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Formulation and evaluation of amoxapine mucoadhesive buccal films

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Abstract

Among innovative drug delivery methods, buccal mucoadhesive systems have been attracting much interest recently because of their capacity to stick to the oral mucosa, stay there, and gradually release their drug content. By improving medication absorption through the oral mucosa and reducing the hepatic first-pass impact, buccal mucoadhesive films can increase the drug's bioavailability and enhance its therapeutic effect. The current study aimed to synthesize the medicine as a buccal bioadhesive film, which reduces the frequency of dosage form administration by releasing the drug at a sufficient concentration over time. Because this formulation is simple to administer and requires no water to swallow, improved patient compliance is one of its benefits. Dissolving profile as investigated in USP dissolving apparatus type 1 using saliva at pH 6.8. The impact of factors such as polymer type, concentration, and release profile of Amoxapine was investigated. The formulation was optimized Based on several evaluation criteria, including drug content and in-vitro drug release. Formulation F6 successfully releases the drug in 7 hours. The stability studies followed ICH recommendations, and the results showed that the optimized formulation was stable. The IR spectra demonstrated the stable qualities of Amoxapine in a mixture of polymers utilized and revealed the absence of interaction between the drug and the selected polymer.

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INTRODUCTION

Mucoadhesive buccal films that adhere to mucous-covered biological surfaces. Usually, there are multiple ways and dose forms to deliver medications. Despite being the preferred method of administration, drug solubility and sensitivity to first-pass metabolism are essential qualities that must exist for the drug to be absorbed by the oral route. The most painful method of administration is the parent route. Only local or topical therapy can be performed with topical medicines. Alternative delivery systems are necessary for drugs with high molecular weight,

Table 1 Formulation details of Amoxapine mucoadhesive buccal films

Formulation code	Drug (mg)	Polymer and its composition (mg)			Polyethylene glycol (mL)	Sodium saccharin (mg)	Vanillin (mg)	Distilled water (ml)
		HEC	HPMC K 100	HPC				
F1	125	200			0.1	2	2	10
F2	125	240			0.1	2	2	10
F3	125	300			0.1	2	2	10
F4	125		200		0.1	2	2	10
F5	125		250		0.1	2	2	10
F6	125		300		0.1	2	2	10
F7	125			200	0.1	2	2	10
F8	125			250	0.1	2	2	10
F9	125			300	0.1	2	2	10

limited water solubility, low skin penetration, and significant first-pass metabolism. More and more medications are being given using the mucoadhesive method [1]. Mucoadhesive drug delivery systems through the nasal, rectal, buccal, and sublingual mucosa may be a faster and more comprehensive noninvasive method of administration. Different methods are used to administer medications to prevent first-pass metabolism. Mucoadhesive administration has been shown to enhance bioavailability and speed up drug delivery. These days, a particular process is used to create buccal films that dissolve on the buccal mucosa of the patient. When compared, for example, to lozenges and tablets, films have also improved patient compliance because of their smaller size and thinner thickness. Because buccal films are a practical and patient-friendly dose form, the pharmaceutical industry has focused more on them [2].

METHODOLOGY

Preformulation Study:

Compatibility study:

FTIR Studies:

The combined FT-IR spectra of pure Amoxapine and HPMC K100, HEC, and HPC are displayed in (Figure). Principle absorption peaks were seen in pure Amoxapine at 3500- 3000 cm-1 (NH Stretch), 1600-1475 cm-1 (C=C Strech), 1350-1000 cm-1 (C-N Strech), and 900-690 cm-1 (CH bend). Without moving in the Amoxapine spectra along with the polymers, the identical peaks of NH-Stretch, C=C Stretch, N-H stretch, and CH Bend bonds were present as that of the pure drug. This implied no chemical reaction between the medication and the polymer [3].

DSC study:

The drug's thermal compatibility was tested using a DSC thermogram, as well as the physical combinations. The pure drug had a melting point of 218.22 0C, while the physical mixture of medicines containing HPMC K100 had a melting point of 215.27 0C, drugs containing HPC 216.52 0C, and drugs containing HEC 201.12 0C. The drug's melting point peak was maintained in the physical mixture without changing, suggesting that the drug and polymers are not interacting [4].

Preparation of mucoadhesive buccal film:

The solvent casting method is the preferred approach for formulating the films. The necessary polymer was added, mixed, and dissolved in distilled water. The drug's tiny amount dissolves in the solution mentioned above. Mix thoroughly after adding plasticizers to the solution above. After that, the solution was placed on the Petri plate and dried at 40° C in a hot air oven. After drying, films were cut into the appropriate form and size after being removed with a sharp knife and placed in a desiccator for 24 hours.

CHARACTERIZATION OF MUCOADHESIVE BUCCAL FILMS:

Scanning Electron Microscopy (SEM)

Using scanning electron microscopy (SEM), the Amoxapine buccal films' form and surface features were evaluated [5].

