Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

Combination of Natural and Cellulose Derivative Polymers to Control Sumatriptan Succinate Release from Unidirectional Buccal Patches

SANDHYA MURALI[1,2]*, PRASANTH VV[1], SANJAY K BAIS[3]

[1] Department of Pharmaceutics, Mount Zion College of Pharmaceutical Sciences and Research. Chayalode PO Ezhamkulam, Adoor, Pathanamthitta, Kerala – 691556, India.

[2] Department of Pharmaceutical Science, Shri Jagdishprasad Jhabarmal Tibrewala University, Rajasthan, India.

[3] Department of Quality Assurance, Shri Jagdishprasad Jhabarmal Tibrewala University, Rajasthan, India.

ARTICLE DETAILS

Article history:
Received on 4 March 2024
Modified on 21 March 2024
Accepted on 25 March 2024

Keywords:
Transmucosal Drug Delivery,
Unidirectional Buccal Patches,
Mucoadhesion,
Sumatriptan Succinate,
Migraine,
Sodium Alginate.

ABSTRACT

This study aimed to develop unidirectional mucoadhesive buccal patches of sumatriptan succinate (SUS) with the aid of natural polymers by solvent casting method. The SUS mucoadhesive buccal patches were fabricated using solvent casting combined with a 3^2 factorial design. Sodium alginate was used as a base polymer with Carbapol 934P, Chitosan, Hydroxy Propyl Methyl Cellulose and Poly Vinyl Pyrollidine K- 30. Polyethylene glycol and propylene glycol were employed as plasticizers. The final patches were cut into 2 cm diameters, backed with a water-resistant membrane, and covered in aluminum foil until further research. Sumatriptan succinate muco-adhesive buccal patches had good physicochemical characteristics. Mass uniformity varied from 41.36% to 84.18% and the thickness from 0.2 mm to 0.4 mm. The drug loading efficiency varied from 6.0 to 9.2 mg, with some formulations showing folding endurance over 300. Water-soluble characteristics of PVP K-30 and Carbapol 934P affected swelling index, residence time and drug release. In this study, formulation SC11 showed maximum drug release of 99.51% at 160 min and 99 % permeation rate at 140 min. Stability experiments showed that SC11's drug content, residence time, and appearance are rarely affected. The prepared buccal patches of SUS appear to be potential formulations with respect to the physicochemical characteristics and *in vitro* evaluation data. These buccal patches may provide better bioavailability by avoiding the hepatic first-pass metabolism and provide more patient compliance.

INTRODUCTION

Oral drug administration is the most common local and systemic drug delivery method, primarily due to greater patient compliance. However, conventional oral drug delivery methods have disadvantages such as low therapeutic activity due to first-pass metabolism and consequently lower bioavailability [1]. To address this deficiency, the transmucosal route of drug delivery, i.e., drug delivery through the mucosal lining of the nasal, buccal, rectal, vaginal, ocular, and oral cavities may be preferred. Because transmucosal membranes have dense blood flow, rapid drug absorption into the systemic circulation will maximize bioavailability. Buccal drug delivery is superior to other transmucosal routes due to its ease of administration and higher patient compliance [2].

Sumatriptan succinate (SUS) is a potent triptan-class prescription drug used to treat migraines and their associated symptoms. Typically, SUS can be administered orally in dosages of 25 mg, 50 mg, and 100 mg. Orally administered SUS is rapidly but incompletely absorbed and undergoes first-pass metabolism, resulting in a low absolute bioavailability of approximately 15%. By avoiding the first-pass metabolism, SUS can be administered buccally for greater therapeutic efficacy, thereby resolving this deficiency. Additional benefits include self-administration, site accessibility, low enzymatic activity, rapid onset of action, simple drug

Author for Correspondence:
Email: sandhyam993@gmail.com

withdrawal, suitability for drugs or excipients that damage the mucosa, painless administration, low cost, and high patient compliance [3].

Therefore, the objective of the present study was to prepare and evaluate the buccal patches of SUS using various polymer combinations.

MATERIALS AND METHODS

Materials

SUS was purchased from Yarrow Chem, Mumbai (India). Sodium Alginate, Chitosan, Carbapol 934P, Poly Vinyl Pyrollidine (PVP-K30), Hydroxy Propyl Methyl Cellulose (HPMC), Poly Ethylene Glycol (PEG), Propylene Glycol (PG), and sodium saccharin were procured from SD Fine Chemicals, Bangalore (India). All chemicals and reagents used were of analytical grade.

Formulation of Mucoadhesive Buccal Patches of SUS

The solvent casting method with 3^2 factorial design prepared SUS mucoadhesive buccal patches [4]. In Table 1, various polymeric formulation combinations are listed. PEG and PG were used as plasticizers. To obtain a clear, homogenous solution, 2 mL of plasticizer was added to the polymeric solutions and continuously mixed with the homogenizer (Biochem D-160, Molbiogen, Guwahati, India) for 1 hour. The previously prepared polymer-plasticizer mixture was combined with 10 mg of SUS and sodium saccharin and then vigorously stirred until it produced a solution free of bubbles.

The mixture was carefully poured into circular dishes coated with Teflon (9.6 cm diameter). The same mixture was left to dry for 2 hours at room temperature and then dried for 36 hours in a hot air oven (Labtronics Hot Air Oven, India).These prepared patches were vacuum-dried for 4 hours at room temperature in a vacuum desiccator.

These dried patches were carefully removed from the Teflon-coated circular dishes and examined for any flaws or air bubbles. The patches were cut into 2 cm diameter pieces using a stainless steel blade cutter. On one side of the patch, a water-resistant Pidilite® BOPP backing layer was attached. This was then covered with aluminum foil and stored at room temperature in an airtight glass container for further research [5].

Evaluations

Weight Variation, Thickness, Surface pH and Folding Endurance

Five patches were chosen at random for these tests. Patches were weighed in an electronic balance for weight variation (mass uniformity) and thickness was measured using a standard screw gauge. The mean and standard deviation were then calculated. The surface pH was measured by placing the prepared patch on top of a 2 percent w/v agar plate and allowing it to swell for 15 minutes. The pH meter electrode was placed on the swollen/enlarged patch surface and allowed to equilibrate for one minute. An average of 3 readings was taken. The patch's folding endurance was tested by folding it 300 times in a row until it broke [6, 7].

Drug Content Uniformity

The formulated patches (without the backing membrane) were dissolved with gentle stirring in 10 mL of simulated saliva solution (pH 6.7). The solution mentioned above was filtered through a microfilter paper with a 0.46 µ pore size to obtain a clear, transparent solution. After dilution, the amount of SUS in the solution was determined using a UV spectrophotometer (Shimadzu 1800, Japan) at 282 nm) [8].

Swelling Studies

The patch's diameter was measured without the backing membrane. This patch was left on the agar plate's top surface and set in an incubator at 37 °C. The diameter of the swollen patch was measured using vernier scale at various intervals.

