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FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL PATCHES OF ATOMOXETINE HYDROCHLORIDE

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ABSTRACT

Atomoxetine hydrochloride (ATH) is a selective norepinephrinereuptake inhibitor commonly prescribed for the management of attention deficit hyperactivity disorder (ADHD). This study focuses on the development of mucoadhesive buccal patches for Atomoxetine Hydrochloride to enhance its bioavailability and provide extended drug release. The formulation process involves selecting appropriate polymers and excipients to optimize the mucoadhesive properties, mechanical strength, and drug release kinetics of the patches. Characterization studies will evaluate physical properties such as thickness, weight variation, and surface pH, along with mucoadhesive strength using techniques like texture analysis. In vitro drug release studies will be conducted to determine the release profile of Atomoxetine Hydrochloride, with data analysis using mathematical models to understand the underlying release mechanisms. The goal is to create an effective buccal delivery system that improves the therapeutic efficacy of Atomoxetine Hydrochloride.

KEYWORDS: Atomoxetine Hydrochloride, HPMC E15, HEC, and PVP.

1. INTRODUCTION

The oral route is widely preferred for drug delivery but faces challenges like hepatic first-pass metabolism and enzymatic breakdown in the gastrointestinal tract, limiting its efficacy for certain drugs, especially peptides and proteins. To address these issues, alternative mucosal surfaces such as the nasal, rectal, vaginal, ocular, and oral cavities have been explored. These transmucosal routes bypass the first-pass effect, avoid presystemic degradation, and often provide a more favorable enzymatic environment for drug absorption. Among these, buccal delivery is particularly useful for localized treatments, like periodontal disease and infections, and is increasingly favoured for systemic drug delivery due to its ability to bypass hepatic metabolism via direct entry into systemic circulation through the jugular vein. Mucoadhesive systems, including tablets, films, patches, and gels, have gained popularity for their

ability to prolong drug contact with mucosal surfaces, with buccal patches offering added benefits like flexibility, comfort, and resistance to saliva. The oral mucosa, a multi-layered structure with an outer epithelial layer and an underlying lamina propria, offers advantages like high permeability and a rich blood supply, enabling rapid drug absorption. However, saliva, enzymatic activity, and potential mucosal irritation can limit drug retention and efficacy. Buccal drug absorption primarily occurs through passive diffusion, where nonionized drug species move across the intercellular spaces of the buccal epithelium, driven by a concentration gradient, with lipophilicity playing a significant role in drug absorption. This process follows first-order kinetics, with the rate of absorption proportional to the drug concentration in the mouth. However, saliva secretion can alter drug concentration over time, influencing absorption kinetics, a relationship that can be mathematically described to optimize buccal drug delivery.The relationship between salivary secretion and the drug concentration over time can be described by the following equation:[1-5]

$$-\frac{dm}{dt} = \frac{K \cdot C}{Vi \cdot Vt}$$

In this equation, M represents the mass of the drug present in the mouth at a given time t. The constant K is a proportionality factor that connects the rate at which the drug is lost to its concentration in the mouth. C indicates the concentration of the drug in the mouth at the specific time t. The term Vi refers to the volume of the drug solution initially introduced into the oral cavity, while Vt represents the rate at which saliva is secreted. And also highlights how the interplay between drug concentration, solution volume, and salivary flow rate influences the rate at which the drug is absorbed or cleared from the buccal cavity. As salivary secretion increases, it dilutes the drug concentration in the mouth, potentially slowing down the absorption process and altering the overall pharmacokinetics of the drug. Understanding these dynamics is crucial for optimizing buccal drug delivery systems, as it allows for better control over drug release and absorption, ensuring more consistent therapeutic outcomes.[6,7]

Several factors influence buccal drug absorption, with drug solubility and lipophilicity being crucial. A balanced partition coefficient (P) allows the drug to effectively diffuse through the lipid-rich mucosal membrane. A moderately high P ensures efficient penetration, while an excessively high or low P can hinder absorption. The buccal mucosa's thinness and rich vascularization facilitate rapid drug diffusion and direct entry into the systemic circulation, bypassing hepatic first-pass metabolism and improving bioavailability. Mucoadhesive polymers like carbomers, HPMC, and chitosan enhance drug retention and efficacy by adhering to the mucosal surface, enabling controlled and prolonged drug release. These polymers form strong bonds with the mucosa, improving bioavailability and allowing for targeted delivery with reduced dosing frequency, ultimately optimizing therapeutic outcomes.