IR spectroscopy:

FTIR was used to record the IR spectra of the drug, co-former, and buccal films to identify any predictable interactions between the drug and co-former. Potassium bromide (K-Br) was combined with the co-crystals and subsequently compressed using a hydraulic press to create pellets. These pellets were then scanned at 4000 and 400 cm−1 [6].

Evaluation of Mucoadhesive Buccal Films:

Physical appearance and surface texture of films:

This parameter was verified by looking at the films and assessing the texture with the senses of touch or feel.

a. Weight uniformity of films:

A digital balance was used to weigh each of the three 2x2 cm films, and the average weights were computed [7].

b. **The thickness of films:**

Screw gauges with a minimum count of 0.01 mm were used to measure the thickness of the films at various locations. Three separate locations in the movie were used to determine their thickness, and the average was calculated.

c. Folding endurance of patches:

Film flexibility can be statistically assessed using a concept called folding endurance. A short strip of the film, measuring about two by 2 cm, was folded repeatedly at the exact location until it broke to test its folding durability. The value of folding endurance is determined by how many times a film might be folded in the same direction without breaking [8].

d. **Swelling property [9]**

A saliva simulation solution was created to test the patch's capacity to swell. The patch was first weighed and inserted into the stainless steel mesh that had been previously weighed. The artificial saliva solution was dipped into the system. Weighing the device regularly allowed us to detect the growth in patch weight. This formula was used to determine the extent of swelling:

$$Degree\ of\ swelling = \frac{Finalweight\ (Wt) - Initialweight(Wo)}{Initialweight(Wo)}$$

e. Drug content uniformity of films:

The films were subjected to a UV Spectrophotometric technique to check for uniform drug content. Two-by-two-centimeter films were cut from the cast films in three distinct locations. [10] After each film was dissolved in simulated saliva at a pH of 6.8, it was transferred to a 100 mL volumetric flask, and 5 mL was collected and diluted with water to make 10 mL. A UV/visible spectrophotometer (Shimadzu) was used to measure the absorbance of the solution at λ max 279 nm. It was established what proportion of drugs were present.

f. **Surface pH**

The patch was slightly moist from the water. The pH was determined by touching the electrode to the patch's surface. Each composition was tested using three patches, and an average was calculated [11].

g. **Moisture loss [12]**

One measure of a film's hygroscopicity is its percent moisture loss. This metric is often found by determining the film's initial weight and putting it in a desiccator for three days. The desiccator has calcium carbonate in it. The strips are removed and weighed once more after three days. Use the following formula to calculate moisture loss.

$$\%\ Moisture\ loss\ = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100$$

In Vitro Mucoadhesive Strength

The mucoadhesive strength of the mucoadhesive buccal patches was determined at room temperature using a two-arm balance with minor modifications. Fresh sheep buccal mucosa was obtained. The mucosal membrane was separated by removing underlying fat and loose tissues, obtaining a thickness of 2 mm. The membrane was then washed with distilled water and subsequently with BSpH 6.5 at 37°C.

***In-vitro* dissolution studies:**

Using USP Dissolution Testing Apparatus II at 50 RPM, the release rate of Amoxapine dissolving Buccal films was ascertained. Under 37°C temperature control, a 2x2 cm film was dissolved in 300 mL of simulated saliva with a pH of 6.8. At various times, 2 milliliters of the sample solution

were removed from this dissolving media. Whitman filter paper was used to filter the samples, and a double-beam UV-visible spectrophotometer was used to measure absorbance at 285 nm [14].

Permeation study:

The prepared mucoadhesive buccal films are placed into the diffusion cell on the donor compartment's upper membrane. The receptor compartment, which holds 20 milliliters of simulated saliva, is in contact with the dialysis membrane.

The donor compartment's upper side has a film attached to it that is two by 2 centimeters long and wide and contains 20 milligrams of medication. Additionally, the receptor compartment holds simulated saliva and a magnetic bead [15]. The diffusion compartment is situated within a magnetic stirrer, and as a result, drug permeation begins through the dialysis membrane and enters the receptor compartment. Two milliliters of this solution are required every hour to maintain the sink condition by adding two milliliters of simulated saliva to the receptor compartment. Samples are taken at each interval and examined using Shimadzu UV-visible spectra.

Permeation kinetics [16-17]

It was observed that the drug permeated the matrix systems using the diffusion mechanism and the zero-order penetration rate. The data was fitted into Peppa's model and the Zero-order First-order Higuchi matrix to examine the mechanism behind the dosage form's permeation and permeation rate kinetics. The best-fit model was chosen in this by comparing the r values that were discovered.

Zero order kinetics:

The formula for drug dissolution from pharmaceutical dosage forms that do not disintegrate and release the drug gradually assumes that the area remains unchanged and no equilibrium conditions are reached.

$Qt=Qo+Kot$

First-order kinetics:

To study the first order release kinetics the release rate data were fitted to the the following equation.

$LogQt=logQo+k1t/2.303$.

