Original Research Article

Mucoadhesive tablets of acetaminophen

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Abstract

Mucoadhesive drug delivery systems have gained significant attention in pharmaceutical research due to their potential to enhance drug bioavailability, provide controlled drug release, and improve patient compliance. Acetaminophen, a widely used analgesic and antipyretic drug, has limitations such as short half-life and hepatic first-pass metabolism, which can reduce its therapeutic efficacy. To overcome these challenges, the formulation of mucoadhesive buccal tablets has emerged as an effective alternative drug delivery approach. This review highlights various studies on the formulation and evaluation of mucoadhesive buccal tablets of acetaminophen, focusing on polymer selection, drug release kinetics, and bioadhesion strength. Key mucoadhesive polymers such as Carbopol, Hydroxypropyl Methylcellulose (HPMC), Sodium Carboxymethyl Cellulose (NaCMC), and Polyvinyl Pyrrolidone (PVP) have been extensively studied for their role in enhancing mucoadhesion and sustaining drug release. Studies have demonstrated that combining these polymers results in improved adhesion, prolonged retention time, and controlled drug release, leading to enhanced therapeutic efficacy.Additionally, the incorporation of permeation enhancers like propylene glycol has shown significant improvement in drug absorption through the buccal mucosa. Advances in multi-layered tablets and pH-sensitive formulations have further optimized drug release profiles. In-vivo and in-vitro studies have validated the effectiveness of these formulations in achieving prolonged therapeutic action.Overall, mucoadhesive buccal tablets of acetaminophen offer a promising alternative to conventional oral administration, improving bioavailability and patient compliance. Future research should focus on clinical trials, optimization of polymer blends, and innovative formulation strategies to enhance therapeutic outcomes.

Keywords: Mucoadhesive Buccal Tablet, Acetaminophen, Bioavailability, Controlled Release, Polymers, Permeation Enhancers.

Introduction

Drug delivery through the buccal mucosa has emerged as an effective approach to enhance bioavailability, provide controlled drug release, and improve patient compliance. Mucoadhesive buccal tablets, in particular, offer several advantages over conventional oral dosage forms by allowing the drug to be absorbed directly into the systemic circulation, thereby bypassing hepatic first-pass metabolism. This delivery route is especially beneficial for drugs like acetaminophen (paracetamol), a widely used analgesic and antipyretic agent with a short half-life and extensive first-pass metabolism when administered orally.

Need for Mucoadhesive Buccal Drug Delivery

Traditional oral formulations of acetaminophen exhibit rapid gastric degradation and metabolism in the liver, leading to fluctuations in plasma drug levels and a reduced duration of therapeutic action. Furthermore, frequent dosing is required to maintain effective drug concentration, which may result in poor patient adherence and an increased risk of side effects such as hepatotoxicity. Mucoadhesive buccal tablets provide a solution to these challenges by ensuring prolonged drug retention at the site of absorption, controlled release, and enhanced systemic bioavailability[1-4]

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Mechanism of Mucoadhesion

Mucoadhesion is the phenomenon where a dosage form adheres to the mucosal surface, ensuring prolonged contact time and improved drug absorption. Mucoadhesive buccal tablets achieve adhesion through the interaction between polymeric excipients and the mucin layer of the buccal mucosa. This interaction is facilitated by hydrogen bonding, electrostatic interactions, and van der Waals forces, which help in forming a stable adhesive bond. The ideal mucoadhesive polymer should be biocompatible, non-toxic, and capable of forming strong hydrogen bonds to ensure optimal adhesion.

Stages of Mucoadhesion

Mucoadhesion occurs in a sequential process involving distinct stages, each playing a critical role in ensuring effective adhesion between the polymer and the mucosal surface. These stages include:

i. Contact Stage (Wetting and Spreading): In this initial phase, the mucoadhesive polymer makes contact with the mucosal membrane. The presence of moisture from the mucus facilitates polymer hydration, allowing it to spread over the surface and establish an initial bond. The effectiveness of this stage depends on factors such as the surface tension, viscosity of the mucus, and the physicochemical properties of the polymer.

ii. Adhesion Stage (Interpenetration and Bond Formation): As the polymer hydrates further, it swells and begins to interact with the mucus layer. During this phase, polymer chains penetrate the mucus network, leading to the formation of various physicochemical interactions such as hydrogen bonding, van der Waals forces, and electrostatic interactions, which contribute to the adhesion process.

iii. Consolidation Stage (Strengthening of Adhesion): In this final stage, the polymer chains interlock with mucin glycoproteins, further strengthening the mucoadhesive bond. The interaction is reinforced by secondary chemical forces, such as hydrogen bonds and covalent interactions, ensuring prolonged adhesion and retention at the site of application.