Mechanism of Bioadhesion

The mechanism of bioadhesion involves two steps: initial contact and consolidation. During contact, the mucoadhesive polymer interacts with the mucus, causing the formulation to swell and spread. In consolidation, moisture activates the polymer, leading to plasticization and the formation of weak bonds, such as Van der Waals and hydrogen bonds, with the mucus. Diffusion theory explains the interpenetration of bioadhesive molecules and mucosal glycoproteins, while dehydration theory suggests gel formation and enhanced bond formation due to water motion. Buccal patches, designed for drug delivery, come in two types: matrix-type for bidirectional release and reservoir-type for unidirectional release. They contain active ingredients, mucoadhesive polymers like hydroxyethyl cellulose and Carbopol, diluents, sweeteners, flavoring agents, and a backing layer. Preparation methods include solvent casting, direct milling, solid

dispersion extrusion, semi-solid casting, and hot melt extrusion, each offering advantages like reduced solvent risks and improved material uniformity.[8-16]

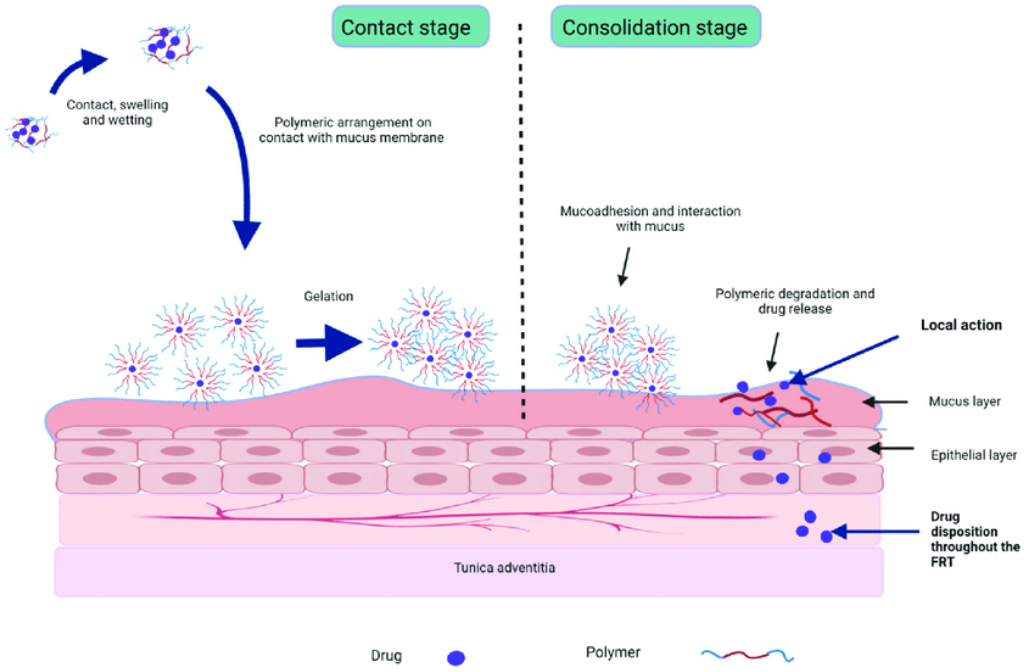

Figure-1: Stages of Mucoadhesion and Drug release.

2. EXPERIMENTAL

Materials

Atomoxetine hydrochloride was obtainedas gift sample from Mann Medix Pharma ltd, Mumbai.HPMC E15, HEC, PVP, Ethanolwas produced from commercial sources. All other materials were of pharmacopoeial grade.