Higuchi model:

Higuchi created several theoretical models to investigate the release of medications incorporated into semisolids or solid matrices that are either water-soluble or low-soluble. Mathematical formulas were developed for drug particles distributed in a homogeneous matrix acting as the diffusion media. Furthermore, the equation was

$Qt=KH-t1/2$

Korsmeyer and Peppa's model:

To study this model the release rate data are fitted to the following equation.

$Mt/M\alpha=K.tn$

Stability studies:

Stability testing is done to show how different environmental conditions affect a drug's quality over time, resulting in varying drug substances or drug products. Stability studies were conducted following ICH recommendations to evaluate the stability of the medication and formulation. The prepared mucoadhesive buccal films were wrapped in aluminum foil for twelve weeks at 45 ± 0.5°C. The movie underwent in vitro drug release, appearance, and content testing three months later [18].

RESULTS AND DISCUSSION

Compatibility study:

FTIR Studies:

FTIR spectral analysis was used to characterize the drug and polymers to look for any physical or chemical changes to the drug's properties. The primary peaks of the Amoxapine were unchanged in the spectra of the drug-polymer mixture, indicating no interference in the functional groups, according to the data.

Preparation of mucoadhesive buccal film:

The solvent casting procedure is ideally used to formulate the films. The necessary amount of polymer was added in small amounts and thoroughly combined to dissolve in distilled water. The solution mentioned above dissolves a small amount of the drug. To the solution above, add the plasticizers and thoroughly mix.

Table 2 FTIR Spectra of Drug and Physical mixtures

Functional Group	Amoxapine	HEC	HPMC K100	HPC
OH (Alcohols)	3691.88	3632.92	2748.65	3244.38
NH (2^0 amines)	3524.99	3466.20	3020.63	3091.99
CH (Aromatic Rings)	3122.48	3138.29	3174.94	3217.37
C=C (Alkynes)	2360.95	2438.10	2332.02	2171.92