Forces Involved in Mucoadhesion

The adhesion between mucoadhesive polymers and the mucus layer is influenced by various physicochemical forces, which play a crucial role in ensuring effective drug delivery. These forces include:

i. Electrostatic Interactions: These occur due to the attraction between oppositely charged functional groups in the polymer and the negatively charged mucin present in the mucus layer, aiding in the initial adhesion[5-8]

ii. Hydrogen Bonding: Hydrogen bonds are formed between functional groups such as hydroxyl (-OH), carboxyl (-COOH), and amino ($-NH_2$) in the polymer and mucin glycoproteins, strengthening the adhesive bond.

iii. Van der Waals Forces: These weak intermolecular forces contribute to the stabilization of adhesion by facilitating close contact between the polymer and mucosal surface.

iv. Hydrophobic Interactions: Non-polar regions of certain polymers interact with hydrophobic segments in the mucus, influencing adhesion and retention in the buccal cavity.

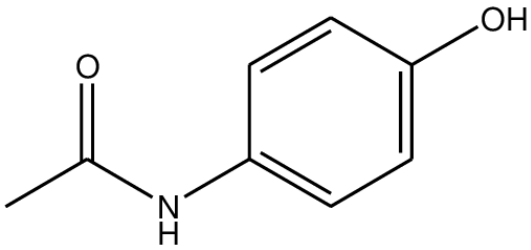
v. Covalent Bonding: Some advanced mucoadhesive systems utilize covalent interactions, such as thiolated polymers (thiomers), which form disulfide bonds with mucus glycoproteins, leading to prolonged mucoadhesion and sustained drug release.

Acetaminophen (Paracetamol)

Acetaminophen, commonly referred to as paracetamol, is a widely utilized analgesic and antipyretic agent across the globe. It is frequently prescribed and available over the counter (OTC) for alleviating mild to moderate pain and fever. Due to its efficacy and relatively safe profile when administered correctly, acetaminophen is extensively used for managing conditions such as headaches, muscle aches, arthritis, and symptoms of the common cold.

Various dosage forms of acetaminophen are available, including oral tablets, capsules, syrups, and suppositories. However, these conventional formulations come with certain drawbacks, such as:

- The necessity for frequent dosing.
- Potential gastrointestinal discomfort associated with oral administration.
- Variability in absorption when administered rectally.



Drug Profile

- Pharmacokinetic Properties:

- Absorption: Rapidly absorbed through the gastrointestinal tract.
- Metabolism: Extensively metabolized in the liver, undergoing first-pass metabolism.
- Elimination Half-life: Ranges between 2 to 3 hours.
- Bioavailability: Estimated between 60% and 80%, largely influenced by metabolic activity.

Mechanism of Action of Acetaminophen

Acetaminophen (paracetamol) primarily exerts its analgesic and antipyretic effects through central mechanisms, although its exact mode of action remains partially elucidated. The following key mechanisms are believed to contribute to its pharmacological activity:

Inhibition of (COX):

Unlike NSAIDs , acetaminophen selectively inhibits COX-1 and COX-2 in the central nervous system (CNS), reducing prostaglandin synthesis. This inhibition decreases pain perception and fever without significant peripheral anti-inflammatory effects .

Action on the Endocannabinoid System: Acetaminophen is metabolized to AM404, an active metabolite that influences the endocannabinoid system by inhibiting anandamide reuptake. This modulation enhances pain relief through cannabinoid receptors. Acetaminophen enhances descending serotonergic pathways in the CNS, contributing to its analgesic effects by modulating pain signal transmission at the spinal level.

The AM404 metabolite also interacts with transient receptor potential vanilloid-1 (TRPV1) receptors, which are involved in pain and temperature regulation. This contributes to its analgesic and antipyretic properties.

Scope and Significance of Acetaminophen

Scope: ***Acetaminophen is a widely used and well-researched drug due to its effectiveness and broad therapeutic applications. It serves as a first-line analgesic and antipyretic agent in various medical conditions, such as:***

- Pain Management: Used in treating headaches, musculoskeletal pain, osteoarthritis, and postoperative pain.