Methods

2.1. Preformulation Studies

Preformulation testing is the initial phase in developing dosage forms, focusing on assessing the physical and chemical properties of a drug substance, both in isolation and in combination with excipients. This testing aims to provide crucial information for creating stable and effective dosage forms. The primary objectives of preformulation studies include determining the essential physicochemical characteristics of the drug, understanding its release kinetics, and evaluating its compatibility with various excipients. Key preformulation tests involve identification procedures such as infrared spectroscopy, where FTIR studies are used to detect potential interactions between the drug and excipients, and solubility analysis to choose appropriate solvents and dissolution mediums. Additionally, the melting point of the drug is determined using the capillary tube method. For calibration, a UV scan of Atomoxetine Hydrochloride involves preparing a series of dilutions from an initial stock solution and measuring absorbance at 221 nm to construct a calibration curve, thus establishing a relationship between concentration and absorbance.[17]

2.2. Preparation of Buccal Patches

Patches containing Atomoxetine Hydrochloride with varying proportions of HPMC E15, HEC, and PVP were prepared using the solvent casting method. The drug was dissolved in 10 ml of methanol, while the polymers were separately dissolved in 20 ml of distilled water with continuous stirring for 4 hours. After combining the drug and polymer

solutions, propylene glycol was added as a plasticizer, and the mixture was stirred until homogeneous. The viscous solution was allowed to settle overnight to eliminate bubbles. It was then poured into a glass petri dish and dried at 40°C to form flexible patches. The dried patches were inspected for defects, cut into 1 cm^2 pieces, and stored in aluminum foil within desiccators to preserve their integrity and flexibility. The composition of the different buccal patches is detailed in the accompanying Table-1.

Table-1: Composition of buccal patches of Atomoxetine Hydrochloride.

Ingredients	Formulations								
	AH1	AH2	AH3	AH4	AH5	AH6	AH7	AH8	AH9
Atomoxetine HCl (mg)	10	10	10	10	10	10	10	10	10
HPMC E15(mg)	10	20	30	-	-	-	-	-	-
HEC(mg)	-	-	-	10	20	30	-	-	-
PVP(mg)	-	-	-	-	-	-	10	20	30
Ethanol(ml)	20	20	20	20	20	20	20	20	20
Distilledwater	5	5	5	5	5	5	5	5	5

2.3. Evaluation Parameters

A. Physical Parameters

The physical properties of the buccal patches were assessed through various tests. The thickness was measured at five randomly selected spots using a screw gauge, with the mean and standard deviation calculated. Folding endurance was determined by repeatedly folding a 20 mm diameter patch at the same location until it broke, with the number of folds recorded and averaged over three tests. Mechanical strength was evaluated using a microprocessor-controlled force gauge with a motorized test stand. Patches measuring 60×10 mm and free from defects were positioned between clamps 3 cm apart, with the upper clamp pulling at a rate of 2 mm/sec until the patch broke. The force and elongation at the break point were recorded. Tensile strength was calculated using the formula:[18-20]

$$Tensile\ Strength\ (kg.mm^2) = \frac{Force\ at\ Break\ (kg)}{Initial\ cross\ sectional\ area\ of\ sample\ (mm^2)}$$

$$Elongation\ at\ break\ (\%.mm^{-2}) = \frac{Increase\ in\ lenght\ (mm)}{Original\ length} \times \frac{100}{cross\ scetional\ area\ (mm^2)}$$

B. Water uptake Study

Moisture uptake studies evaluate the ability of polymers to absorb moisture while maintaining structural integrity. In this test, a 5% w/v agar solution was prepared, poured into Petri dishes, and solidified. Six drug-free patches from each formulation were weighed and dehydrated in a vacuum oven overnight. The patches were then laminated with a water-impermeable backing, incubated at 37°C for one hour, and reweighed. The percentage of moisture absorption was calculated to assess the performance of the patches.[21]

$$\%\ Moisture\ Absorption = \frac{Final\ Weight - Initial\ Weight}{Initial\ Weight} \times 100$$

C. Surface pH

To determine the surface pH, three films from each formulation were allowed to swell for 2 hours on an agar plate. The pH was then measured using pH paper placed on the swollen film's surface. The average of three readings was recorded.

