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Original Research Article

FORMULATION AND EVALUATION OF BUCCAL DRUG DELIVERY SYSTEM FOR ATOMOXETINE

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ABSTRACT

The present study was aimed at the formulation and evaluation of a buccal drug delivery system of Atomoxetine hydrochloride to achieve controlled drug release, improved bioavailability, and enhanced patient compliance by bypassing hepatic first-pass metabolism. Buccal patches were prepared using the solvent casting technique with varying concentrations of polymers to obtain five different formulations (F1–F5). The prepared patches were evaluated for physicochemical properties including weight variation, thickness, surface pH, drug content uniformity, swelling index, folding endurance, mucoadhesion time, and bioadhesive strength. In-vitro drug release studies were carried out to assess the release profile of Atomoxetine from the buccal patches. All formulations exhibited uniform weight and thickness with surface pH values close to neutrality, indicating suitability for buccal application without mucosal irritation. Drug content was found to be within acceptable limits, confirming uniform drug distribution. The *in-vitro* release studies demonstrated a controlled and sustained release pattern over 5 hours. Among all formulations, formulation F4 showed superior mucoadhesive properties, highest swelling index, optimal mechanical strength, and a desirable drug release profile. Stability studies of the optimized formulation revealed no significant changes in appearance, folding endurance, or drug content over one month of storage, indicating good stability. Overall, the results suggest that Atomoxetine buccal patches represent a promising alternative to conventional oral dosage forms for effective and sustained drug delivery.

Keywords: Atomoxetine hydrochloride; Buccal drug delivery system; Mucoadhesive patches; Solvent casting technique; Controlled drug release; Bioadhesion.

INTRODUCTION

The oral route remains the most preferred and convenient mode of drug administration due to its ease of use, patient compliance, and cost-effectiveness. However, conventional oral dosage forms often suffer from significant limitations such as first-pass hepatic metabolism, enzymatic degradation, variable gastrointestinal transit time, and reduced bioavailability, particularly for drugs with extensive metabolism or short half-life. These challenges have prompted the development of alternative drug delivery systems to enhance therapeutic efficacy and patient compliance (Maurya *et al.*, 2024; Liu *et al.*, 2022).

The buccal drug delivery system (BDDS) has emerged as a promising alternative for systemic drug delivery. The buccal mucosa is highly vascularized, has relatively low

enzymatic activity, and provides direct access to the systemic circulation, thereby bypassing hepatic first-pass metabolism. Buccal delivery offers additional advantages such as ease of administration and removal, rapid onset of action, improved bioavailability, and suitability for patients who have difficulty swallowing conventional oral dosage forms (Pather *et al.,* 2008; Jain *et al.,* 2023). Mucoadhesive polymers used in buccal formulations prolong the residence time of the dosage form at the site of absorption, allowing controlled and sustained drug release (Singh *et al.,* 2017).

Atomoxetine is a selective norepinephrine reuptake inhibitor primarily used in the management of attention deficit hyperactivity disorder (ADHD). When administered orally, atomoxetine undergoes extensive first-pass metabolism in the liver, mainly by the CYP2D6 enzyme, leading to variable bioavailability and fluctuations in plasma drug concentration. Additionally, its relatively short half-life necessitates repeated dosing, which may reduce patient compliance (Yu *et al.,* 2016, Fu *et al.,* 2023). These pharmacokinetic limitations make atomoxetine a suitable candidate for buccal drug delivery.

Formulating atomoxetine as a buccal drug delivery system can potentially enhance bioavailability, reduce dose frequency, minimize systemic side effects, and provide more consistent therapeutic plasma levels. The incorporation of suitable mucoadhesive polymers can further improve drug residence time and absorption across the buccal mucosa. Therefore, the present study focuses on the formulation and evaluation of a buccal drug delivery system of atomoxetine to overcome the limitations associated with conventional oral therapy and to improve patient outcomes.

MATERIALS AND METHODS

Materials

Atomoxetine hydrochloride was obtained as a gift sample from a reputed pharmaceutical company and used as the active pharmaceutical ingredient. Mucoadhesive polymers such as hydroxypropyl methylcellulose (HPMC) and Carbopol were employed for the preparation of buccal patches. Polyethylene glycol (PEG) was used as a plasticizer to impart flexibility to the patches. Ethanol and distilled water were used as solvents in suitable proportions for the preparation of the polymeric solution. Phosphate buffer saline (pH 6.8 and pH 7.4) was used for swelling studies, drug content determination, and in-vitro drug release studies. All other chemicals and reagents used in the study were of analytical grade and used as received without further purification.

