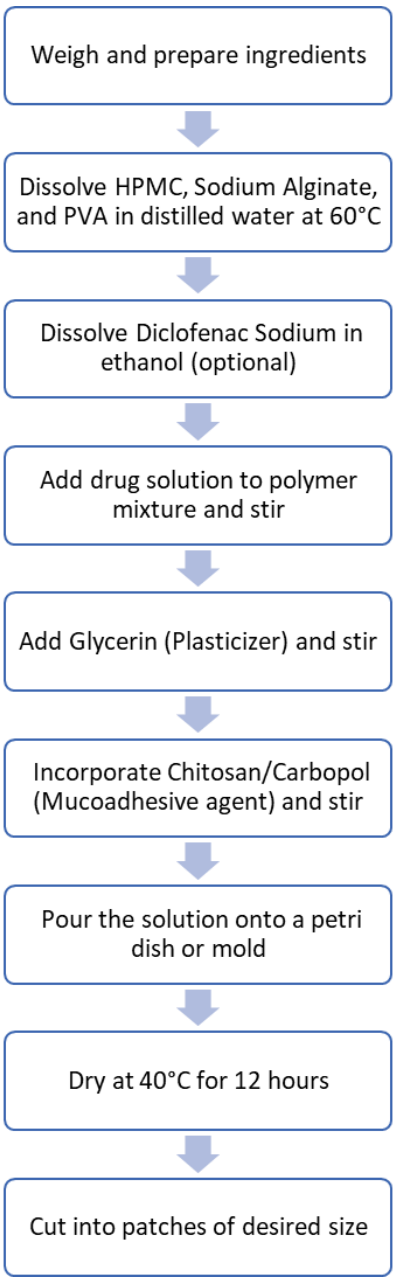
- Active Drug: Diclofenac sodium (model drug for pain relief).
- Polymers: Hydroxypropyl methylcellulose (HPMC), sodium alginate, and polyvinyl alcohol (PVA) for film formation.
- Plasticizer: Glycerin to enhance film flexibility.
- Solvent: Distilled water or ethanol.
- Mucoadhesive agents: Chitosan or Carbopol for adhesion to buccal mucosa.

Table 1 Formulation Table

Sr No	Ingredients	Quantities
1	Diclofenac Sodium (Active Drug)	25 mg per patch
2	Hydroxypropyl Methylcellulose (HPMC, Polymer)	1.0 g
3	Sodium Alginate (Polymer)	0.5g
4	Polyvinyl Alcohol (PVA, Polymer)	0.5g
5	Glycerin (Plasticizer)	0.5ml
6	Chitosan (Mucoadhesive Agent)	0.3g
7	Distilled Water	q.s. to 100 mL
8	Ethanol (Solvent)	5ml

4.2. Methods

4.2.1. Preparation of Buccal Films



- Polymer Dissolution

Dissolve HPMC, Sodium Alginate, and PVA in 50 mL of distilled water with continuous stirring using a magnetic stirrer at 60°C for 30 minutes.

- Drug Incorporation

Dissolve Diclofenac Sodium in 5 mL of ethanol (optional) and add it to the polymer solution with continuous stirring for 15 minutes.

- Plasticizer Addition

Add 0.5 mL of glycerin to the polymer-drug solution as a plasticizer to increase the flexibility of the film.

- Mucoadhesive Agent Incorporation

Disperse Chitosan or Carbopol into the solution and continue stirring for an additional 20 minutes at room temperature (25°C).

- Film Casting

Pour the resulting solution onto a petri dish or a film-casting mold and spread evenly using a glass rod. Ensure the thickness is controlled to about 0.15 mm.

- Drying

Allow the cast solution to dry in a hot air oven at 40°C for 12 hours.

- Cutting the Films

After drying, cut the films into 2x2 cm patches (or desired size) using a sharp blade or cutter.

Fig.2.1 Preparation Method Of Mucoadhesive Buccal Film

4.3. Evaluation parameters

Film Thickness Measurement

Purpose: Ensures uniformity in film thickness, which is crucial for consistent drug dosing.

Method: Measure the thickness of each film using a digital micrometer at different points on the film.

Expected Result: Thickness should be uniform across all films, ideally around 0.15 mm. This uniformity ensures each film contains the same amount of diclofenac sodium.

4.3.1. Weight Uniformity

Purpose: Guarantees consistent drug content in each film.

Method: Weigh individual films using an analytical balance.

Expected Result: The weight variation between films should be minimal. Each patch should weigh approximately 50 mg to ensure consistent dosing.

4.3.2. Folding Endurance

Purpose: Evaluates the flexibility and durability of the buccal films.

Method: Films are repeatedly folded at the same place until they break or show signs of cracking. The number of folds a film withstands before breaking indicates its flexibility.

Expected Result: A high number of folds (100+) without breaking is desirable, as it indicates good mechanical strength and flexibility for use in the oral cavity.

4.3.3. Surface pH

Purpose: Ensures the pH of the film is compatible with the buccal mucosa to avoid irritation.

Method: The film is allowed to swell in distilled water for 2 hours, and the surface pH is determined using a pH meter.

Expected Result: The surface pH should be close to neutral (6–7), ensuring that the films do not cause irritation or discomfort in the mouth.

4.3.4. Swelling Index:

Purpose: Determines the film's ability to absorb moisture, which is essential for mucoadhesion.

Method: Films are weighed before and after immersion in phosphate buffer (pH 6.8) at 37°C. The swelling index is calculated as: Swelling Index=Final Weight−Initial WeightInitial Weight×100\text{Swelling Index} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Initial Weight}} \times 100Swelling Index=Initial WeightFinal Weight−Initial Weight×100

Expected Result: The films should swell to around 150% of their initial weight, indicating adequate moisture absorption and proper adhesion to the buccal mucosa.