The swelling index was determined using the equation;

$$\text{SI}\ (\%) = \left(\frac{D_t - D_o}{D_o}\right) \times 100 \qquad (1)$$

Where SI (%) is the percent swelling, D_t is the diameter of the swollen patch after time *t, and* D_o is the diameter of the original patch at time zero [6].

In Vitro Residence Time (Ex Vivo Mucoadhesion Time)

With the aid of a modified USP 23 (Wrweka ZT72, Erweka, India) disintegration testing apparatus, the *in vitro* residence time (Ex vivo mucoadhesion time) was determined. The disintegration apparatus consisted of a 1000 mL beaker.

Table 1: Combinations of Various Sodium Alginate-Based SUS Buccal Patches

Formulations [a1,a2]		SA (2% m/v) mL	Cp934P (1% m/v) mL	CH (2% m/v) mL	PVP K-30 (2% m/v) mL	HPMC (2%m/v)	SUS (mg)
SC1	SD1	11.25	11.25	07.50	-	-	10.00
SC2	SD2	12.00	12.00	06.00	-	-	10.00
SC3	SD3	11.25	11.25	07.50	-	-	10.00
SC4	SD4	12.84	08.56	08.56	-	-	10.00
SC5	SD5	13.83	09.22	06.91	-	-	10.00
SC6	SD6	12.84	08.56	03.56	-	-	10.00
SC7	SD7	11.25	11.25	07.50	-	-	10.00
SC8	SD8	12.00	12	06.00	-	-	10.00
SC9	SD9	11.25	11.25	07.50	-	-	10.00
SC10	SD10	12.00	-	06.00	12.00	-	10.00
SC11	SD11	09.99	-	09.99	09.99	-	10.00
SC12	SD12	11.25	-	07.50	11.25	-	10.00
SC13	SD13	10.56	-	05.28	14.08	-	10.00
SC14	SD14	09.00	-	09.00	12.00	-	10.00
SC15	SD15	09.99	-	06.66	13.22	-	10.00
SC16	SD16	13.83	-	06.91	09.22	-	10.00
SC17	SD17	11.25	-	11.25	07.50	-	10.00
SC18	SD18	12.84	-	08.56	08.56	-	10.00
SC19	SD19	08.00	16.00	-	-	06.00	10.00
SC20	SD20	13.32	06.66	-	-	09.99	10.00
SC21	SD21	10.90	10.90	-	-	08.17	10.00
SC22	SD22	07.50	15.00	-	-	07.50	10.00
SC23	SD23	12.00	06.00	-	-	12.00	10.00
SC24	SD24	10.00	10.00	-	-	10.00	10.00
SC25	SD25	06.66	13.32	-	-	09.99	10.00
SC26	SD26	10.00	05.00	-	-	15.00	10.00
SC27	SD27	08.56	08.56	-	-	12.84	10.00
SC28	SD28	03.75	15.00	-	11.25	-	10.00
SC29	SD29	05.45	08.17	-	16.35	-	10.00
SC30	SD30	06.00	06.00	-	18.00	-	10.00
SC31	SD31	04.28	17.12	-	08.56	-	10.00
SC32	SD32	06.66	09.99	-	13.32	-	10.00
SC33	SD33	07.50	07.50	-	15.00	-	10.00
SC34	SD34	04.28	17.12	-	08.56	-	10.00
SC35	SD35	06.66	09.99	-	13.32	-	10.00
SC36	SD36	07.50	07.50	-	15.00	-	10.00

* [a1] SC1- SC36: PEG taken as plasticizer (2mL); SD1- SD36: PG taken as a plasticizer (2mL).

* [a2] Total volume of polymeric solution was 30 mL without plasticizer and drug solution.

SA: Sodium Alginate; Cp934P: Carbapol; CH: Chitosan; PVP K-30: Poly Vinyl Pyrrolidine K-30; HPMC: Hydroxy Propyl Methyl Cellulose; SUS: Sumatriptan Succinate; PG: Propylene Glycol; PEG: Poly Ethylene Glycol.

A pH 6.7 simulated saliva solution (800 mL) was added, and the temperature was maintained at 37°C. A small (2×2 cm) piece of the prepared patch was cut and attached to a porcine mucosa (3cm).This mucosa was attached to a glass slide in a vertical position using cyanoacrylate glue and kept suspended in a beaker containing phosphate buffer (PH 6.7). The motor moved upward and downward after being turned on, and the time taken for the patch to separate from the porcine mucosa was determined. This

experiment was run simultaneously on 6 different patches [9].

In Vitro Drug Release Study

The USP 23 Type II dissolution apparatus performed the *in vitro* drug release (rotating paddle type, eight-station dissolution test apparatus, EDT- 08Lx, Electrolab, India).The temperature was kept at 37.5°C. In a cylindrical vessel with a 1000 mL capacity, 900 mL of dissolution medium with a pH of 6.7 was introduced. Subsequently, a 2 cm diameter patch was affixed to a glass slide using cyanoacrylate glue and positioned within the cylindrical vessel. The paddle was set in motion at 50 rpm through a movable shaft. At appropriate time intervals (5, 10, 15, 30, 45, 60, 90, 120, 140, and 160 minutes), samples (5 mL) were taken out of the cylinder and replaced with the same amount of fresh buffer solution (dissolution medium).These samples were filtered using micro filter paper with a pore size of 0.46 m, and the amount of SUS released from the patch was assessed using a UV spectrophotometer (Shimadzu 1800, Japan) at 282 nm after the proper dilution. The drug release mechanism was determined by identifying the optimal fit of the release data to the Higuchi and Korsmeyer-Peppas plots [10].

Mechanism of Drug Release

Discussing the drug release kinetics from buccal patches using various mathematical models may be helpful. The best fit of the release data to Higuchi was found to determine the kinetics of SUS release from buccal patch formulations. This model explains drug release as a square root time-dependent diffusion process based on Fick's law and can be used to explain drug dissolution from various pharmaceutical dosage forms with modified release.

$$Q = {}_tKH\sqrt{t} \quad (2)$$

Under some experimental conditions, the release mechanism deviates from Fick's equation and exhibits non-Fickian anomalous behavior. For these situations, a more general equation can be applied. A straight forward, semi-empirical model linking the drug release exponentially to the passing of time was developed by Korsmeyer et al. in 1983.

$$\frac{Q_t}{Q_\infty} = Kt^n \quad (3)$$

Qt/Qα is the portion of the drug released at time t; K is a constant comprising the structural and geometric characteristics of the formulation, and n, the release exponent, is a parameter that depends on the release mechanism and is thus used to characterize it. Peppas employed this n value to describe various release mechanisms [11].

