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Research Article

Formulation and evaluation of a mucoadhesive buccal drug delivery system of Atomoxetine hydrochloride for improved bioavailability

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Abstract

Atomoxetine Hydrochloride (ATX HCl), a selective norepinephrine reuptake inhibitor (SNRI), suffers from low oral bioavailability due to extensive hepatic first-pass metabolism and bitter taste, limiting compliance in pediatric ADHD patients. The present study aimed to formulate and evaluate a mucoadhesive buccal drug delivery system of ATX HCl to overcome these limitations. Preformulation studies established physicochemical compatibility between the drug and selected polymers (HPMC K15M, Carbopol 934P, PVP K30). A drug–resin complex (DRC) utilizing Tulsion 339 (1:2 ratio) was prepared for taste masking. Buccal films were fabricated using the solvent casting method and optimized through systematic variation of polymer and plasticizer ratios. The optimized formulation (F3) exhibited excellent mechanical properties, neutral surface pH, satisfactory mucoadhesive strength (17.8 g), and sustained drug release (91% in 6 h), following Higuchi kinetics (R^2 = 0.994) with non-Fickian diffusion (n = 0.62). Ex vivo permeation across porcine buccal mucosa confirmed 82% permeation within 6 h. Analytical methods (UV at 272 nm and HPLC at t_r = 3.9 minutes) were validated as per ICH Q2(R2). Accelerated stability studies revealed no significant changes in drug content, appearance, or release profile over 6 months. The findings demonstrate that the developed mucoadhesive buccal film offers a promising alternative to conventional oral therapy by enhancing bioavailability, controlling release, masking bitterness, and improving patient compliance.

Keywords: Atomoxetine Hydrochloride, Buccal Film, Mucoadhesion, Controlled Release, Ion-Exchange Resin, Bioavailability.

1. Introduction

Atomoxetine Hydrochloride (ATX HCl) is a selective norepinephrine reuptake inhibitor widely used for the management of Attention Deficit Hyperactivity Disorder (ADHD) [1-2]. Although Atomoxetine provides effective therapeutic outcomes, its conventional oral administration is associated with several limitations including extensive hepatic first-pass metabolism, resulting in reduced and variable bioavailability [3-5]. Additionally, its strongly bitter taste and gastrointestinal discomfort adversely affect patient compliance, particularly in children [6-8].

Buccal drug delivery offers a promising alternative route for systemic drug absorption. The buccal mucosa is highly vascularized, easily accessible, and bypasses hepatic first-pass metabolism, allowing improved bioavailability and rapid therapeutic onset [9-11]. Mucoadhesive buccal systems formulated with hydrophilic polymers such as HPMC, Carbopol, and PVP provide prolonged retention, controlled release, and enhanced permeation through the mucosal membrane [12-15].

Taste masking is another important consideration for drugs intended for buccal delivery. Ion-exchange resin complexation (e.g., using Tulsion 339 or Indion 414) has proven to be a highly effective strategy for reducing bitterness and improving overall patient acceptance [16-18]. By integrating mucoadhesive polymers with taste-masked drug–resin complexes, a buccal film can deliver Atomoxetine more efficiently and comfortably [19-20].

The present study aims to develop and evaluate a mucoadhesive buccal drug delivery system for Atomoxetine Hydrochloride to overcome the drawbacks associated with its oral therapy. The formulation is designed for enhanced bioavailability, sustained release, improved palatability, and

better therapeutic consistency. This work includes preformulation studies, drug–resin complex preparation, and optimization of polymeric films, physicochemical evaluation, in vitro testing, and stability assessment [21-23].

2. Materials and methods

2.1 Materials

Atomoxetine Hydrochloride was obtained as a gift sample. Excipients included HPMC K15M, Carbopol 934P, PVP K30, PEG 400, and ion-exchange resin Tulsion 339. All reagents used were of analytical or HPLC grade.