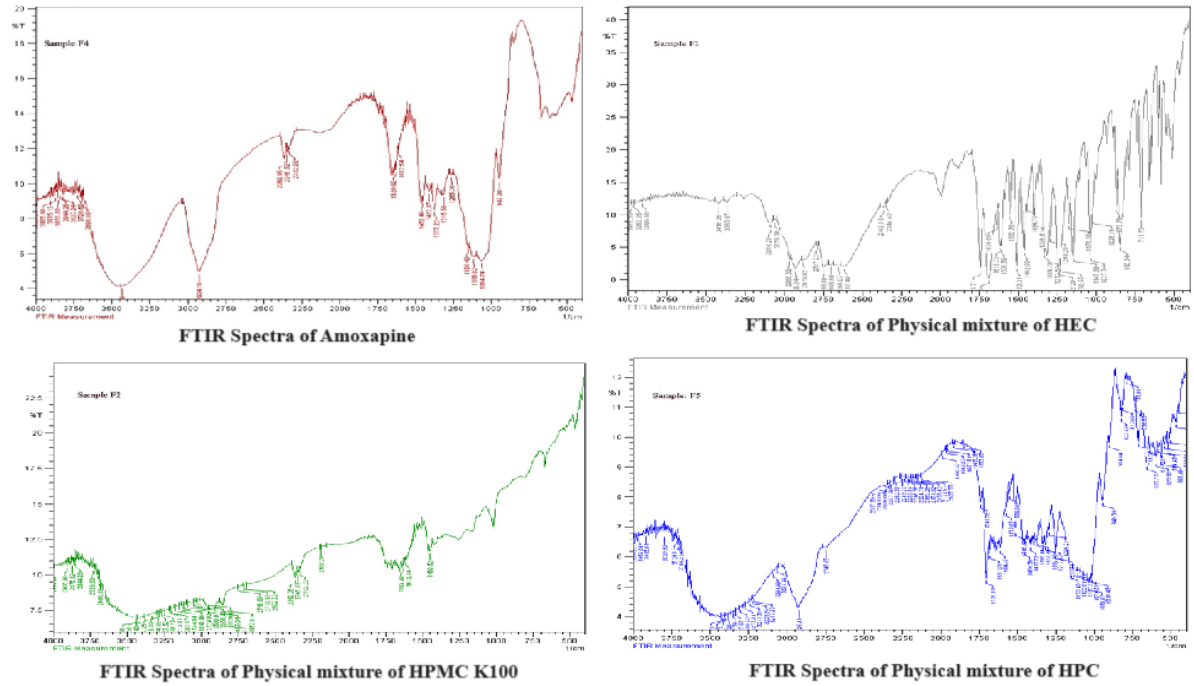

Figure 1 FTIR Spectrums drug and physical mixtures

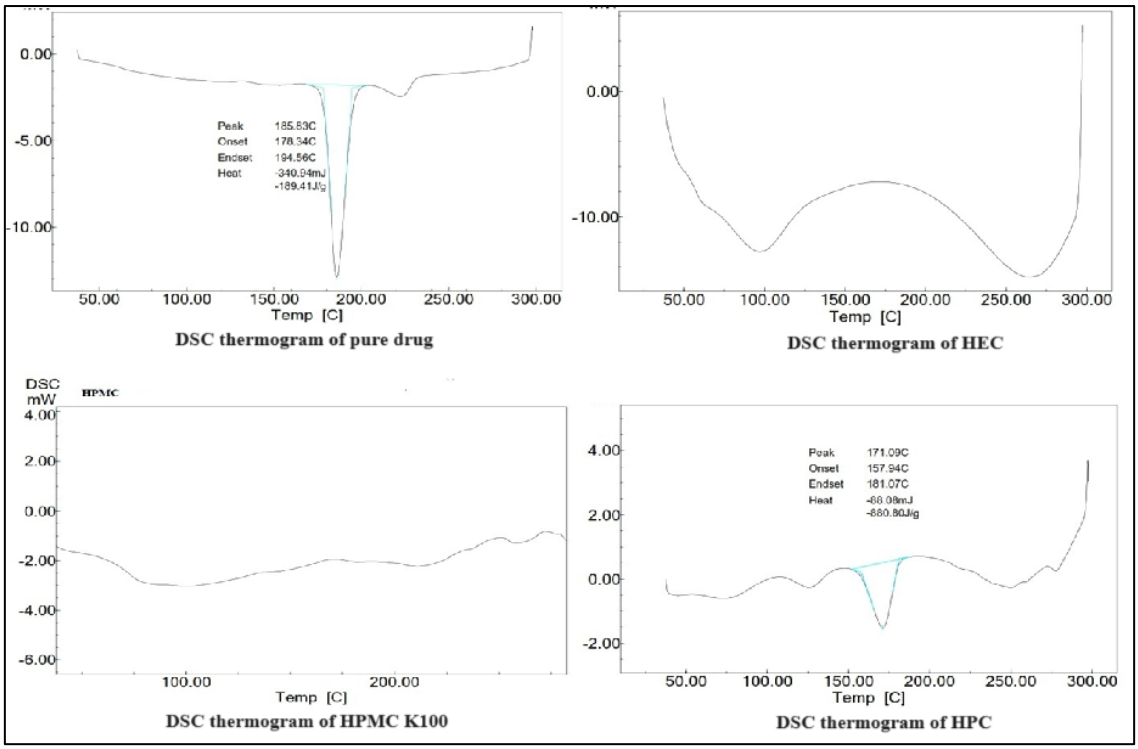

Figure 2 DSC thermograms of drug and polymer mixtures

After casting the solution onto the Petri dish, it was placed in a hot air oven set at 40° C to dry. Films were cut into the appropriate form and size after being withdrawn from the drying process using a sharp knife and placed in a desiccator for a whole day.

CHARACTERIZATION OF MUCOADHESIVE BUCCAL FILMS

ScanningElectronMicroscopy(SEM)

Microscopiccharacterizationof Buccal Films:

A light microscope observed the microscopic characteristics of prepared basal films.

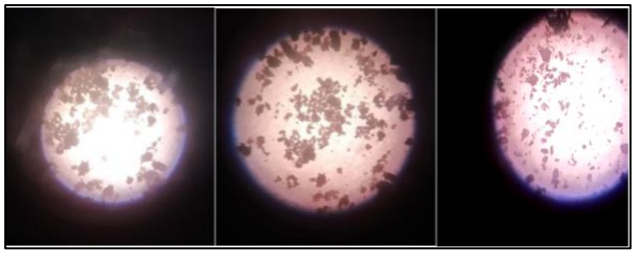

Figure 3 MicroscopicImagesofBuccal Films

Morphological characteristics of buccal films:

The shape and surface characteristics of the ofAmoxapine buccal film were assessed by scanning electron microscopy (SEM).

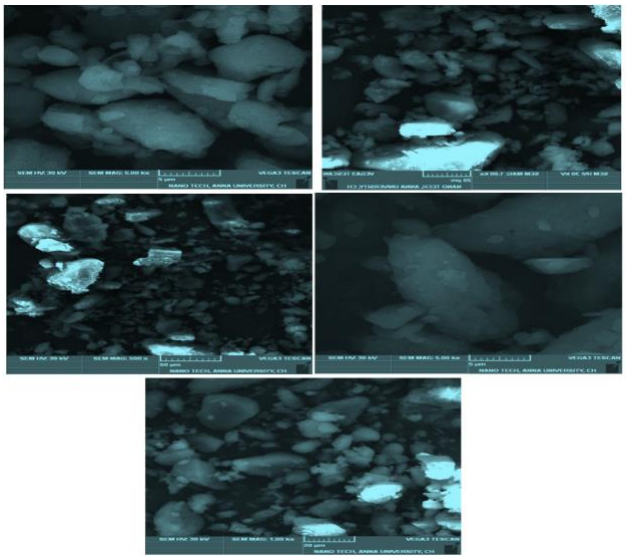

Figure 4 SEM Image of Amoxapine Buccal Films

IR-Spectroscopy:

The FTIR analysis of the pure drug and Amoxapine buccal films was prepared. IR spectra are as shown in Figure 5.