In Vitro Permeation Studies

The amount of drug that permeated through the porcine buccal mucosa was measured in the permeation study using the Franz diffusion cell apparatus. Used within 2 hours of the slaughter, porcine buccal mucosa was obtained from the slaughter house. The necessary mucosal epithelium was removed from the tissue and fixed between the donor and receptor chambers of the Franz diffusion cell for permeation studies. The donor compartment received the necessary amount of simulated saliva solution, while the receptor compartment received the necessary amount of PBS. The prepared patch was applied to the donor compartment's mucosal surface and stirred ferociously with a magnetic stirrer. At 5, 10, 15, 30, 45, 60, 90, and 120 minutes, 2 mL of samples were removed for further analysis and replaced with an aliquot of fresh medium [12].

Accelerated Stability Studies and Stability in Human Saliva

To test the stability of some patches, aluminum foil was placed over them in glass Petri dishes. The patches were then placed in a stability chamber at an accelerated temperature (40±0.5 °C and 75±5 % RH) for 6 months. All of the chosen formulations' drug content, mucoadhesion time, surface pH, and changes in appearance were evaluated after 1, 2, 3, 4, and 6 months. Next, find the average of the 3 determinations. Additionally, the chosen formulations were tested in adults with healthy saliva. The patches were kept in 5 mL of saliva, kept at a temperature of 37± 0.2 °C and their drug content and appearance were monitored over time [13].

Histopathological Evaluation of Buccal Mucosa

Porcine buccal mucosa was incubated in phosphate buffer saline solution (pH 6.7) was compared with the treated buccal patch for 2 h. The buccal mucosa was fastened with 10% formalin, frequently processed and fixed firmly in paraffin. These paraffin segments were cut on glass slides and stained with suitable dyes (hematoxylin and eosin). An expert pathologist

blinded to the investigation to find out any injury or destruction to tissue at Dianova Laboratories, Kottayam, Kerala, India [13].

FTIR Spectral Studies

FTIR spectrometer was used to record the FTIR spectra of the optimized formulation (SC11) (Alpha E Bruker ATR Module).The potassium bromide disk method was employed to analyze the sample and scan for absorbance [14].

Differential Scanning Calorimetry

Utilizing a differential scanning calorimeter, DSC thermal analysis of the improved formulation (SC11) was carried out to examine the drug-polymer interaction (DSC Q100, TA instruments Inc. USA).The optimized sample was kept in sealed, non-hermetic aluminum pans and heated at a rate of 10°C/min in the 25-200°C temperature range [15].

X-Ray Diffraction Studies

A specific amount of the optimized formulation was applied to a copper target at a voltage of 40 kV and a current of 30 mA, and an X-ray diffraction (XRD) pattern of the optimized formulation (SC11) was recorded. The scanning was done over 2° θ range of 10–80° [14, 15].

RESULTS

Evaluation of Mucoadhesive Buccal Patches

Using natural polymers and solvent casting method, 72 formulations of SUS mucoadhesive buccal patches were developed with the help of a 3^2 factorial design. For SUS buccal patches, tests were conducted on various physiochemical characteristics including mass uniformity, film thickness, folding endurance, drug content, drug loading efficiency and surface pH. Table 2 provides information on physiochemical properties.

The mass uniformity of the prescribed patches was in the range of 69 to 87 %. The thickness of patches ranged from 0.2 to 0.4 micrometers. Additionally, the developed patches demonstrated superior folding endurance that exceeded a value of >300. The current patch had a drug content ranging between 6.6±0.4 mg to 9.3±0.6 mg. Determining the surface pH for all patches yielded values ranging from 5.9 to 7.2.

Out of 72 formulations, eight patches (SC3, SC11, SC21, SC31, SD5, SD14, SD22, and SD30) showed good physicochemical properties and folding endurance of more than 300. These 8 patches were evaluated further for swelling index, *in vitro* residence time, *in vitro* drug release, histopathology studies and accelerated stability studies and were considered as optimized formulations.

Swelling Studies

The swelling characteristics of optimized SUS buccal patches are represented in Fig. 1.

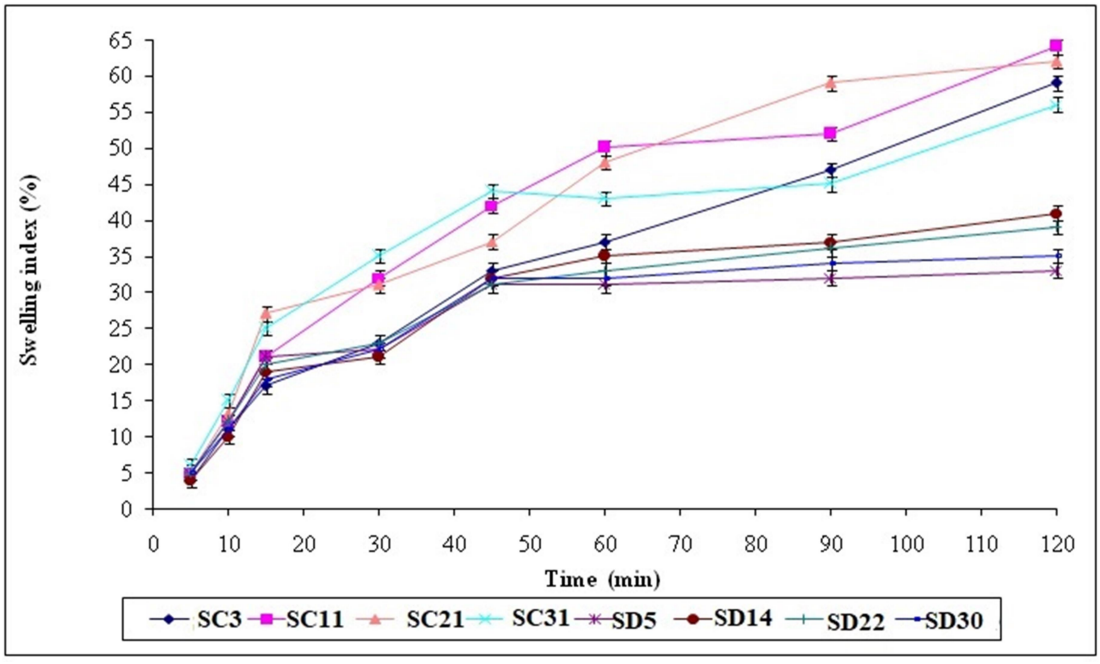

Figure 1: Swelling characteristics of Sodium alginate Based SUS Buccal Patches

Table 2: The Physico-chemical Characteristics of Sodium Alginate-Based SUS Buccal Patches