D. Performance Parameters

Drug content uniformity was assessed by extracting the drug from three patches of each formulation into separate 100 mL volumetric flasks, adding 100 mL of pH 6.8 phosphate buffer, and stirring continuously for 24 hours. The solutions were filtered, diluted, and analyzed at 221 nm using a UV spectrophotometer (Sysronic), with the average of the three readings taken as the final drug content. Bioadhesive strength was measured by determining the force needed to detach the patches from porcine gastric mucosa, using a modified two-arm balance setup with a glass plate and a counterbalance water collecting pan. The mucosa was secured on an acrylate stage in a beaker filled with phosphate buffer (pH 6.8) at 37±0.5 °C, and the detachment time was recorded. Scanning electron microscopy (SEM) was employed to analyze the particle size distribution, surface texture, and morphology of the fractured or sectioned surfaces, providing insights into the porosity and microstructure of the drug delivery system.[22-25]

E. *In-vitro* Release Studies

In vitro release studies of the buccal patches were conducted using the rotating paddle method outlined in the USP XXIII, with 500 mL of phosphate buffer at pH 6.8 maintained at 37±0.5°C and a rotation speed of 50 RPM. Patches (1 cm^2) were enclosed in dialysis membrane and supported by a glass slide to prevent floating. The membrane assembly was secured with closure clips and immersed in the buffer. Samples (5 mL) were withdrawn at specified intervals, replaced with fresh buffer, filtered through Whatman filter paper, and analyzed at 221 nm using a UV spectrophotometer. The experiments were performed in triplicate, and average values were reported. Drug release kinetics were analyzed using Zero-Order, First-Order, and Higuchi equations. Zero-Order kinetics was determined by plotting cumulative percentage drug release versus time, with a linear relationship indicating the zero-order rate constant (K_0). First-Order kinetics was analyzed by plotting log cumulative percentage of drug remaining versus time, with the slope representing the first-order rate constant (k). The Higuchi model was evaluated by plotting cumulative percentage of drug released versus the square root of time, where the release rate (Q) is proportional to the square root of time. Korsmeyer-Peppas equations were used to characterize the release mechanism, with log cumulative percentage drug released versus log time plotted to determine the release exponent (n). For cylindrical matrices, an exponent (n) of 0.45 indicates Fickian diffusion, $0.45 < n < 0.89$ suggests non-Fickian or anomalous diffusion, and $n = 0.89$ corresponds to Case-II Transport or zero-order release.[26-28]

3. RESULTS AND DISCUSSION

The drug was initially tested using UV spectroscopy to determine its significant absorption maximum for diffusion studies. The analysis revealed that Atomoxetine Hydrochloride has a lambda max of 221 nm, which was used for subsequent diffusion studies.

3.1. Standard Calibration Curve

Table-1: Standard graph of Atomoxetine Hydrochloride.

Concentration (µg/ml)	Absorbance (at 221nm)
0	0
10	0.109
20	0.205
30	0.302
40	0.401
50	0.498

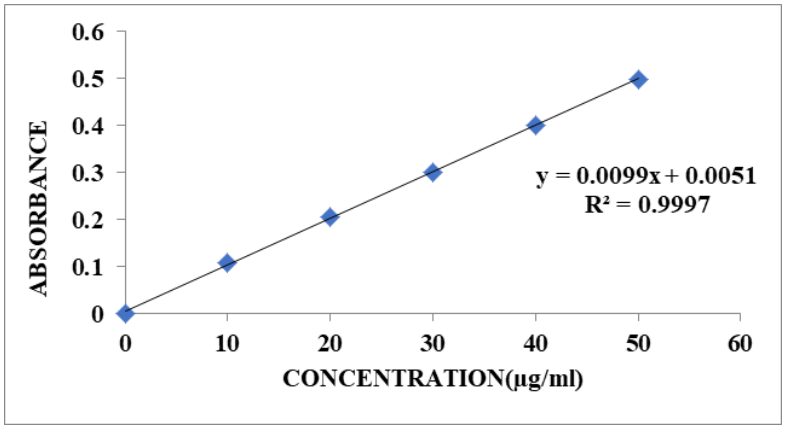

Figure-2: Standard calibration curve of Atomoxetine Hydrochloride.

3.2. Preformulation Studies

A total of nine formulation trials were conducted to develop successful matrix-type mucoadhesive patches for Atomoxetine Hydrochloride. The prepared blends were evaluated for various physical parameters and drug content uniformity using UV analysis. Identification tests revealed the active pharmaceutical ingredient to be white in color, odorless, with a bitter taste, and in a white powder appearance. The melting point of the drug sample was consistent with the reported value of 171°C, confirming the drug's purity. Additionally, the solubility determination of Atomoxetine Hydrochloride revealed the following results: 0.0403 mg/ml in distilled water, 78.31 mg/ml in pH 7.4 phosphate buffer, and 82.64 mg/ml in pH 6.8 phosphate buffer.