- Fever Reduction: Recommended for managing fever in adults and children, particularly in viral and bacterial infection.

- Combination Therapy: Frequently combined with opioids or NSAIDs to enhance pain relief while minimizing opioid dependence.

Significance:

- Safety Profile: Acetminophen is considered safer than NSAIDs for patients with gastric ulcers, renal impairment, or those at risk of cardiovascular events, as it lacks significant anti-inflammatory and platelet-inhibitory effects.

- Accessibility and Affordability: Available globally in both prescription and OTC forms, making it one of the most accessible and cost-effective pain

Preferred over NSAIDs in pediatric and geriatric populations due to its lower risk of gastrointestinal bleeding and cardiovascular complications.

-Recent advancements in drug formulation, including mucoadhesive buccal tablets, transdermal patches, and nanoformulations, aim to improve bioavailability, reduce dosing frequency, and enhance patient compliance [9-11]

Materials and method

Materials

The formulation of mucoadhesive buccal tablets of acetaminophen involves the use of various excipients to achieve optimal drug delivery, mucoadhesion, and controlled release. The key materials typically include:

Table 1:Composition of tablets

Ingredients	Function	Quantity (mg/tablet)
Acetaminophen (API)	Analgesic, Antipyretic	250mg
Carbopol 934P	Mucoadhesive polymer	10mg
HPMC K100M	Mucoadhesive polymer, Controlled release	15mg
Sodium CMC	Mucoadhesive polymer, pH modifier	10mg
Ethyl Cellulose (Backing Layer)	Unidirectional drug release	5mg
Sodium Lauryl Sulfate	Penetration enhancer	2mg
Mannitol	Sweetener	10mg
Magnesium Stearate	Lubricant	2mg
Peppermint Flavor	Taste masking	1mg
Talc	Glidant, Anti-adherent	2mg

. Preformulation Studies

- Drug-excipient compatibility was assessed using Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC).

Fourier Transform Infrared Spectroscopy (FTIR) Analysis

Principle: FTIR is used to detect potential chemical interactions between Acetaminophen and excipients by identifying characteristic functional groups and shifts in peak intensities.

Procedure:

- Pure Acetaminophen and physical mixtures of the drug with excipients were analyzed using an FTIR spectrophotometer.
- Samples were mixed with KBr powder, compressed into pellets, and scanned in the 4000–400 cm^{-1} range.
- FTIR spectra of pure Acetaminophen and the drug-excipient mixtures were compared.

Table 2:Expected FTIR Peaks of Acetaminophen

Functional Group	Expected Wavenumber (cm^{-1})
N-H Stretching (Amide)	~3329 cm^{-1}
C=O Stretching (Amide Carbonyl)	~1650 cm^{-1}
C-C Stretching (Aromatic Ring)	~1510 cm^{-1}
C-O Stretching (Phenolic Group)	~1255 cm^{-1}

FTIR Results & Interpretation:

- If peaks remain unchanged, it indicates no significant interaction between the drug and excipients.
- If peak shifts or disappearance occur, it suggests potential incompatibility or formation of new bonds.

Differential Scanning Calorimetry (DSC) Analysis

Principle: DSC measures thermal transitions (melting, crystallization, decomposition) to detect possible physical or chemical interactions between Acetaminophen and excipients.

Procedure:

- Pure Acetaminophen and drug-excipient mixtures were analyzed using DSC equipment.
- Samples (2–5 mg) were heated in an aluminum pan from 30°C to 300°C at a rate of 10°C/min under a nitrogen atmosphere.

Table 3:Expected DSC Peak for Acetaminophen:

Sample	Endothermic Peak (Melting Point)	Observation
Pure Acetaminophen	168–172°C	Sharp peak at ~170°C
Drug + Compatible Excipients	168–172°C	No major shift
Drug + Incompatible Excipients	Peak shift or broadening	Interaction possible

DSC Results & Interpretation

- A sharp endothermic peak at ~170°C confirms Acetaminophen's crystallinity.
- No significant peak shift in the mixture suggests compatibility.
- Broadening or disappearance of the peak indicates possible interaction.