Formulation code	Mass uniformity (%)	Film thickness (mm±SD)	Folding endurance (times)	Drug content (mg±SD)	Drug loading efficiency (%)	Surface pH
SC1	82.44±5.9	0.3±0.001	210	7.8±0.3	78	6.4
SC2	80.03±6.2	0.4±0.003	215	8.0±0.2	80	6.2
SC3	86.62±3.4	0.3±0.002	**>300**	8.9±0.1	89	6.7
SC4	83.14±7.0	0.3±0.005	174	9.3±0.6	93	7.0
SC5	80.22±5.3	0.4±0.002	183	8.4±0.7	84	6.6
SC6	75.63±6.0	0.3±0.003	157	7.0±0.2	70	6.3
SC7	84.18±2.7	0.4±0.004	168	8.4±0.4	84	6.2
SC8	80.63±6.4	0.3±0.002	205	8.6±0.5	86	7.0
SC9	81.53±4.9	0.3±0.004	200	7.3±0.4	73	7.3
SC10	82.31±3.3	0.4±0.004	185	7.9±0.4	79	6.8
SC11	85.44±6.4	0.4±0.001	**>300**	9.2±0.3	92	6.6
SC12	83.20±5.6	0.4±0.005	192	8.9±0.7	89	6.1
SC13	81.03±3.7	0.4±0.003	185	8.7±0.3	87	6.9
SC14	83.51±5.6	0.4±0.005	195	7.9±0.3	79	6.6
SC15	86.45±1.9	0.3±0.004	173	8.8±0.1	88	6.4
SC16	80.14±2.0	0.3±0.003	165	8.6±0.4	86	5.9
SC17	83.23±3.8	0.2±0.002	170	7.8±0.3	78	6.3
SC18	81.55±4.9	0.2±0.001	165	7.7±0.7	77	6.6
SC19	87.42±5.4	0.3±0.006	175	8.7±0.2	87	6.6
SC20	83.23±5.7	0.3±0.003	180	8.3±0.3	83	6.9
SC21	86.65±6.4	0.2±0.003	**>300**	9.0±0.4	90	6.8
SC22	80.45±6.9	0.3±0.003	190	9.0±0.4	90	6.0
SC23	84.22±7.0	0.3±0.001	185	8.5±0.2	85	6.3
SC24	83.41±2.9	0.2±0.003	165	8.1±0.2	81	6.1
SC25	83.05±5.3	0.4±0.002	215	6.8±0.4	68	6.4
SC26	86.14±2.4	0.2±0.003	167	8.2±0.5	82	6.8
SC27	84.26±6.7	0.3±0.005	186	7.8±0.3	78	6.4
SC28	84.25±5.3	0.2±0.002	160	6.7±0.5	67	6.6
SC29	83.25±2.4	0.2±0.003	163	6.9±0.3	69	7.0
SC30	86.60±4.1	0.2±0.003	160	8.6±0.7	86	6.8
SC31	80.24±6.6	0.4±0.002	**>300**	8.8±0.6	88	6.8
SC32	85.13±6.1	0.3±0.004	180	8.7±0.5	87	6.9
SC33	82.32±5.6	0.2±0.003	185	8.0±0.6	80	6.4
SC34	81.66±3.2	0.3±0.005	169	8.2±3.4	82	5.9
SC35	80.75±2.1	0.4±0.001	179	7.9±5.6	79	6.6
SC36	82.22±3.6	0.2±0.004	163	8.0±3.3	80	6.1
SD1	75.66±6.0	0.3±0.001	184	7.7±0.3	77	6.7
SD2	71.23±5.5	0.4±0.002	195	7.8±0.4	78	6.4
SD3	71.06±4.6	0.3±0.003	180	8.0±0.4	80	6.2
SD4	72.43±2.7	0.2±0.003	171	8.1±0.3	81	6.6
SD5	77.54±6.4	0.4±0.003	**>300**	7.9±0.5	79	6.8
SD6	75.25±5.3	0.4±0.003	217	6.9±0.6	69	6.1
SD7	76.59±6.1	0.3±0.001	185	8.1±0.5	81	6.4
SD8	77.32±4.5	0.4±0.002	196	7.4±0.7	74	7.1
SD9	73.62±4.3	0.4±0.003	205	7.7±0.3	77	6.8

Continued……

SD10	73.45±2.9	0.2±0.001	178	8.1±0.3	81	7.2
SD11	76.32±3.8	0.3±0.003	168	7.9±0.6	79	6.2
SD12	75.55±2.7	0.4±0.002	192	6.6±0.4	66	6.8
SD13	73.45±6.9	0.2±0.003	177	8.8±0.6	88	6.5
SD14	78.21±6.4	0.4±0.003	**>300**	9.2±0.4	92	6.6
SD15	76.45±5.2	0.2±0.002	166	7.9±0.2	79	6.7
SD16	70.41±5.0	0.4±0.002	195	8.6±0.4	86	6.0
SD17	70.46±4.7	0.2±0.002	160	7.9±0.6	79	5.9
SD18	73.33±3.9	0.4±0.005	182	7.9±0.4	79	6.0
SD19	75.21±5.6	0.3±0.002	176	8.5±0.4	85	6.6
SD20	76.01±5.7	0.4±0.001	210	8.1±0.1	81	6.2
SD21	75.32±6.9	0.3±0.002	175	8.9±0.1	89	6.5
SD22	77.65±3.4	0.4±0.002	**>300**	8.9±0.6	89	6.7
SD23	73.22±6.4	0.3±0.002	175	7.6±0.5	76	6.4
SD24	73.25±2.1	0.4±0.002	199	7.9±0.3	79	5.9
SD25	74.36±2.4	0.2±0.003	170	8.3±0.1	83	6.1
SD26	75.22±3.5	0.3±0.002	176	6.8±0.6	68	6.4
SD27	73.35±3.7	0.2±0.003	160	7.7±0.3	77	5.9
SD28	71.25±4.6	0.3±0.001	166	7.9±0.2	79	6.3
SD29	75.32±6.3	0.4±0.002	180	8.1±0.4	81	6.5
SD30	76.53±3.4	0.4±0.001	**>300**	8.9±0.4	89	6.7
SD31	75.63±5.7	0.3±0.002	172	6.7±0.4	67	6.4
SD32	71.21±3.9	0.2±0.001	166	7.1±0.3	71	6.9
SD33	70.55±2.6	0.2±0.004	165	7.0±0.5	70	6.6
SD34	73.45±1.2	0.3±0.004	167	7.7±0.4	77	6.4
SD35	69.95±2.3	0.3±0.006	162	7.3±0.2	73	5.9
SD36	70.56±4.5	02±0.004	166	7.5±0.5	75	7.0

*Mean ± SD, *n* = 3

As a result of the presence of PVP- K30 and Carbapol 934P, a highly water-soluble polymer and high PEG water uptake, SC11 exhibits high swelling behaviour (64±1%) at 120 min compared to patches with PG, patches with PEG plasticizer produce more swelling character. Due to the polymer matrix's resistance to the movement of water molecules, SD5 exhibits the least swelling property (33±2%) when compared to SC3 (59±2%), SC21 (62±3%), SC31 (56±1%), SD14 (41±4%), SD22 (39±2%), and SD30 (35±4%) [16].