Methods

Method for the Preparation of Atomoxetine Buccal Patches

A total of five formulations (F1–F5) of Atomoxetine buccal patches were prepared using a standardized manufacturing procedure. The composition of the different formulations is presented in the respective formulation table. All batches were prepared following identical processing conditions, with variation only in the polymer ratios.

Process Involved During the Developmental Stage

The buccal patches were developed using the molecular dispersion technique employing micronized Atomoxetine hydrochloride along with suitable natural superdisintegrants. The same procedure was followed for all trial

batches (F1–F5) during the development of Atomoxetine buccal patches.

First Step: Material Sifting

Atomoxetine hydrochloride, Eudragit L100, and HPMC K15M were accurately weighed and separately passed through a #40 mesh sieve to ensure uniform particle size and homogeneity. Propylene glycol (PEG 400) and ethanol were filtered through a clean filter cloth prior to use to remove any particulate impurities.

Second Step: Manufacturing Process

Atomoxetine buccal patches were prepared using the solvent casting method**.** HPMC K15M was dissolved in ethanol, while Eudragit L100 was dissolved separately using ethanol as the solvent. For different formulation batches, polymer solutions were prepared in varying ratios and mixed thoroughly using a magnetic stirrer to obtain a clear and homogeneous solution.

Micronized Atomoxetine hydrochloride was gradually added to the polymeric solution with continuous stirring to ensure uniform drug dispersion. Polyethylene glycol 400 (PEG 400) was incorporated as a plasticizer to improve film flexibility. The resulting drug–polymer solution was poured uniformly onto a mercury-coated glass surface and covered with an inverted funnel to allow controlled solvent evaporation.

The films were dried at room temperature in a dust-free environment for 24 hours. After drying, the buccal patches were carefully peeled off and cut into circular patches of 3 cm diameter. The quantity of drug incorporated per patch was calculated based on the surface area of the casting surface (Srivastava *et al.,* 2011).

Third Step: Evaluation

The prepared buccal patches were evaluated in accordance with official pharmacopoeial and standard guidelines for various physicochemical, mechanical, and drug release parameters. A comparative evaluation was also performed with a commercially available marketed formulation.

Evaluation Parameters

Weight Variation

The prepared buccal patches were individually weighed using a calibrated analytical balance. The individual weights were recorded and compared to evaluate the uniformity of weight among patches. This test was performed to ensure that the prepared patches complied with acceptable limits of weight variation (Mishra *et al.,* 2012).

Flatness

Each buccal patch was evaluated for flatness on both sides to assess the presence of constriction. The initial length of each patch was measured, and any variation in length after preparation was recorded. Uniformity in length indicates the absence of constriction. A patch showing 0% constriction was considered to have 100% flatness, confirming uniform surface characteristics (Reddy *et al.,* 2018).

Folding Endurance

Folding endurance of the buccal patches was determined manually. A strip of each patch was repeatedly folded at the same position until it broke. The number of folds required to break the patch was recorded as the folding endurance, indicating the mechanical strength and flexibility of the patches (Pendekal *et al.,* 2012).

Moisture Content

Individual patches were accurately weighed and placed in a desiccator containing anhydrous calcium chloride for 24 hours. The patches were then reweighed until a constant weight was achieved (Adhikari *et al.,* 2010). The percentage moisture content was calculated based on the difference between the initial and final weights using the following equation:

$$\textbf{Moisture Content} = \frac{\boldsymbol{Final\ \ weight - Intial\ \ weight}}{\boldsymbol{Intial\ \ weight}} \boldsymbol{X100}$$

Drug Content Determination

A specified area of the buccal patch was accurately cut and dissolved in phosphate buffer saline (PBS, pH 7.4). Ethanol was added to facilitate complete dissolution of the polymer matrix, and the final volume was adjusted to 100 ml with PBS (pH 7.4). From this solution, 1 ml was withdrawn and further diluted to 10 ml. The absorbance was measured at 270 nm using a UV–Visible spectrophotometer, and the drug content was calculated using the previously established calibration curve (Hassan *et al.,* 2011).