4.3.5. In Vitro Drug Release

Purpose: Evaluates the release profile of diclofenac sodium from the buccal films.

Method: The films are placed in a dissolution apparatus with phosphate buffer (pH 6.8) at 37°C. At regular intervals, samples are withdrawn, and the amount of diclofenac sodium released is determined by UV spectrophotometry.

Expected Result: The drug should release in a controlled manner, with 80% of the drug being released over 8 hours. A sustained release profile is ideal for pain management.

4.3.6. Mucoadhesion Strength:

Purpose: Measures the force required to detach the film from the buccal mucosa, reflecting its adhesive strength.

Method: The film is adhered to porcine buccal mucosa, and a mucoadhesion tester measures the detachment force.

Expected Result: The films should have strong adhesive properties, ideally adhering for over 6 hours, ensuring prolonged contact and drug release.

4.3.7. Stability Studies

Purpose: Evaluates the stability of the films over time under different storage conditions.

Method: Films are stored at various temperatures (25°C, 40°C) and relative humidity (60%) for 3 months. Physical appearance, drug content, and mucoadhesive strength are evaluated at regular intervals.

Expected Result: Films should remain physically stable, with no significant changes in drug content or adhesion properties. The drug content should remain above 98% after 3 months.

5. Results

Table 3 Result Table

Parameter	**Measured Value (Your Patch)**	**Standard Value/Range**	**Inclusion Criteria**	**Inclusion**
Film Thickness (mm)	0.15 ± 0.02	0.14 - 0.16 mm	≤ 5% deviation	Ensures uniform drug distribution. Low variability indicates good film casting technique.
Weight Uniformity (mg)	50.5 ± 1.2 mg	50 ± 2 mg	≤ 5% deviation	Consistent weight ensures equal drug content across patches. Low standard deviation preferred.
Surface pH	6.8 ± 0.3	6.5 - 7.0	6.5 - 7.0	Surface pH should be close to neutral to avoid irritation and

				maintain compatibility with buccal mucosa.
Folding Endurance	> 300 folds	> 250 folds	> 250 folds	Folding endurance indicates mechanical stability and flexibility of the patches during handling.
Swelling Index (%)	150 ± 10%	120 - 160%	100 - 200%	Higher swelling index enhances mucoadhesion, allowing for better interaction with buccal tissue.
Mucoadhesive Strength (N)	0.35 ± 0.05 N	0.2 - 0.5 N	0.2 - 0.5 N	Mucoadhesion strength determines how long the patch stays attached to the mucosal membrane.
In Vitro Drug Release (% cumulative in 8 hrs)	80 ± 5%	75 - 85%	75 - 85%	Drug release in line with controlled delivery profile, ensuring sustained release over 8 hours.
Stability Testing (after 3 months)	>98% drug content, no physical changes	>95% drug content, no changes	>95% drug content	Stability under various conditions (25°C/60% RH and 40°C/75% RH) indicates long-term usability.

6. Result and discussion

In the development and evaluation of mucoadhesive buccal films for the sustained release of Diclofenac Sodium, several key parameters were assessed to ensure the efficacy and quality of the films.

Film Thickness: The mucoadhesive films measured 0.15 ± 0.02 mm, which falls within the acceptable range of 0.14 - 0.16 mm. This indicates that the film thickness is consistent and within the required specifications for effective drug delivery and comfort.

Weight Uniformity: The average weight of the films was 50.5 ± 1.2 mg, aligning with the standard range of 50 ± 2 mg. This uniformity in weight is crucial as it ensures that each patch contains a consistent amount of drug, thereby providing reliable dosing.

Surface pH: The surface pH of the films was recorded at 6.8 ± 0.3, which is within the neutral range of 6.5 - 7.0. This pH level is ideal for minimizing irritation and ensuring compatibility with the buccal mucosa.

Folding Endurance: With a folding endurance of over 300 folds, the films demonstrated excellent mechanical stability and flexibility. This attribute is essential for ensuring that the films can withstand handling and application without compromising their integrity.

Swelling Index: The films exhibited a swelling index of 150 ± 10%, which is within the range of 120 - 160%. A higher swelling index contributes to better mucoadhesion, enhancing the film's ability to adhere to the buccal mucosa and improve drug delivery.

Mucoadhesive Strength: The mucoadhesive strength was measured at 0.35 ± 0.05 N, falling comfortably within the range of 0.2 - 0.5 N. This strength is critical for ensuring that the films remain in place during the drug release period.

In Vitro Drug Release: The cumulative drug release over 8 hours was 80 ± 5%, which is consistent with the target range of 75 - 85%. This sustained release profile ensures that Diclofenac Sodium is delivered over an extended period, providing prolonged pain relief.

Stability Testing: After 3 months, the films retained more than 98% of their drug content with no observed physical changes, exceeding the standard requirement of >95%. This indicates that the films are stable under various storage conditions, ensuring long-term effectiveness.

Figure 5 Prepared Mucoadhesive Buccal Film

7. Conclusion

The results from the development and evaluation of the mucoadhesive buccal films for Diclofenac Sodium demonstrate that the films meet all the required standards for effective and sustained drug delivery. The consistency in film thickness, weight, surface pH, and drug release profile, combined with excellent mucoadhesive strength and stability, indicates that these films are well-suited for pain management applications. The positive outcomes from the tests confirm that the films are not only mechanically robust and biocompatible but also capable of providing a controlled and sustained release of Diclofenac Sodium, making them a promising innovative approach for managing pain.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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