In Vitro Residence Time (Ex Vivo Mucoadhesion Time)

The results for *In vitro* residence time for optimized SUS buccal patches are mentioned in Table 3.

The residence time values ranged from 105 to 129 minutes.

Table 3: *In Vitro* Residence Time for Sodium Alginate-Based SUS Buccal Patches

Formulations	Mucoadhesion Time (min)
SC3	116±3
SC11	129±2
SC21	121±3
SC31	109±4
SD5	105±1
SD14	125±4
SD22	120±3
SD30	112±2

*Mean ± SD, *n* = 3

In Vitro Drug Release Study

The hydrophilic polymers' capacity to absorb water may factor in how quickly each buccal patch formulation dissolves, which may affect how quickly SUS is released. Fig. 2 shows the drug's *in vitro* release from particular patches.

Initially, each patch of SUS demonstrated a slow rate of drug release. After 45 minutes, the rate of drug release significantly increased with respect to time. The formulation SC11 demonstrates a significant drug release (97.21%) at 120 minutes, sustained until 140 minutes and reaches its maximum drug release of 99.51% at 160 minutes. SC21 demonstrates maximum drug release (97.51%) after 160 minutes. The formulations SC3, SC31, SD5, SD14, SD22, and SD30 have maximum drug release rates of 96.80%, 95.52%, 94.13%, 98.45%, 96.19%, and 95.15%, respectively. Based on the Higuchi and Korsmeyer-Peppas equation kinetics, the *in vitro* drug release was described. Each model's release rates k and n were determined using linear regression analysis in Microsoft Excel 2003. Correlation coefficients (r^2) were employed to evaluate the fit's precision. The r^2, k, and n values are given in Table 4.

Considering the r^2 values for the Higuchi and Peppas kinetic models, all the selected formulations fit the Higuchi model well.

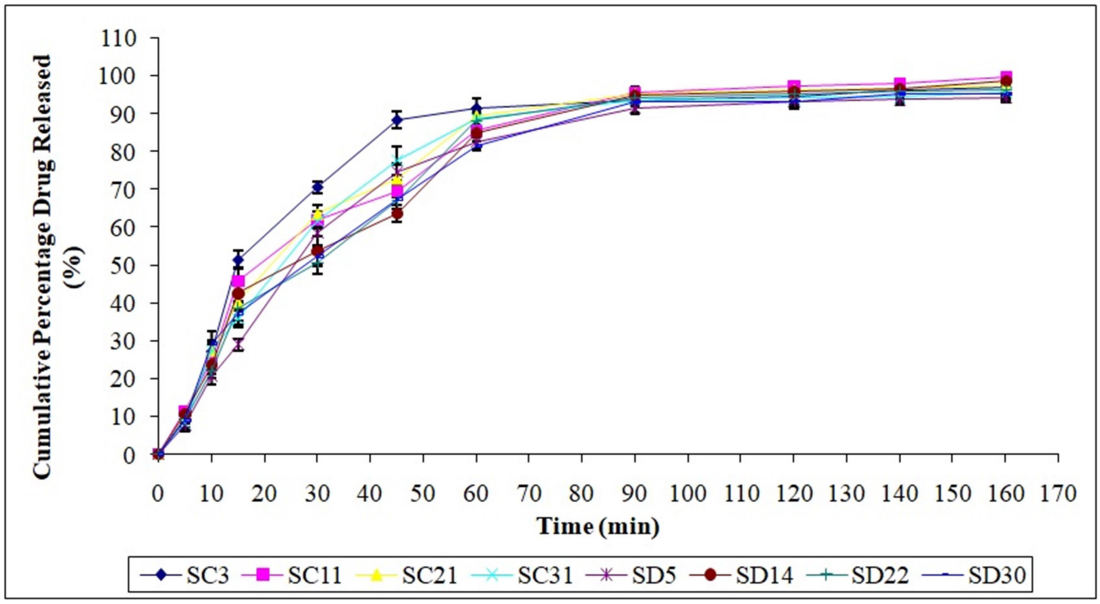

Figure 2: *In Vitro* Drug Release of Sodium alginate-Based SUS Buccal Patches

Table 4: R^2, *k* and *n* values of selected Sodium alginate-Based Buccal Patches of SUS

Formulations	Higuchi			Korsmeyer-Peppas			Mechanism of drug release
	R^2	y	k ($min^{-1/2}$)	R^2	y	n	
SC3	0.849	y = 10.34x + 3.206	10.34	0.803	y = 0.584x - 1.160	0.584	Higuchi
SC11	0.929	y = 10.76x - 2.050	10.76	0.890	y = 0.570x - 1.151	0.570	Higuchi
SC21	0.911	y = 10.68x - 1.507	10.68	0.880	y = 0.583x - 1.174	0.583	Higuchi
SC31	0.896	y = 10.59x - 2.072	10.59	0.861	y = 0.631x - 1.269	0.631	Higuchi
SD5	0.909	y = 10.73x - 5.731	10.73	0.898	y = 0.679x - 1.379	0.679	Higuchi
SD14	0.941	y = 10.79x - 4.429	10.79	0.912	y = 0.593x - 1.210	0.593	Higuchi
SD22	0.927	y = 10.87x - 5.521	10.87	0.906	y = 0.635x - 1.290	0.635	Higuchi
SD30	0.937	y = 10.47x - 3.546	10.47	0.888	y = 0.595x - 1.223	0.595	Higuchi

In Vitro Drug Permeation Study

Fig. 3 depicts the *in vitro* drug permeation study results.

The drug permeation exhibits a similar pattern to its *in vitro* drug release. The formulation SC11 achieves its maximum permeation rate (99%) at 140 minutes and maintains it until 160 minutes. The formulation SC21 provides 98% drug permeation after 140 minutes, whereas other formulations (SC3, SC31, SD5, SD14, SD22, and SD30) provide 97 to 98% at 160 minutes. This study observed a strong correlation between *in vitro* drug release and *in vitro* drug permeation.

This is how the R^2 value (correlation coefficient) was determined between *in vitro* drug release and *in vitro* drug permeation. The formulation SC3 indicates 0.841, SC11 indicates 0.927, SC21 indicates 0.910, SC31 indicates 0.910, SD5 indicates 0.911, SD14 indicates 0.939, SD22 indicates 0.925 and SD30 indicates 0.939. The correlation between *in vitro* drug release and *in vitro* permeation was studied and plotted in Fig. 4a and 4b.