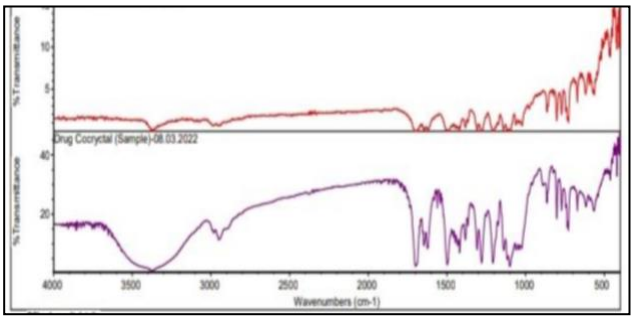

Figure 5 Comparison Between Pure Drug and Drug Buccal Film

According to FT-IR spectroscopy, Amoxapine and sorbitol conformer interacted in the buccal film production process. Specific peaks in the Amoxapine spectrum have an interaction-affected OH shift when hydrogen bonding happens between the Amoxapine and the former. There are two carbonyl groups and an amine group in the ring of Amoxapine where hydrogen bonding might occur. When this hydrogen bonding happens, there is a peak shift to lower frequencies and a drop in bond energy at the N-H or C=O bond. The N-H stretch peak at 3376.43cm-1, the C-H stretch at 2948.28cm-1, and the C=O stretch peak at 1699.72cm-1 were the locations where this peak shift was most visible. These shifting peaks could represent the likely group implicated in the sorbitol-mediated bond formation that leads to buccal film (co-crystal) synthesis.

Evaluation of Mucoadhesive Buccal Films:

Physical appearance and surface texture of films

The appearance Shows that the drug has been distributed uniformly.

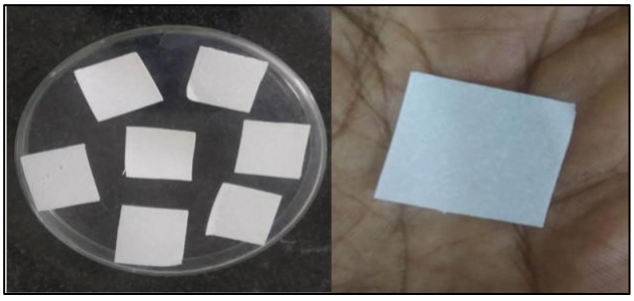

Figure 6 Images of Buccal Film

a. Weight uniformity of films:

The weight uniformity of the films is mentioned in Table 3, in which the values varied between a minimum of 42.94±0.138 to 47.94±0.142.

Table 3 Physical appearance and surface texture of buccal films

Formulation Code	Weight variation (mg)	Thickness (mm)	Folding endurance	Swelling Property	Drug Content	Surface pH	% Moisture Loss
F1	42.94± 0.138	0.13± 0.0104	334.66±1.504	6.48	92.74 ± 0.83	6.3	1.91
F2	45.06± 0.081	0.16± 0.0031	316.67±1.505	5.89	94.12 ± 1.72	6.5	3.14
F3	51.05± 0.179	0.22± 0.0034	346.62±0.508	5.48	95.44 ± 0.48	6.6	3.24
F4	41.82± 0.185	0.18± 0.0051	357.34±1.349	5.24	97.08 ± 1.24	6.6	2.38
F5	45.08± 0.288	0.14± 0.0052	345.31±0.193	5.98	95.41 ± 1.68	6.8	2.58
F6	47.56± 0.145	0.22± 0.0034	332.64±1.348	6.64	98.06 ± 1.26	6.5	2.21
F7	49.78± 0.168	0.17± 0.0032	352.12±0.332	6.22	92.08 ± 2.08	6.3	3.34
F8	51.69± 0.308	0.18± 0.0104	334.34±1.348	6.27	95.43 ± 2.05	6.6	3.34
F9	47.94± 0.142	0.21± 0.0052	322.35±1.668	6.28	96.44 ± 1.68	6.5	2.95