Preparation of Mucoadhesive Layer

- Weigh all ingredients accurately.
- Blend Acetaminophen, Carbopol 934P, HPMC K100M, Sodium CMC, and Mannitol using geometric dilution for uniform mixing.
- If using wet granulation, dissolve PVP K30 (optional binder) in ethanol or isopropanol and granulate the mixture.
- Dry the granules at 40–50°C, then pass through a #40 mesh sieve.
- Add Magnesium Stearate and Talc and mix gently to enhance flow properties[12-15]

Preparation of Backing Layer

- Ethyl Cellulose was used as a backing layer to ensure unidirectional drug release.
- It was dissolved in a small volume of ethanol or acetone and coated onto one side of the tablet.

Compression of Tablets

- The direct compression method was used.
- The blend was compressed into flat-faced buccal tablets (10–12 mm diameter) using a rotary tablet press.
- Compression force was optimized to ensure sufficient hardness (5–7 kg/cm²) while maintaining mucoadhesive properties.

Evaluation

To ensure the quality, efficacy, and safety of the formulated mucoadhesive buccal tablet of acetaminophen, various evaluation parameters are assessed. These include pre-compression and post-compression characteristics, in-vitro mucoadhesion strength, drug release kinetics, and stability studies.

Pre-Compression Parameters

Before tablet compression, the powdered blend is evaluated for its flow and compressibility properties to ensure uniformity and tablet integrity.

Angle of Repose (θ)

- Determines the flow properties of the powder mixture.
- Measured using the fixed funnel method.
- A θ value of <30° indicates good flowability.

Bulk Density and Tapped Density

- Bulk density (ρb) and tapped density (ρt) help assess packing properties.
- The Carr's Index and Hausner's ratio are derived to evaluate compressibility.
- Formula:

  - Carr's Index (%) = [(Tapped Density - Bulk Density) / Tapped Density] × 100
  - Hausner's Ratio = Tapped Density / Bulk Density

Post-Compression Parameters

Once the tablets are compressed, they undergo various evaluations.

Tablet Thickness and Diameter

- Measured using a Vernier caliper to ensure uniformity.

Weight Variation

- Determined by weighing 20 tablets and calculating the average weight.
- A deviation of ±5% is acceptable for tablets weighing ≥250 mg (as per USP).

Hardness (Tablet Tensile Strength)

- Evaluated using a Monsanto or Pfizer hardness tester.
- Acceptable range: 4-8 kg/cm².

Friability

- Assessed using a Roche friabilator by subjecting 10 tablets to mechanical stress.
- Acceptable limit: ≤1% weight loss.

Mucoadhesion Testing

The strength of mucoadhesion determines the tablet's ability to remain attached to the buccal mucosa.

Ex Vivo Mucoadhesion Strength

- Measured using a Modified Physical Balance Method.
- A goat or porcine buccal mucosa is used as the test substrate.

Mucoadhesion Time

- The duration for which the tablet remains attached to the buccal mucosa in simulated saliva fluid (SSF, pH 6.8) is recorded.

Swelling Index

- Evaluated by placing the tablet in phosphate buffer pH 6.8 and measuring weight gain at specific intervals.
- Formula:
  Swelling Index (%) = [(Final Weight - Initial Weight) / Initial Weight] × 100

In-Vitro Drug Release Study

- Conducted using a USP Type II dissolution apparatus (Paddle Method).
- Dissolution Medium: Phosphate buffer (pH 6.8)
- Sampling: 5 mL at regular intervals, analyzed using UV spectrophotometry at λmax 243 nm.

Drug Release Kinetics

The release profile is analyzed using mathematical models:

- Zero-order: Drug release independent of concentration.
- First-order: Drug release proportional to remaining drug.
- Higuchi Model: Drug release based on diffusion.
- Korsmeyer-Peppas Model: Mechanism of drug release analyzed using the release exponent (n-value).
- The formulation follows Korsmeyer-Peppas kinetics, indicating non-Fickian diffusion (anomalous transport)

Stability Studies

- Performed as per ICH guidelines (40°C ± 2°C / 75% ± 5% RH for 3 months).
- Tablets are evaluated for appearance, hardness, drug content, and dissolution profile over time.

Powder Flow Properties (Pre-Compression Studies)

To ensure uniform compression, the blend was tested for flowability.

Table 4:Flow properties

Parameter	Result	Acceptable Range
Angle of Repose (°)	28.5	<30° (Good Flow)
Bulk Density (g/mL)	0.45	0.3–0.7 g/mL
Tapped Density (g/mL)	0.56	0.5–0.9 g/mL
Carr's Index (%)	19.6	12–20% (Fair)
Hausner's Ratio	1.24	1.0–1.25 (Good)

The results indicate good flow properties, suitable for tablet compression.