3.3. Physical Properties

The thickness of the prepared buccal patches varied between 0.30±0.10 and 0.58±0.08, as detailed in the table. Folding endurance values ranged from 180±5.70 to 203±1.00, also listed in the Table-2. Mechanical strength assessments, performed on three patches per formulation, showed mean values between 6.28±0.07 and 13.84±0.07/mm², indicating robust mechanical strength. Water uptake studies, conducted at the third hour, revealed values from 2.99±0.095 to 3.41±0.10, with results detailed in the table, reflecting the mean of three replicate measurements.

Table-2: Evaluation of Physical parameters.

Formulation Code	Thickness (mm) ±S.D (n=3)	Folding endurance ±S.D (n=3)	Mechanical strength ±S.D (n=3) (kg/mm2)	Water uptake ±S.D (n=3)
AH1	0.41 ± 0.08	186 ± 2.22	11.14±0.04	3.26 ±0.35
AH2	0.50±0.07	197±3.16	8.45±0.05	3.14 ±0.11
AH3	0.46±0.05	180±5.70	8.23±0.32	3.10 ±0.10
AH4	0.42±0.04	185±2.54	13.84± 0.07	3.28 ±0.24
AH5	0.40±0.07	188±1.22	7.86±0.13	2.99 ±0.095
AH6	0.58±0.08	188±1.58	6.64±0.12	3.93±0.15
AH7	0.52±0.08	201 ±1.22	8.94±0.09	3.01 ±0.35
AH8	0.30±0.10	205 ±2.82	7.04±0.05	3.10 ±0.24
AH9	0.44±0.05	203 ±1.00	6.28±0.07	3.41 ±0.10

3.4. Performance Parameters

The performance parameters for Atomoxetine mucoadhesive buccal patches were comprehensively evaluated to ensure their effectiveness. This evaluation encompassed several critical metrics: bioadhesive strength, which measures the patch's ability to adhere to mucosal surfaces; force of adhesion (N), indicating the force required to detach the patch from its application site; bond strength, reflecting the quality of adhesion between the patch and mucosal surface; drug

content percentage, which assesses the uniformity and concentration of Atomoxetine in the patches; surface pH, important for ensuring compatibility with the mucosal environment; and in vitro residence time, which determines how long the patch remains effectively in place. These parameters provide essential insights into the functional performance and reliability of the mucoadhesive buccal patches, and the results are detailed in Table-3.

Table-3: Evaluation of Performance parameters of different mucoadhesive buccal patches of Atomoxetine Hydrochloride.

Formulation Code	Drug content %	Bioadhesive strength (gms) ±S.D (n=3)	Force of adhesion (N) ± S.D (n=3)	Bond strength ± S.D (n=3) (kg/mm2)	Surface pH	*In-Vitro* residence time (min) (kg/mm^2)
AH1	83± 0.12	150.1±2.6	1.11±0.01	323.6±5.34	7.4±0.5	410±10
AH2	88± 0.31	156.3±2.1	1.23±0.05	333.1±3.65	7.5±0.3	421± 05
AH3	81± 0.01	161.7±0.8	1.33±0.02	386.9±5.23	7.4±0.5	430±15
AH4	90± 0.04	166.2±0.9	1.51±0.01	423.3±1.86	7.6±0.4	450±05
AH5	95± 0.16	187.3±1.4	1.64±0.02	433.8±4.33	7.5±0.5	380±10
AH6	99± 0.55	192.6±3.7	1.73±0.01	441.2±6.98	7.3±0.5	411±10
AH7	88±0.38	134.3±2.7	1.23±0.06	315.7±5.32	7.4±0.3	300±10
AH8	96±0.11	147.5±1.4	1.38±0.04	334.5±6.90	7.5±0.4	311±15
AH9	93±0.21	158.3±1.5	1.47±0.02	353.4±3.23	7.4±0.3	380±05