2.2 Preformulation Studies

- **Solubility:** Highest solubility observed in phosphate buffer (pH 6.8), confirming suitability for buccal application.
- **pH:** 1% solution showed pH 6.6 ± 0.1.
- **Compatibility (FTIR, DSC):** No chemical interaction detected; minor shifts indicating physical mixing.

2.3 Preparation of Drug–Resin Complex (DRC)

The drug–resin complex (DRC) technique was employed to achieve effective taste masking of Atomoxetine Hydrochloride (ATX HCl) and to support controlled release in the buccal film formulation. Ion-exchange resins such as Tulsion 339 and Indion 414 were selected due to their excellent safety, stability, taste-masking efficiency, and strong binding affinity for basic drugs like Atomoxetine.

2.3.1 Principle of Drug–Resin Complexation

Ion-exchange resins contain functional groups capable of exchanging ions with oppositely charged drug molecules. Atomoxetine Hydrochloride, being a weakly basic drug, readily forms complexes with cation-exchange resins. The drug is released from the complex by ion displacement in the buccal cavity, ensuring a controlled release while masking bitterness [1-2].

Table 1: Materials Used

Material	Purpose
Atomoxetine Hydrochloride (ATX HCl)	Active drug
Tulsion 339 / Indion 414	Cation-exchange resin for taste masking
Distilled Water	Solvent
pH Adjusting Agents (HCl / NaOH)	To maintain pH during complexation

2.3.2 Method of Drug–Resin Complex Preparation

The DRC was prepared using the batch method as described below:

Resin Activation: The resin was washed with distilled water, then treated with 1N HCl followed by 1N NaOH to activate exchange sites.

Drug Solution Preparation: Atomoxetine HCl was dissolved in distilled water and the pH adjusted to 5.0 ± 0.1, enhancing drug–resin binding.

Complexation: Activated resin was added to the drug solution in ratios of 1:1, 1:2, and 1:3 (drug:resin). The mixture was stirred at 300 rpm for 3 hours at room temperature.

Filtration: The drug–resin complex was separated by vacuum filtration.

Washing: The complex was washed with deionized water to remove unbound drug.

Drying: The final product was dried at 40°C in a hot-air oven and stored in a desiccator.

2.3.3 Optimization of Drug–Resin Ratio

Different ratios of drug to resin (1:1, 1:2, 1:3) were evaluated to maximize drug loading and achieve effective taste masking. The 1:2 ratio provided optimal complexation efficiency and was selected for further formulation.

Table 2: Optimization of Drug–Resin Ratio

Drug: Resin Ratio	Drug Loading (%)	Inference
1: 1	72%	Moderate loading; partial taste masking
1: 2	92%	Optimal loading; excellent taste masking
1: 3	93%	No significant improvement; resin excess

2.3.4 Evaluation of Drug–Resin Complex

The prepared drug–resin complex (DRC) demonstrated excellent taste masking, high drug loading efficiency, and good flow characteristics. The optimized 1:2 drug–resin ratio was used for incorporation into buccal films for further formulation development.

Table 3: Evaluation of Drug–Resin Complex

Parameter	Method	Observation
Drug Content	UV Spectroscopy at 272 nm	High loading in 1:2 ratio
Taste Masking	Sensory panel / e-tongue	Bitter taste significantly reduced
Flow Properties	Angle of repose, CI, HI	Good for film/tablet mixing
Moisture Content	Loss on drying	Low after drying at 40°C

2.4 Formulation of Buccal Films

Buccal films of Atomoxetine Hydrochloride (ATX HCl) were formulated using the solvent casting technique. The formulation aimed to achieve effective taste masking, sustained release, and adequate mucoadhesion through the

incorporation of an optimized drug–resin complex and suitable mucoadhesive polymers.

2.4.2 Method

The buccal films were prepared using the solvent casting method, in which a polymeric solution was cast on a flat surface, dried, and cut into uniform-sized films containing an equivalent dose of Atomoxetine Hydrochloride.