Post-Compression Studies

The formulated tablets were tested for weight variation, hardness, friability, and thickness.

Table 5:Physical Evaluation of Tablets

Parameter	Result	Acceptance Criteria
Weight Variation	±4.2%	±5% (USP Limit)
Hardness (kg/cm²)	5.8	4–8 kg/cm²
Friability (%)	0.72	<1%
Thickness (mm)	3.2	Uniform

All results met USP standards, ensuring the tablets' mechanical integrity.

Swelling Index

The swelling capacity of the mucoadhesive tablets was assessed in phosphate buffer pH 6.8.

Results and discussion

Preformulation Studies

Preformulation studies were conducted to assess the physicochemical characteristics of the drug and excipients, as well as their compatibility.

Drug-Excipient Compatibility Studies

Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) were utilized to investigate possible interactions between acetaminophen and the selected excipients.

FTIR Analysis **-** *The FTIR spectrum of pure acetaminophen exhibited prominent peaks at:*

- 3329 cm^{-1} (N-H stretching)
- 1650 cm^{-1} (C=O stretching of amide)
- 1510 cm^{-1} (C-C stretching of the benzene ring)
- 1255 cm^{-1} (C-O stretching)

The **drug-excipient mixture** displayed similar peaks without significant shifts, confirming the absence of chemical interactions.

DSC Analysis

- The DSC thermogram of pure acetaminophen exhibited a sharp endothermic peak at 170-175°C, corresponding to its melting point.
- The DSC profile of the drug-excipient mixture retained the acetaminophen peak, indicating no significant interaction between the drug and excipients.

Table 6:Swelling index

Time (min)	Swelling Index (%)
30	45
60	78
120	110
180	135

The progressive swelling confirms the tablet's ability to maintain prolonged mucoadhesion.

Ex Vivo Mucoadhesion Time

The tablets were evaluated for their retention time on goat buccal mucosa.

- Mucoadhesion time: 6–8 hours
- This prolonged adhesion ensures sustained drug release and enhances therapeutic efficacy.

In-Vitro Drug Release Study

The dissolution study was conducted in phosphate buffer pH 6.8 using a USP Type II apparatus.

Table 7:Drug release studies

Time (hours)	% Drug Release
1	20.5
2	38.7
4	59.2
6	78.5
8	91.4

The drug release profile suggests a controlled-release pattern, ensuring prolonged therapeutic action.

Drug Release Kinetics

The release data were analyzed using various mathematical models.

Table 8:Drug release kinetics

Model	R^2 Value
Zero Order	0.945
First Order	0.897
Higuchi Model	0.978
Korsmeyer-Peppas	0.989

The highest R^2 value (0.989) in the Korsmeyer-Peppas model confirms that drug release follows anomalous (non-Fickian) diffusion, indicating that both polymer swelling and erosion contribute to drug release.

Stability **Studies**

Tablets were stored under accelerated conditions (40°C ± 2°C, 75% ± 5% RH) for 3 months.

Table 9:Stability studies

Parameter	Initial	After 3 months
Hardness (kg/cm²)	5.8	5.6
Drug Content (%)	99.2	98.7
% Drug Release	91.4	89.6

No significant changes were observed, confirming stability under storage conditions.

Discussion

1. FTIR and DSC confirmed significant drug-excipient interactions, ensuring stability.
2. Pre-compression studies indicated good flowability, essential for uniform tablet compression.
3. Physical parameters were within USP specifications, proving acceptable tablet quality.
4. Swelling and mucoadhesion studies confirmed prolonged adhesion, supporting extended drug retention.
5. In-vitro drug release showed a controlled release pattern, reducing the need for frequent dosing.
6. Release kinetics followed anomalous (non-Fickian) diffusion, meaning drug release is controlled by both polymer swelling and matrix erosion.
7. Stability studies confirmed no significant degradation, proving the formulation's stability over time.

Conclusion

The formulated mucoadhesive buccal tablet of acetaminophen successfully met preformulation, physical, and release evaluation criteria. The sustained drug release profile and prolonged mucoadhesion time support its use as an effective alternative to conventional dosage forms, ensuring enhanced bioavailability and patient compliance.

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