The evaluation of content uniformity for the active ingredient in each buccal patch formulation revealed a mean drug content ranging from 68 to 99 across the formulations, as detailed in the table. Bioadhesive strength, a crucial parameter for ensuring effective adhesion to the buccal mucosa, was assessed using porcine gastric mucosa and provided an indirect measurement of adhesion in grams. The bioadhesive strength values varied from 134.3±2.7 to 192.6±3.7 for formulations AH1 through AH9, respectively. Surface pH measurements, which are essential for ensuring compatibility with the mucosal environment, showed values between 7.3±0.5 and 7.6±0.4, closely aligning with the physiological pH range of saliva (7.2 to 7.4). This indicates good patient acceptability of the formulations.

3.5. Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) was employed to examine the surface morphology of the mucoadhesive buccal patches. This technique provided detailed images, revealing the texture, porosity, and overall structure of the patches. The SEM analysis allowed for the observation of the uniformity of the patch surface, the distribution of the drug within the polymer matrix, and any potential imperfections, contributing valuable insights into the quality and performance of the buccal patches.

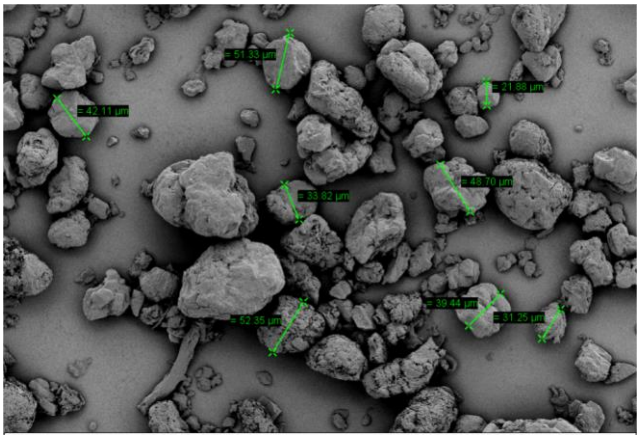

Figure-3: SEM of optimized formulation.

3.6. In-vitro Release Studies

The in vitro diffusion study for all formulations was conducted using a Franz-type diffusion cell, with the temperature precisely controlled at 32 ± 0.5°C to simulate physiological conditions. The diffusion process was carried out over a 12-hour period to thoroughly assess the release profile of the drug from the buccal patches. At each hour, a 5 ml sample was withdrawn from the receptor compartment to measure the concentration of the drug that had diffused through the membrane. This sampling procedure ensured accurate monitoring of the drug release kinetics throughout the duration of the experiment. The results from this study were used to evaluate the effectiveness and consistency of the drug release from each formulation. (Table-4)

Table-4: *In-Vitro* drug permeation of Atomoxetine Hydrochloride.

TIME (H)	% of Drug release								
	AH1	AH2	AH3	AH4	AH5	AH6	AH7	AH8	AH9
0	0	0	0	0	0	0	0	0	0
1	21.94	18.72	16.23	20.86	26.36	24.26	22.86	24.36	18.26
2	24.83	22.25	23.44	27.17	31.84	28.45	27.17	28.84	24.45
3	32.25	29.34	27.12	34.77	39.21	36.29	34.77	36.21	31.29
4	39.12	36.55	33.30	47.68	49.28	44.11	47.68	45.28	41.11
5	48.88	45.41	42.13	56.42	59.67	55.72	57.42	59.67	52.72
6	59.37	54.42	54.40	62.22	68.29	63.33	62.22	68.29	61.33
7	66.90	62.63	58.91	69.31	75.58	69.54	67.13	73.58	69.54
8	68.41	65.95	64.86	74.71	80.75	74.22	72.71	78.72	74.22
9	77.46	73.77	69.74	78.91	85.62	82.41	78.91	83.26	82.41
10	83.17	78.18	75.22	86.63	92.71	86.83	84.63	89.71	84.83
11	87.23	85.29	82.53	93.54	96.32	91.86	9.54	94.35	88.86
12	93.82	92.61	90.21	98.88	99.93	95.14	96.88	97.93	95.14