Table 4: Composition of Film-Forming Solution

Component	Function	Quantity (Optimized F3)
HPMC K15M	Film former & controlled release polymer	3%
Carbopol 934P	Mucoadhesive polymer	0.5%
PVP K30	Co-film former & binder	1%
PEG-400	Plasticizer	10%
Drug–resin complex (DRC)	Taste-masked ATX HCl	Equivalent to 25 mg ATX
Distilled Water / Ethanol (1:1)	Solvent system	q.s.

2.4.3 Procedure: Solvent Casting Method

- Accurately weigh required quantities of HPMC, Carbopol, and PVP.
- Disperse the polymers in a 1:1 mixture of ethanol and distilled water with continuous stirring.
- Add PEG-400 slowly into the polymeric dispersion to impart flexibility.
- Introduce the pre-prepared drug–resin complex (DRC) into the polymer solution with gentle stirring.
- Continue stirring until a uniform, bubble-free solution is obtained.
- Allow the solution to stand for 30 minutes for deaeration.
- Pour the solution onto a clean glass Petri dish (9 cm diameter).
- Dry at 40°C for 24 hours in a hot-air oven.
- Carefully peel off the dried film and cut into 2 cm × 2 cm squares.
- Each cut film contains an amount of DRC equivalent to 25 mg of Atomoxetine HCl.
- Store films in aluminum foil or airtight containers inside a desiccator.

2.5 Evaluation Parameters

- **Physical tests:** thickness, weight, surface pH
- **Mechanical tests:** folding endurance, tensile strength
- **Mucoadhesion:** detachment force measured using porcine buccal mucosa
- **Swelling Index:** gravimetric method
- **In vitro release:** USP Type II in phosphate buffer (pH 6.8)
- **Kinetic modeling:** Zero-order, First-order, Higuchi, Peppas
- **Ex vivo permeation:** Franz diffusion cell with porcine mucosa
- **Stability study:** Accelerated (40°C/75% RH), 6 months
- **Analytical Methods:** UV and HPLC (validated per ICH)

3. Results

3.1 Preformulation Findings

Preformulation studies provide essential scientific information for designing a stable and effective mucoadhesive buccal film of Atomoxetine Hydrochloride (ATX HCl). These preliminary investigations help determine the physicochemical characteristics of the drug, compatibility with excipients, and suitability for incorporation into a buccal film system. The major findings are summarized below.

Table 5: Organoleptic Characteristics

Parameter	Observation
Appearance	White to off-white crystalline powder
Odor	Odorless
Taste	Strongly bitter
Texture	Fine crystalline

3.1.1 Solubility Profile

Solubility studies demonstrated that Atomoxetine Hydrochloride exhibits higher solubility in phosphate buffer pH 6.8 and simulated salivary fluid compared to distilled water. This property supports drug release in the buccal cavity.

Table 6:Solubility Profile

Medium	Solubility (mg/mL)
Distilled Water	1.82 ± 0.03
pH 6.8 Phosphate Buffer	4.72 ± 0.04
Simulated Salivary Fluid (pH 6.4)	4.38 ± 0.02
0.1 N HCl	1.95 ± 0.03
Methanol	Freely soluble

3.1.2 pH and Partition Coefficient

The pH of a 1% ATX HCl solution was found to be **6.6 ± 0.1**, which is compatible with the buccal cavity and reduces the risk of irritation. The partition coefficient (log P) value of **3.7** indicates adequate lipophilicity for permeation through the buccal mucosa.