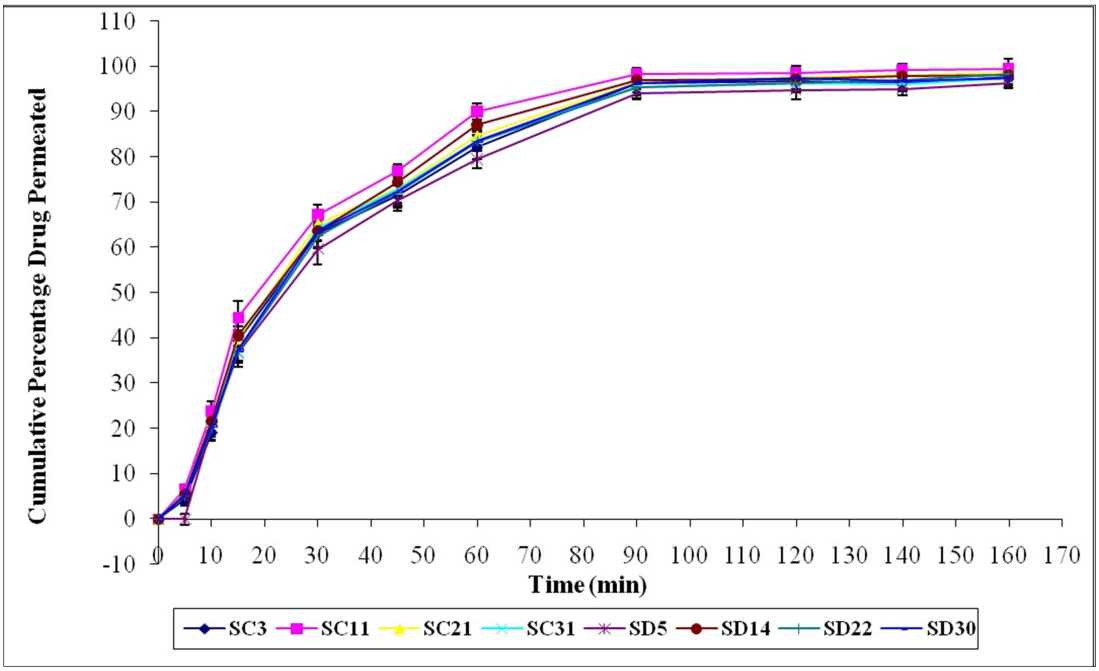

Figure 3: The permeation characters of SUS Buccal Patches

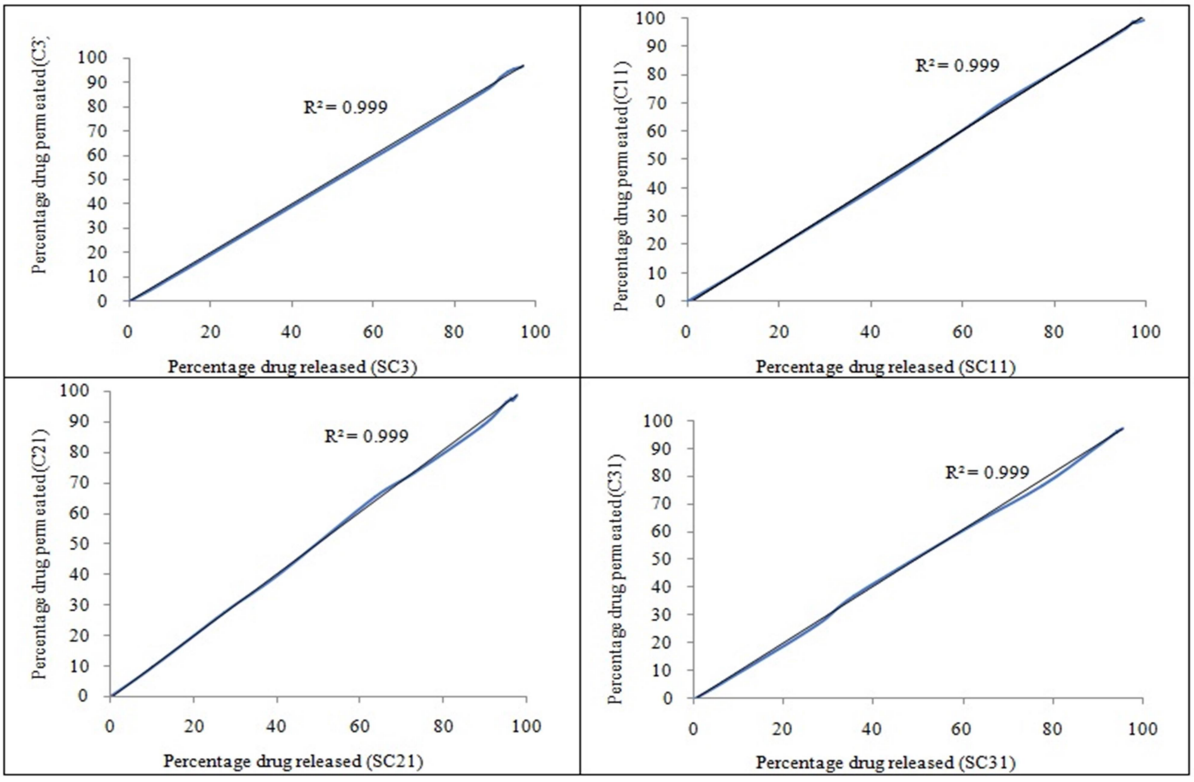

Figure 4a: Correlation between *in vitro* drug release *in vitro* drug permeation of optimized patches (SC3, SC11, SC21 and SC31).