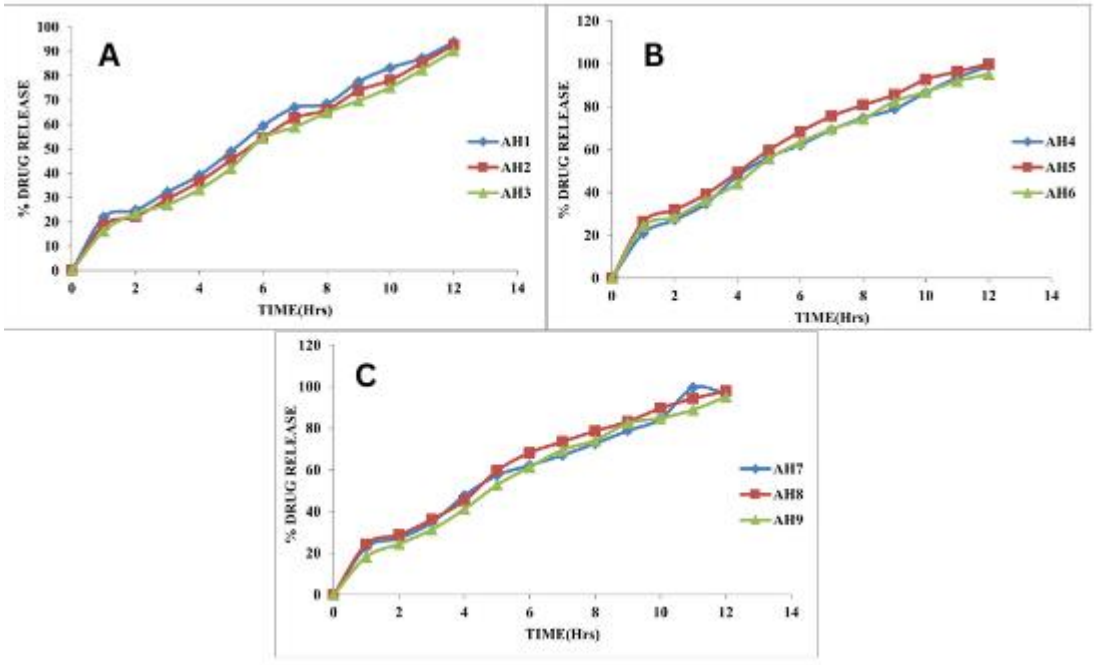

Figure- 4: Cumulative % drug permeation of Atomoxetine Hydrochloridepatch of different formulations. A- (AH1, AH2, AH3); B- (AH4, AH 5, AH6); C- (AH7, AH8, AH9)

A: Formulations AH1 to AH3, which incorporated varying concentrations of HPMC E15 (10, 20, and 30 mg), demonstrated that drug release and permeation from the patches were dependent on the polymer concentration in the

matrix. Specifically, at lower polymer concentrations, the patches exhibited higher drug permeation, with complete drug release achieved within 8 hours. **B:** The 20 mg concentration of the polymer exhibited the highest drug release, achieving 99.93% total drug release within 12 hours. Among the three formulations, formulation AH5 achieved complete drug release within the desired time period. **C:** Formulations AH7 to AH9 were developed using varying concentrations of PVP (10, 20, and 30 mg). The drug release or permeation from the patches was dependent on the polymer concentration in the matrix. The formulation with 20 mg of PVP (AH8) demonstrated the highest drug release, achieving 98.12% within 12 hours. Among all nine formulations, AH5 exhibited the best drug permeation performance. Additionally, AH5 met all the in vitro evaluation criteria successfully.

3.7. Kinetic models for Atomox etine Hydrochloride

Various models were employed to elucidate the kinetics of drug release from the dosage forms. The obtained data were analyzed by fitting them into different release models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. This comprehensive analysis aimed to determine the mechanism and rate of drug release from the formulation.

Table-5: Kinetics data of AH5Atomoxetine Hydrochloride patch.