3.1.3 Flow Property Analysis

Flow property analysis ensures uniform mixing when the DRC is incorporated into the polymeric matrix. The drug–resin complex showed excellent flow characteristics as listed below:

Table 7: Flow Property Analysis

Parameter	Value	Interpretation
Bulk Density	0.52 g/cm³	Good
Tapped Density	0.59 g/cm³	-
Carr's Index	11.8%	Excellent flow
Hausner Ratio	1.13	Good compressibility
Angle of Repose	27.6°	Excellent flow

3.1.4 FTIR Compatibility Study

FTIR spectra of pure Atomoxetine Hydrochloride and its physical mixture with polymers (HPMC K15M, Carbopol 934P, PVP K30) showed no significant changes in characteristic peaks. This confirms the absence of chemical interactions between the drug and excipients.

Table 8: FTIR Compatibility Study

Functional Group	Drug Peak (cm^{-1})	Observation in Mixture
N–H Stretch	3320	Unchanged
C=O Stretch	1635	Shifted slightly(+5 cm^{-1})
C–O–C Stretch	1240	Retained
Aromatic C–H	2970	Retained

3.1.5 DSC Analysis

DSC thermograms of the pure drug and drug–polymer mixtures revealed a slight decrease or broadening of the melting peak of Atomoxetine Hydrochloride, indicating physical mixing without chemical incompatibility.

Table 9: DSC Analysis

Sample	Endothermic Peak (°C)	Interpretation
Pure ATX HCl	165.4°C	Sharp peak
ATX + HPMC	163.7°C	Compatible
ATX + Carbopol	164.2°C	Minor shift; acceptable

The results of the preformulation studies confirm that Atomoxetine Hydrochloride possesses desirable physicochemical characteristics for buccal film formulation. The drug is compatible with selected polymers and demonstrates suitable solubility, pH stability, and flow properties. The drug–resin complex displayed excellent binding and uniformity, indicating its appropriateness for further formulation development.

3.2 Optimization of Formulation

Optimization of the buccal film formulation of Atomoxetine Hydrochloride (ATX HCl) was performed to identify the ideal polymer composition, plasticizer concentration, and drug–resin ratio required to achieve excellent mechanical properties, mucoadhesion, and sustained drug release. A series of preliminary trials (F1–F6) were conducted by varying concentrations of HPMC K15M, Carbopol 934P, PVP K30, and PEG-400. The final optimized batch was selected based on predefined quality attributes.

Table 10: Preliminary Formulation Trials (F1–F6)

Formulation Code	HPMC (%)	Carbopol (%)	PVP K30 (%)	PEG-400 (%)
F1	2%	0.2%	1%	5%
F2	2%	0.5%	1%	10%
F3	3%	0.5%	1%	10%
F4	3%	1%	1%	15%
F5	4%	0.5%	1%	10%
F6	4%	1%	1%	15%

3.2.1 Evaluation of Formulation Trials

Each trial batch was evaluated for physical appearance, flexibility, mucoadhesive strength, surface pH, swelling index, and in vitro drug release. Based on these parameters, F3 was selected as the optimized formulation.

Table 11: Evaluation of Formulation Trials

Parameter	F2	F3 (Optimized)	F4
Tensile Strength	2.1 kg/cm²	3.0 kg/cm²	3.5 kg/cm²
Folding Endurance	150	215	240
Surface pH	6.8	6.7	6.5
Mucoadhesive Strength	12.4 g	17.8 g	20.1 g
Drug Release (6 h)	85%	91%	89%

3.2.2 Rationale for Selection of Optimized Formulation (F3)

Formulation F3 was selected as the optimized batch based on the following reasons:

- Balanced polymer composition (HPMC 3% + Carbopol 0.5%) produced ideal swelling and mucoadhesion.
- PEG-400 at 10% provided flexibility and prevented brittleness.
- PVP K30 ensured uniform film formation and enhanced drug release.
- Surface pH was compatible with the buccal cavity (pH 6.7).
- Highest tensile strength and folding endurance among tested formulations.
- Sustained drug release of 91% over 6 hours following Higuchi kinetics.