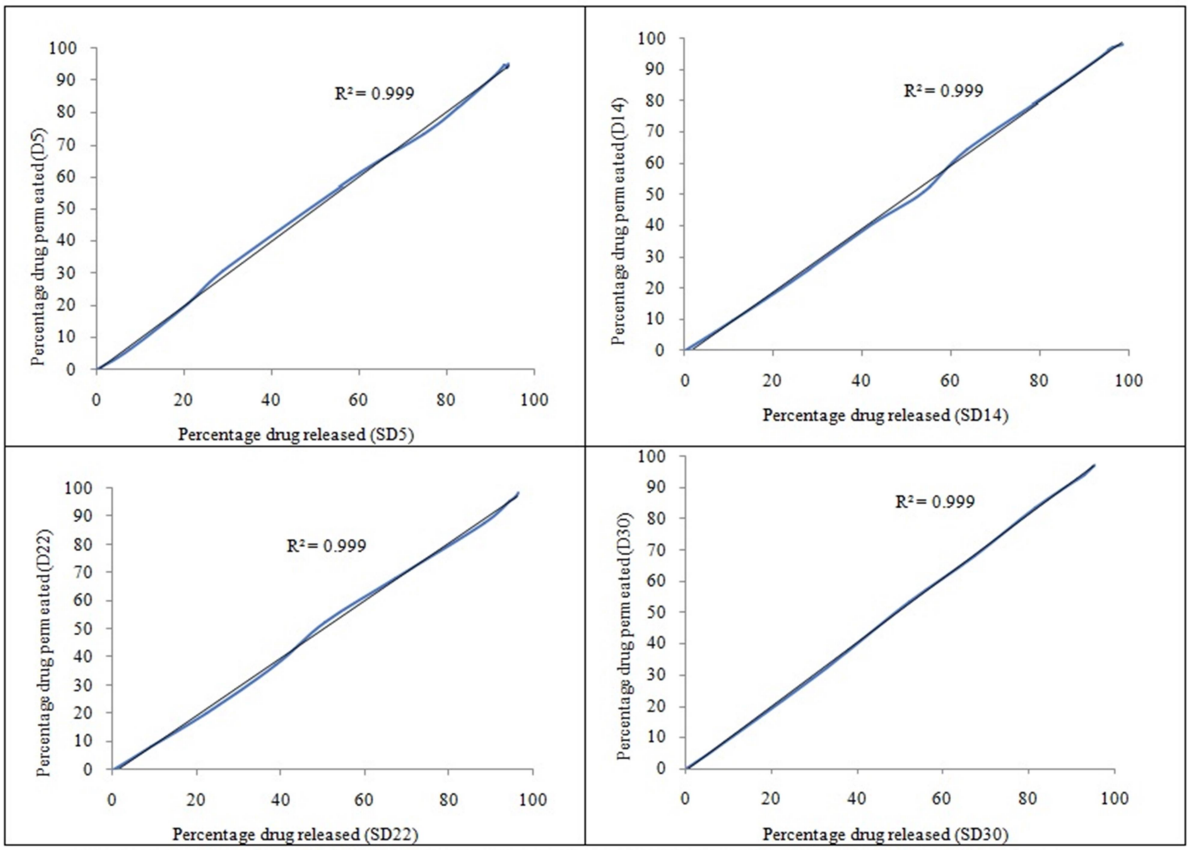

Figure 4b: Correlation between *in vitro* drug release *in vitro* drug permeation of optimized patches (SD5, SD14, SD22 and SD30).

Accelerated Stability Studies

Stability studies were carried out for selected patches for 6 months and mentioned in Table 5.

In accelerated temperatures (40±0.5°C and 75 ± 5% RH), selected patches show very few fluctuations in drug content, residence time, and appearance due to the slight degradation of polymers. Stability in human saliva was also performed, and slight changes in appearance were observed. Drug content and residence time are in the range between 7.6±0.5 mg to 9.1±0.4 mg and 102±3 to 125 ±6, respectively. The surface pH of selected formulations was at a satisfactory level.

Histopathological Evaluation of Buccal Mucosa

The microscopic examinations of porcine buccal mucosa (both treated and non-treated) indicated that no remarkable effect observed on microscopic structure of mucosa. Also no cell necrosis was seen (Fig. 5a and 5b).

FTIR Spectral Studies

The FTIR spectrum of the selected formulation (SC11) was collected using the potassium bromide (KBr) disk method (Fig. 6).

The spectrum exhibits distinct peaks within the range of 500 to 3500 cm^{-1}, which encompass the following notable features: a peak at 3439 cm^{-1} corresponding to aliphatic primary amine, a peak at 1704 cm^{-1} indicative of hydrocarbons (specifically alkane, alkene, and CH bond), and a peak at 1233 cm^{-1} associated with the sulfonyl group.

Differential Scanning Calorimetry

DSC thermal analysis of optimized formulation (SC11) was done to check the crystallization and presented in Fig. 7.

The purpose of DSC analysis was to investigate whether any alterations in the inherent melting point occur throughout the formulation process, potentially impacting the drug's stability. The thermogram of pure SUS exhibits a distinct endothermic peak at a temperature of 169.55°C. The thermographic image of the chosen formulation, SC11, shows the peak at 168.64°C.

Table 5: Accelerated Stability Study of Sodium Alginate-Based SUS Buccal Patches

Evaluation parameter	Formulation code	1st month	2nd month	3rd month	5th month	6thmonth
Drug content (mg)*	SC3	8.8±0.4	8.8±0.5	8.7±0.6	8.6±0.5	8.5±0.4
	SC11	9.1±0.5	9.1±0.6	9.0±0.6	9.0±0.5	8.9 ±0.5
	SC21	8.9±0.6	8.9±0.5	8.9±0.4	8.9±0.6	8.8±0.6
	SC31	8.7±0.5	8.7±0.6	8.6±0.6	8.5±0.4	8.5±0.5
	SD5	7.8±0.6	7.8±0.6	7.7±0.6	7.6±0.6	7.6±0.5
	SD14	9.1±0.4	9.1±0.6	9.1±0.5	8.9±0.4	8.9±0.4
	SD22	8.8±0.6	8.8±0.4	8.6±0.6	8.6±0.5	8.5±0.6
	SD30	8.8±0.5	8.8±0.6	8.7±0.5	8.7±0.6	8.6±0.5
Residence time (min)*	SC3	116±3	116±6	114±3	114±6	113±6
	SC11	129±2	129±6	128±5	127±6	125±6
	SC21	121±3	121±6	121±5	120±4	120±5
	SC31	109±4	109±6	106±5	106±6	104±5
	SD5	105±1	105±6	103±6	103±5	102±3
	SD14	125±4	125±6	124±6	124±3	123±6
	SD22	120±3	120±5	119±5	119±6	118±3
	SD30	112±2	112±3	111±6	111±4	110±6
Surface pH	SC3	6.7	6.7	6.7	6.6	6.6
	SC11	6.6	6.6	6.7	6.6	6.5
	SC21	6.8	6.8	6.6	6.7	6.6
	SC31	6.8	6.8	6.7	6.5	6.5
	SD5	6.8	6.8	6.8	6.6	6.5
	SD14	6.6	6.6	6.5	6.5	6.4
	SD22	6.7	6.7	6.6	6.6	6.7
	SD30	6.7	6.8	6.8	6.6	6.7
Stability in Human Saliva						
Appearance	SC3	No change	No change	No change	No change	Change
	SC11	No change	No change	No change	No change	No change
	SC21	No change	No change	No change	No change	No change
	SC31	No change	No change	No change	No change	Change
	SD5	No change	No change	No change	No change	Change
	SD14	No change	No change	No change	No change	No change
	SD22	No change	No change	No change	No change	Change
	SD30	No change	No change	No change	No change	Change

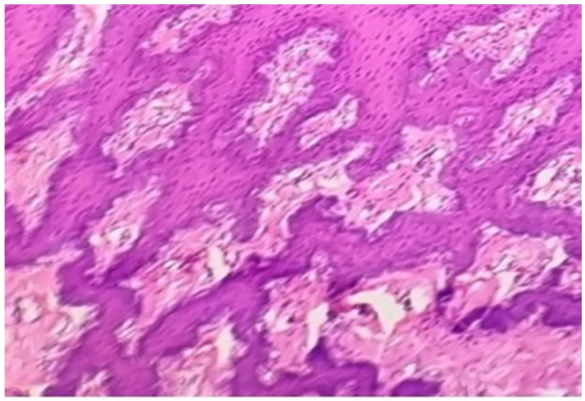

Figure 5a: Porcine buccal mucosa treated with phosphate buffer (pH 6.7)