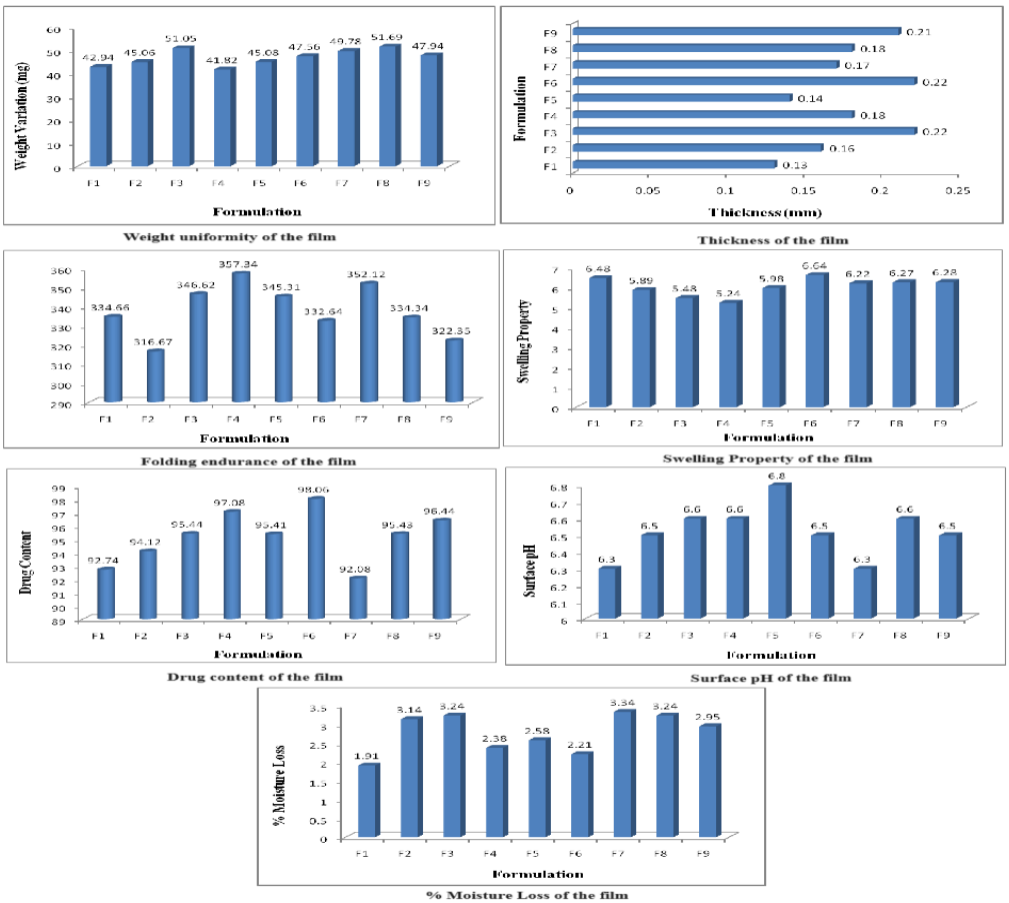

Figure 7 Physical appearance and surface texture of buccal films

b. The thickness of films:

Since the number of polymers in each formulation varies, the thickness increases progressively as the number of polymers increases. It was discovered that all of the film compositions were within the limitations and had thicknesses between 0.13±0.0104 and 0.21±0.0052 mm (Table 3).

c. Folding endurance of patches:

The mucoadhesive buccal membrane was folded repeatedly at one spot until it broke to measure the folding endurance physically. The endpoint was thought to be the breaking time. F4 had the most excellent folding endurance, while F2 had the lowest. It was discovered that an increase in carrier concentration impacted the mucoadhesive buccal films' folding durability. Because the mucoadhesive buccal films' folding endurance values were determined to be at their optimal level, they demonstrated good mechanical and physical qualities. It was discovered that the folding endurance of films ranged from 334 to 322 (Table 3).

d. **Selling property**

A saliva simulation solution was created to verify the patch's ability to swell. The stainless-steel mesh was pre-weighed before the first weight of the patch was inserted. A solution simulating saliva was dipped into the system. Periodically weighing the system allowed for observing the patch's increasing weight. The formula indicated how much of the edema was present. A mean swelling of 6.64 was discovered.

$$Degree\ of\ swelling\ = \frac{Finalweight\ (Wt) - Initialweight(Wo)}{Initialweight(Wo)} \times 100$$

e. Drug content uniformity of films:

The drug content of the produced film formulations was examined. The medication was distributed between 92.74% and 96.44% (Table 3). Implying that the drug was distributed evenly during every film.

f. Surface pH:

The patch was slightly moist from the water. The pH was determined by touching the electrode to the patch's surface. Three patches were used in the trial for each formulation, and an average was taken. The surface had a pH range of 6.3–6.5 (Table 3).

g. **Percent moisture loss**

The test aimed to determine the patch's hygroscopicity and integrity under dry conditions. Three patches measuring two by two centimeters were cut out and precisely weighed. Next, a desiccator containing fused anhydrous calcium carbonate was placed over the patch. The patches are taken off after three days, and the weight and percentage of weight reduction are computed.

In Vitro Mucoadhesive strength

Finding the mucoadhesive strength was crucial since it guarantees that the dosage form will adhere and that the drug will be delivered to the administration site. Numerous writers have detailed the direct correlation between adhesion strength and the swelling index. Because of their highest swelling indices, formulations F9 and F6 demonstrated the highest adhesion (Table 4), guaranteeing patch adherence at the administration site. After using the factorial design, the program recommended the quadratic model, which was shown to be significant. Each model term was shown to be substantial when the model p-value F" was less than 0.0007.