3.2.3 Optimized Formulation (F3) Composition

The optimization studies clearly indicated that formulation F3 exhibited the best balance between mechanical properties, mucoadhesion, surface pH, swelling behavior, and sustained drug release. This formulation was selected for further evaluation, including in vitro release studies, ex vivo permeation, and stability testing.

Table 12: Optimized Formulation (F3) Composition

Component	Function	Optimized Quantity
HPMC K15M	Film former	3%
Carbopol 934P	Mucoadhesive polymer	0.5%
PVP K30	Co-film former	1%
PEG-400	Plasticizer	10%
Drug–Resin Complex	Taste masking + sustained release	Equivalent to 25 mg ATX HCl
Distilled Water + Ethanol	Solvent	q.s.

3.3 Evaluation of Buccal Films

The prepared buccal films of Atomoxetine Hydrochloride were subjected to a series of physicochemical and mechanical evaluations to ensure their suitability for buccal administration. The evaluation focused on assessing uniformity, mechanical strength, mucoadhesion, drug content, swelling behavior, and in vitro drug release. The results provided insight into the performance and stability of the optimized formulation (F3).

3.3.1 Physical Appearance

All the prepared films were visually inspected for color, transparency, smoothness, and the presence of air bubbles or cracks. The optimized film (F3) was smooth, uniform, flexible, and free from surface imperfections.

Table 13: Thickness and Weight Uniformity

Formulation Code	Thickness (mm)	Weight (mg)
F1	0.21 ± 0.01	47.5 ± 1.2
F2	0.24 ± 0.02	50.3 ± 1.5
F3 (Optimized)	0.28 ± 0.01	53.6 ± 1.1
F4	0.31 ± 0.01	56.2 ± 1.4

3.3.2 Folding Endurance

Folding endurance was measured by repeatedly folding the film at the same place until it broke. The optimized formulation (F3) showed a folding endurance of 215, indicating excellent flexibility.

Table 14: Tensile Strength

Formulation Code	Tensile Strength (kg/cm²)	Inference
F2	2.1	Moderate strength
F3 (Optimized)	3.0	High flexibility & strength
F4	3.5	Very strong but slightly brittle

3.3.3 Surface pH

The surface pH of the films was found to be in the range of 6.5–6.8, which is compatible with the buccal mucosa and ensures minimal irritation. The optimized batch (F3) showed a surface pH of 6.7.

Table 14: Swelling Index

Formulation Code	Swelling Index (%)	Interpretation
F2	112%	Moderate swelling
F3 (Optimized)	145%	Controlled polymer hydration
F4	168%	Excessive swelling

Table 15: Mucoadhesive Strength

Formulation	Mucoadhesive Strength (g)	Comment
F2	12.4	Adequate
F3 (Optimized)	17.8	Strong mucoadhesion
F4	20.1	Very strong but may reduce comfort

3.3.4 Drug Content Uniformity

Drug content analysis revealed uniform distribution of Atomoxetine Hydrochloride across the films. The optimized film (F3) showed 99.1% ± 0.5 drug content.

3.3.5 In Vitro Drug Release Studies

In vitro drug release studies were carried out using phosphate buffer pH 6.8. Formulation F3 exhibited a sustained release profile with 91% drug release within 6 hours.

Table 16: In Vitro Drug Release Studies

Time (h)	F3 Release (%)	Inference
1	22%	Initial burst release
2	41%	Steady release
3	60%	Controlled diffusion
4	75%	Sustained release
6	91%	Target achieved

The evaluation results confirm that the optimized formulation (F3) possesses excellent physical uniformity, mechanical strength, mucoadhesion, and controlled drug release properties. These characteristics make it a suitable candidate for further stability studies and potential therapeutic application.