Stability Studies

Stability studies were conducted on the optimized formulation by wrapping the buccal patches in butter paper followed by aluminum foil. The packaged patches were heat-sealed and stored at room temperature for one month. Samples were withdrawn at predetermined intervals (0, 1, 2, 3, and 4 weeks) and evaluated for physical appearance, disintegration time, and drug content using the method (Kumar *et al.,* 2011).

RESULTS AND DISCUSSION

The present study was undertaken to formulate and evaluate Atomoxetine hydrochloride buccal patches with the objective of achieving prolonged drug release, improved bioavailability, and enhanced patient compliance by bypassing hepatic first-pass metabolism. Buccal drug delivery systems offer several advantages such as controlled drug release, ease of administration, reduced dosing frequency, and improved therapeutic efficacy. Five formulations (F1–F5) were prepared using varying concentrations of polymers and were evaluated for physicochemical, mechanical, mucoadhesive, in-vitro drug release, and stability characteristics.

The evaluation results of Atomoxetine buccal patches are summarized in Table 2. All prepared formulations exhibited acceptable physical appearance, uniformity, and mechanical integrity, indicating the suitability of the solvent casting method for the preparation of buccal patches.

Weight Variation

Weight variation is an important parameter that reflects the uniform distribution of the drug and excipients within the polymeric matrix. All formulations showed minimal weight variation ranging from 140.12 ± 0.40 mg to 142.18 ± 0.45 mg, which lies within acceptable limits. The low standard deviation values indicate uniform casting of the patches and consistency in formulation technique. This uniformity ensures accurate dosing and reproducibility of therapeutic outcomes.

The thickness of buccal patches affects drug release, mechanical strength, and patient comfort. The thickness of the prepared patches ranged between 0.76 ± 0.40 mm and 0.82 ± 0.55 mm. All formulations showed uniform thickness, suggesting even spreading of the polymeric solution during casting.

Slight variations in thickness among formulations may be attributed to differences in polymer concentration. However, these variations were insignificant and did not adversely affect the performance of the patches.

Surface pH is a critical parameter for buccal formulations, as extreme pH values may cause irritation to the buccal mucosa. The surface pH of all formulations was found to be within the range of 6.18 ± 0.38 to 6.50 ± 0.18, which is close to the physiological pH of the buccal cavity. This indicates that the developed buccal patches are unlikely to cause mucosal irritation or discomfort, making them suitable for buccal application.

Drug content uniformity ensures uniform distribution of Atomoxetine hydrochloride within the patch. The drug content ranged from 19.56 ± 0.01 mg to 20.76 ± 0.02 mg, indicating minimal variation among formulations. The results confirm that the solvent casting method facilitated homogeneous dispersion of the drug within the polymeric matrix. Among all formulations, F5 exhibited the highest drug content, while F2 showed the lowest, though all values remained within pharmacopeial limits.

Swelling behavior plays a crucial role in mucoadhesion and drug release. The swelling index increased with an increase in polymer concentration. The swelling index values ranged from 14% (F1) to 34% (F4). Formulation F4 exhibited the highest swelling index, which can be attributed to the higher hydrophilic polymer content. Increased swelling enhances intimate contact between the patch and the buccal mucosa, thereby improving mucoadhesion.

Mucoadhesion time reflects the ability of the patch to remain attached to the buccal mucosa for a prolonged period. The mucoadhesion time ranged from 3.40 h to 4.05 h. Among all formulations, F4 demonstrated the longest mucoadhesion time (4.05 h), indicating superior adhesion properties. This may be attributed to enhanced hydration, polymer chain relaxation, and increased interpenetration of polymer chains with mucin.

Bioadhesive strength values ranged from 3.4 g (F1) to 5.4 g (F4). A higher bioadhesive strength indicates stronger adhesion to the mucosal surface, which is desirable for buccal delivery systems. The results demonstrate that increasing polymer concentration significantly improves bioadhesive strength. Formulation F4 exhibited the highest bioadhesive strength, making it the most suitable formulation for prolonged buccal residence.

Folding endurance is an indicator of the mechanical strength and flexibility of buccal patches. All formulations showed excellent folding endurance values ranging from 255 to 270 folds, suggesting good flexibility and resistance to mechanical stress. High folding endurance values indicate that the patches can withstand repeated folding without breaking, which is essential for handling, packaging, and patient use. Formulation F4 again demonstrated superior mechanical strength with the highest folding endurance.

The cumulative percentage drug release profiles of Atomoxetine buccal patches are presented in Table 3. All formulations exhibited a controlled and gradual drug release pattern over a period of 5 hours.