Table 4 : In Vitro Mucoadhesive strength data for mucoadhesive buccal films

Formulation	Mucoadhesive Strength
F1	5.7
F2	5.9
F3	7.6
F4	5.4
F5	6.7
F6	7.9
F7	6.4
F8	7.3
F9	9.5

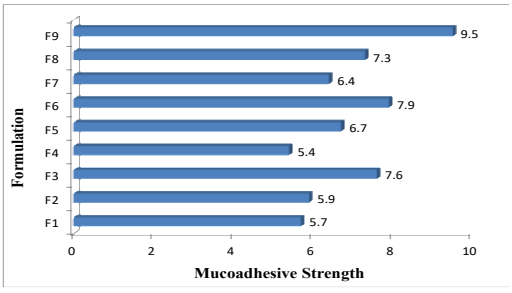

Figure 8 In Vitro Mucoadhesive strength of the film

Table 5 In-vitro release data of various Amoxapine mucoadhesive buccal films prepared using HPMC K100, HPC, HEC Cumulative % drug release from buccal films F1 to F9 prepared from HEC, HPMC K100, HPC

Formulation Code	F1	F1	F2	F3	F4	F5	F6	F7	F8	F9
15 mins	15.96	15.96	16.92	18.13	14.79	21.09	23.78	12.43	19.34	18.33
30 mins	28.08	28.08	24.08	34.14	31.98	37.03	42.98	28.46	32.45	35.43
One h	42.19	42.19	42.17	43.17	43.97	45.97	57.07	45.47	41.49	48.54
Two h	48.22	48.22	52.22	53.18	53.05	57.08	65.08	54.52	47.54	59.58
Three h	55.18	55.18	59.24	58.25	66.07	71.14	73.13	62.57	63.59	71.63
Four h	64.25	64.25	68.28	71.28	72.08	76.18	81.17	68.61	72.62	75.62
Five h	75.27	75.27	77.34	78.32	83.14	84.12	88.22	78.66	83.66	81.67
Six h	79.34	79.34	83.32	88.36	91.22	91.24	94.18	84.63	89.72	88.72
Seven h	88.37	88.37	93.37	96.08	95.17	96.17	98.26	92.73	94.68	94.67

Table 6 Permeability data of films

Formulation Code	F1	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0	0
0.5	18.74	18.74	22.86	27.23	28.33	28.52	36.24	24.86	28.08	26.53
1	33.25	33.25	36.24	44.08	44.71	46.93	52.88	42.09	46.92	42.92
2	44.08	44.08	46.92	48.88	53.96	53.84	61.69	49.91	54.74	56.73
3	49.89	49.89	54.72	59.71	63.55	64.51	74.35	58.72	62.55	66.53
4	59.71	59.71	65.54	67.52	68.48	72.36	82.17	65.54	71.38	73.32
5	67.52	67.52	75.34	77.33	74.33	77.29	87.13	69.51	73.34	82.15
6	74.35	74.35	76.33	78.29	83.16	85.13	88.97	77.32	82.18	84.13
7	76.31	76.31	85.14	87.13	85.13	87.99	91.95	81.18	83.14	88.97
8	83.16	83.16	87.98	88.99	87.98	92.95	95.78	84.13	87.96	92.98

Table 7 Percentage of drug content of optimized formulation F6 during stability studies

Trial No.	1st Day	After four weeks	After 6 weeks	After 12 weeks
I	95.21	96.31	96.95	97.14
II	97.25	96.42	97.05	97.05
III	97.22	96.42	97.12	97.17
Mean	97.22 ± 0.01	96.42 ± 0.03	97.12 ± 0.05	97.17 ± 0.04

Table 8 In vitro release data of optimized formulation F6 during stability studies

Time (hours)	% CDR			
	1 st Day	After 4 weeks	After 6 weeks	After 12 weeks
15m	25.00	21.32	23.84	23.84
30m	43.92	42.44	42.14	43.76
1h	57.92	56.03	57.84	55.88
2h	69.87	67.92	69.98	65.96
3h	78.98	76.85	78.98	74.81
4h	84.28	83.92	85.87	83.87
5h	93.11	92.54	92.89	93.52
6h	98.68	96.88	96.73	97.00

Table 9 Release kinetics of Mucoadhesive buccal films of Amoxapine (F1 to F5)

Model	F 1		F 2		F 3		F 4		F 5	
	R^2	m	R^2	m	R^2	M	R^2	m	R^2	M
Zero order	0.655	69.4	0.939	1123	0.007	15.93	0.202	72.88	0.928	1414
First order	0.494	0.061	0.540	0.067	0.257	0.038	0.352	0.044	0.438	0.062
Higuchi's Matrix	0.516	4508	0.767	7420	0.023	212.0	0.189	515.5	0.803	9618
Korsmeyer-Peppar	0.835	2.354	0.884	2.545	0.572	1.709	0.663	1.813	0.806	2.517