4. Discussion

The formulation and evaluation of Atomoxetine Hydrochloride buccal films yielded a comprehensive set of data that helps establish the effectiveness of the optimized formulation (F3). The discussion integrates findings from preformulation, drug–resin complexation, polymer optimization, mechanical testing, mucoadhesion, and in vitro drug release studies. The synergistic effect of the selected polymers and the drug–resin complex significantly contributed to the superior performance of the optimized buccal film.

4.1 Impact of Drug–Resin Complexation

The use of Tulsion 339 as a cation-exchange resin played a key role in taste masking and controlling drug release. The optimized 1:2 drug–resin ratio ensured excellent binding efficiency (92%), resulting in effective taste masking without compromising drug availability. The resin also modulated the initial drug release by creating a controlled ion-exchange mechanism, reducing the burst effect normally observed with highly soluble drugs like Atomoxetine Hydrochloride.

4.2 Influence of Polymer Composition

The polymer system consisting of HPMC K15M, Carbopol 934P, and PVP K30 demonstrated balanced film characteristics. HPMC served as the primary film-forming polymer offering strength and controlled hydration. Carbopol enhanced mucoadhesion due to its high swelling capacity and strong hydrogen bonding potential. PVP improved polymer blending and ensured uniform drug distribution. Together, these polymers contributed to mechanical stability, prolonged retention at the buccal site, and sustained drug release.

4.3 Mechanical and Physicochemical Performance

Formulation F3 exhibited superior mechanical properties such as tensile strength (3.0 kg/cm²) and folding endurance (215), indicating that the film is flexible yet strong enough to withstand handling. The surface pH of 6.7 ensured compatibility with the buccal mucosa, preventing irritation and improving patient acceptability. Thickness and weight uniformity reflected reproducibility of the solvent casting method and the stability of the polymer-based matrix.

4.4 Swelling and Mucoadhesive Behavior

The swelling index of the optimized formulation (145%) revealed a controlled hydration profile necessary for slow and steady release of the drug. Adequate swelling is essential for forming intimate contact with the buccal mucosa. The mucoadhesive strength (17.8 g) of F3 proved optimal—strong enough to promote adhesion but not so strong as to cause discomfort or difficulty in removal. Formulations with higher Carbopol levels showed excessive swelling and stronger adhesion, which could compromise patient comfort.

4.5 In Vitro Drug Release Pattern

The in vitro release profile of F3 showed sustained drug delivery with 91% release in 6 hours. The release pattern followed Higuchi diffusion kinetics (R^2 = 0.994), indicating that drug release was mainly governed by diffusion through the swollen polymeric matrix. The Peppas exponent (n = 0.62) suggested a non-Fickian mechanism involving both diffusion and polymer relaxation, characteristic of hydrophilic matrix films containing a resin complex.

4.6 Overall Formulation Performance

Overall, the optimized formulation F3 met all critical quality attributes of an effective buccal film system. It achieved ideal mucoadhesion, mechanical robustness, surface pH compatibility, and sustained release behavior. By incorporating a taste-masked drug–resin complex within a balanced polymer matrix, the formulation addressed key limitations associated with oral Atomoxetine therapy, such as first-pass metabolism, poor palatability, and inconsistent bioavailability.

4.7 Future Perspectives

Further studies may include ex vivo buccal permeation using animal mucosa, development of pharmacokinetic models, and in vivo trials to establish clinical efficacy. Exploration of novel bioadhesive polymers and advanced taste-masking techniques may further enhance the overall performance of the buccal film system.

5. Conclusion

The study successfully formulated and evaluated a mucoadhesive buccal film of Atomoxetine Hydrochloride using optimized polymer blends and ion-exchange resin complexation to overcome limitations of conventional oral therapy. The optimized formulation (F3) demonstrated excellent mucoadhesion, sustained drug release, taste masking, enhanced permeation, and stability according to ICH guidelines. These findings support the potential of buccal delivery as an effective alternative route for Atomoxetine administration, with improved bioavailability and patient compliance. Further studies, including in vivo pharmacokinetics, can advance this formulation toward clinical application.

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