Cumulative (%) Release	Time (T)	Root (T)	Log (%) Release	Log (T)	Log (%) Remain	Release Rate	1/Cum% release	Peppas LogQ/100	% drug Remain	Q01/3	Q01/3	Q01/3-Q01/3
0	0	0			2.000				100	4.642	4.642	0.000
26.36	1	1.000	1.421	0.000	1.867	26.360	0.0379	-0.579	73.64	4.642	4.192	0.450
31.84	2	1.414	1.503	0.301	1.834	15.920	0.0314	-0.497	68.16	4.642	4.085	0.557
39.21	3	1.732	1.593	0.477	1.784	13.070	0.0255	-0.407	60.79	4.642	3.932	0.710
49.28	4	2.000	1.693	0.602	1.705	12.320	0.0203	-0.307	50.72	4.642	3.702	0.940
59.67	5	2.236	1.776	0.699	1.606	11.934	0.0168	-0.224	40.33	4.642	3.429	1.212
68.29	6	2.449	1.834	0.778	1.501	11.382	0.0146	-0.166	31.71	4.642	3.165	1.476
75.58	7	2.646	1.878	0.845	1.388	10.797	0.0132	-0.122	24.42	4.642	2.901	1.740
80.75	8	2.828	1.907	0.903	1.284	10.094	0.0124	-0.093	19.25	4.642	2.680	1.962
85.62	9	3.000	1.933	0.954	1.158	9.513	0.0117	-0.067	14.38	4.642	2.432	2.210
92.71	10	3.162	1.967	1.000	0.863	9.271	0.0108	-0.033	7.29	4.642	1.939	2.703
96.32	11	3.317	1.984	1.041	0.566	8.756	0.0104	-0.016	3.68	4.642	1.544	3.098
99.93	12	3.464	2.000	1.079	-1.155	8.328	0.0100	-0.000	0.07	4.642	0.412	4.229

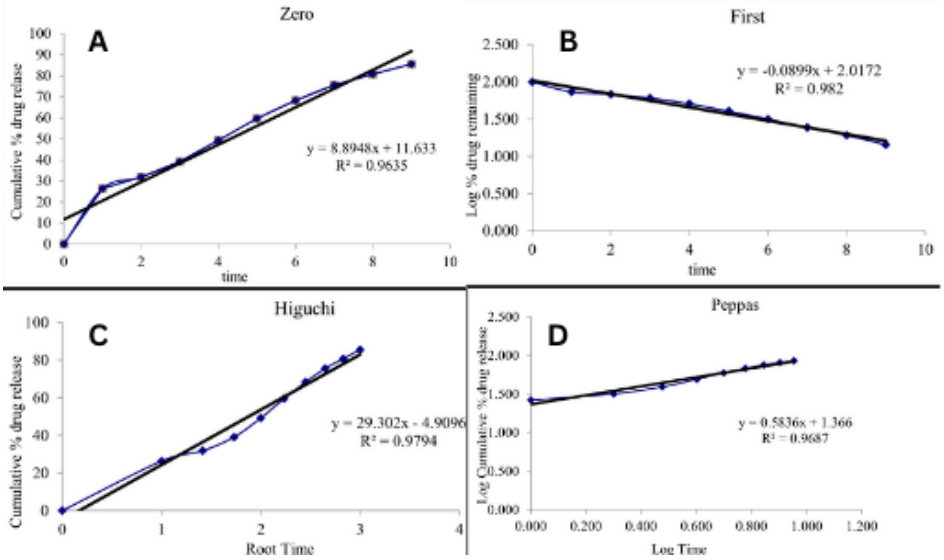

Figure-5: A-Zero order kinetics; B-First order Kinetics; C-Higuchi; D-Peppas.

Based on the data, the AH5 formulation follows zero-order kinetics, indicating that the drug release rate from this formulation is constant over time, demonstrating a steady and predictable release profile.

4. CONCLUSION

In conclusion, the successful development of mucoadhesive buccal patches containing atomoxetine hydrochloride has been achieved through a systematic formulation and evaluation process. The patches exhibited favorable physicochemical properties, including uniform thickness, optimal adhesion, and consistent drug content. Both in vitro and in vivo assessments revealed promising drug release profiles and enhanced bioavailability, indicating the potential of these patches as an effective alternative dosage form for atomoxetine hydrochloride. This study underscores the feasibility and effectiveness of mucoadhesive buccal patches in improving the therapeutic efficacy of atomoxetine hydrochloride, offering benefits such as controlled drug release, reduced dosing frequency, and enhanced patient compliance.

Conflict of Interest: Authors Declare no conflict of interest.

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