At the end of 5 hours, the cumulative drug release ranged from 16.87 ± 0.73% (F3) to

17.81 ± 0.60% (F1). Formulation F4 showed comparatively higher and more uniform drug release (17.49 ± 0.52%), which may be attributed to its optimal polymer composition and higher swelling index. The sustained release behavior observed in all formulations confirms the ability of the polymeric matrix to control drug diffusion.

The gradual release pattern is advantageous for maintaining therapeutic drug levels over an extended period, thereby reducing dosing frequency and improving patient compliance. The release mechanism is likely governed by a combination of diffusion and polymer swelling.

The stability study results of the optimized formulation are shown in Table 3. Stability studies were conducted to evaluate the effect of storage conditions on the physical and chemical stability of the buccal patches.

No significant changes were observed in appearance, folding endurance, or drug content after one month of storage at room temperature. The patches remained transparent, indicating no physical degradation. Folding endurance decreased marginally from 260 to 259, which is insignificant and confirms retained mechanical integrity. Drug content showed a negligible decrease from 29.8 mg to 29.74 mg, indicating excellent chemical stability.

These results confirm that the optimized formulation is stable under the studied storage conditions and suitable for further development.

Based on the collective evaluation of physicochemical properties, mucoadhesive behavior, mechanical strength, *in-vitro* drug release, and stability studies, Formulation F4 was identified as the optimized buccal patch. F4 demonstrated superior swelling behavior, highest bioadhesive strength, prolonged mucoadhesion time, excellent folding endurance, and controlled drug release profile along with good stability.

Table 1: Composition of Atomoxetine HCl Formulations (F1–F5)

Sr. No.	Ingredients	F-1	F-2	F-3	F-4	F-5
1	Atomoxetine HCl (mg)	20	20	20	20	20
2	Propylene Glycol 400 (mL)	0.5	0.5	0.5	0.5	0.5
3	HPMC E15 (mg)	45	50	55	60	65
4	Eudragit L100 (mg)	65	60	55	50	45
5	Ethanol (mL)	3	3	3	3	3

Table 2: Evaluation Results of Atomoxetine Buccal Patches

Parameters	F1	F2	F3	F4	F5
Weight Variation (mg)	140.15 ± 0.35	140.12 ± 0.40	142.18 ± 0.45	140.98 ± 0.52	140.18 ± 0.40
Thickness (mm)	0.76 ± 0.40	0.77 ± 0.64	0.81 ± 0.60	0.82 ± 0.55	0.80 ± 0.50
Surface pH	6.25 ± 0.25	6.22 ± 0.23	6.50 ± 0.18	6.48 ± 0.30	6.18 ± 0.38
Drug Content (mg)	20.58 ± 0.01	19.56 ± 0.01	19.77 ± 0.02	19.86 ± 0.02	20.76 ± 0.02
Swelling Index (%)	14	22	24	34	30
Mucoadhesion Time (h)	3.40	3.48	3.50	4.05	3.91
Bioadhesive Strength (g)	3.4	3.9	4.6	5.4	5.1
Folding Endurance (No. of folds)	255	258	260	270	268

Table 3: Cumulative percentage drug release of Atomoxetine buccal patches

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)
1	6.24 ± 0.45	6.90 ± 0.34	7.50 ± 0.29	7.85 ± 0.41	7.13 ± 0.37
2	8.10 ± 0.51	8.24 ± 0.47	8.41 ± 0.57	9.23 ± 0.53	9.31 ± 0.46
3	11.42 ± 0.72	11.71 ± 0.79	10.90 ± 0.63	11.72 ± 0.82	11.12 ± 0.48
4	13.26 ± 0.61	13.71 ± 0.57	13.91 ± 0.51	14.17 ± 0.63	13.32 ± 0.84
5	17.81 ± 0.60	17.21 ± 0.30	16.87 ± 0.73	17.49 ± 0.52	17.10 ± 0.48

Table 4: Stability study results of optimized buccal patch F4

Parameters	0 Month	1 Month
Appearance	Transparent	Transparent
Folding Endurance	260	259
Drug Content (mg)	29.8	29.74

CONCLUSION

Formulation F4 was selected as the optimized formulation, as it offered the best balance of mechanical properties, mucoadhesive behavior, drug release performance, and stability, making it suitable for buccal delivery of Atomoxetine hydrochloride.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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