Table 10 Release kinetics of Mucoadhesive buccal films of Amoxapine (F6 to F8)

Model	Equation	F 6		F 7		F 8	
		R^2	m	R^2	m	R^2	M
Zero order	Mo-Mt=kt	0.917	15.49	0.949	154.4	0.932	1603
First order	InM=InMo	0.481	0.052	0.465	0.051	0.379	0.060
Higuchi's Matrix	$M_0 - M_t = kt1/2$	0.798	1057	0.848	1067	0.344	0.057
Korsmeyer-Peppar	$\log (M_0 - M_t) = \log k + n \log t$	0.835	2.032	0.827	2.033	0.910	11379

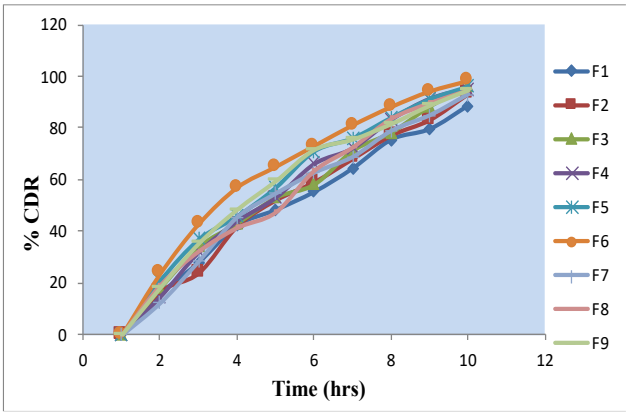

Figure 9 In-vitro release data of various mucoadhesive buccal films of Amoxapine (F1-F9)

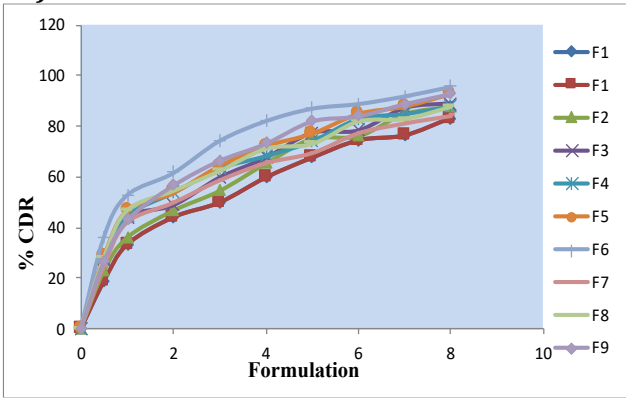

Figure 10 Permeability data of various mucoadhesive buccal films of Amoxapine

STABILITY STUDY:

Optimized formulation F6 was subjected to stability studies for 1 to 3 months. The results obtained are shown in Table 11.

Table 11 Stability studies of the optimized formulation F6

Time in hrs	Drug Content		
	F6	After 1 Month	After 3 Month
1	75.43	75.41	74.31
2	65.43	65.31	64.31
3	79.22	79.14	80.38
4	82.24	82.43	81.61
5	89.41	89.45	90.43
6	87.28	87.14	86.46
7	90.27	90.32	91.65
8	95.67	94.34	94.61
9	94.34	93.25	93.54
10	96.49	95.88	95.68
11	97.32	96.77	96.32
12	98.57	97.57	96.68

CONCLUSION:

Formulation F6, which has a polymer concentration of HPMC K100, demonstrated a better drug release rate over seven hours out of all the formulations that demonstrated acceptable quality control properties. As a result, formulation F6 was determined to be the most promising

formulation based on both the acceptable evaluation property and the in-vitro drug release rate of 98.26%. According to FTIR investigations, there doesn't seem to be any chance of interaction between the polymers of the other excipients utilized in the films and Amoxapine. DSC studies confirmed that specific polymers and drugs do not interact. According to ICH requirements, stability experiments were carried out on the optimized formulation for ninety days, and the results showed that the formulation was stable. According to the findings, the mucoadhesive buccal film created for Amoxapine may work better than the traditional dosage form, improving patient compliance and efficacy.

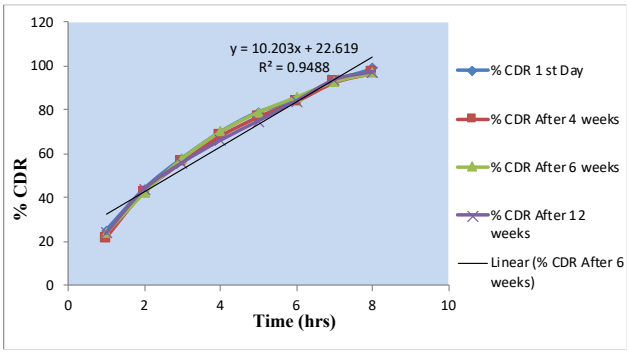

Figure 11 In vitro release data of optimized formulation F6

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