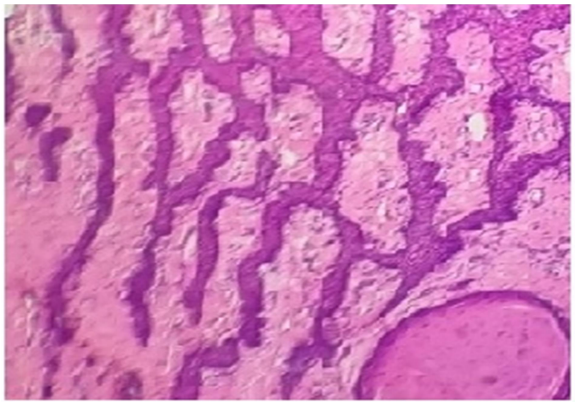

Figure 5b: Porcine buccal mucosa treated with patch

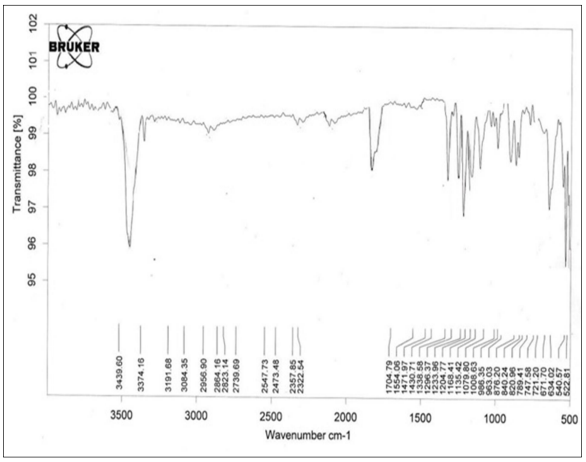

Figure 6: The FTIR spectra of the selected formulation SC11

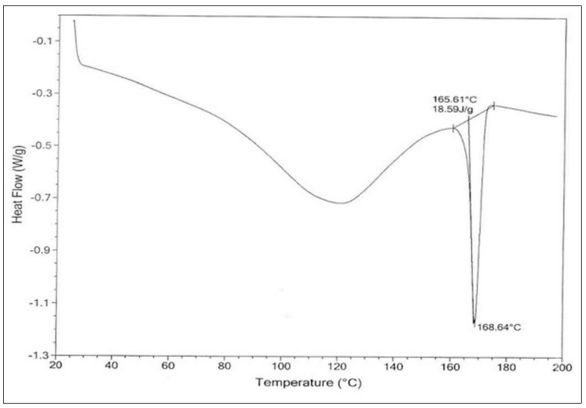

Figure 7: DSC thermal analysis of selected formulation SC11

XRD Studies

The XRD pattern of the selected formulation (SC11) is shown in Fig. 8. The XRD patterns were detected using an X-Ray diffractometer with Cu at an interval of 10-800/2θ.

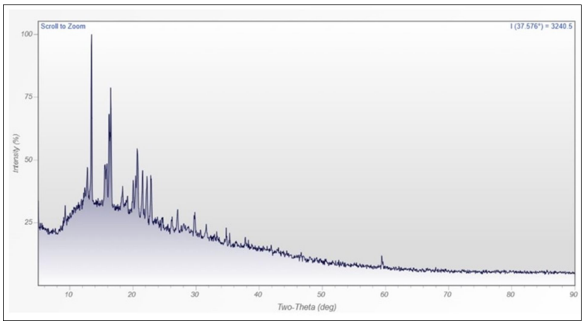

Figure 8: XRD pattern of the selected formulation SC11

The XRD study was conducted to assess any potential alterations in the physical state of the drugs, specifically their crystalline or amorphous form, as a result of the formulation procedure. The alteration in the physical form will influence the bioavailability. The XRD pattern of the selected formulation SC11 exhibited a discernible alteration in the intensity of peaks.

DISCUSSION

In this current research, SUS mucoadhesive buccal patches were formulated with various natural polymeric combinations of Sodium Alginate, Chitosan, Carbapol 934P, PVP-K30, HPMC using solvent casting method. PG or PEG-400 was used as the plasticizer. A total of 72 formulations were developed in triplicate manner with a 3^2 factorial design, which was used only to design the experiments. Currently, we were developed unidirectional buccal patches of SUS to prevent bidirectional flow of SUS. So the impermeable backing membrane is a crucial element of buccal patchs to gain unidirectional drug flow by preventing the loss of drug at the requisite position and also minimize the contact of extra tissues to the drug to prevent bidirectional flow. Therefore, in the present study, we have used BOPP film as backing membrane.

The main care was taken at the formulation period to use only water as solvent instead of organic solvents to avoid unnecessary residual solvent complications with *in vivo*. Lengthy drying time was taken throughout the formulation step (36 hours) due to the usage of water as solvent. From physico-chemical behaviour of the SUS mucoadhesive buccal patches, it was clear that the developed formulations were uniform in thickness, smooth, mass, drug content and noticed no noticeable cracks or folds. The formulations developed with PEG 400 as a plasticizer indicated high increase in mass and may be due to the high molecular weight of PEG-400 when compared to PG. When formulating patches ensuring mass uniformity is crucial because it ensures accurate dosing and confirms that all ingredients fall within the prescribed range. The patch thickness did not significantly fluctuate despite the film's slight variation. The developed patches demonstrated superior folding endurance. The drug content uniformity demonstrated satisfactory drug loading efficiency, which fell from 66% to 89%. The surface pH for all patches indicated that the patches are non-irritating to mucosal tissues.

The suitable swelling behavior is an important parameter when considered the development of

buccal patches to ensure a good adhesion period and identical and extended release of the drug. This also gives an idea about the relation between moisture absorption capacity of polymers and whether the formulations continued the reliability after the absorption of moisture. The hydrophilic properties of the plasticizers and polymers used affect how patches swell highly by water-soluble polymers and plasticizers with high water absorption exhibit more swelling behaviour than other materials. As a result of the presence of PVP- K30 and Carbapol 934P, a highly water-soluble polymer and high PEG water uptake, compared to patches with PG, patches with PEG plasticizer produce more swelling character. The patches were good in their shape and form during the swelling study period.

The porcine buccal mucosa was used as the mucosal membrane in the present study due to its similarity with human buccal membrane in terms of structure and permeability. The optimized buccal patches had good mucoadhesion because none of them came off before the study period, proving that the bioadhesion of each patch was enough to keep it attached to the buccal mucosa. The mucoadhesion force and time are mainly depend upon different factors such as contact time with mucus, mass and swelling index of polymers, , and the use of biological membrane in the study.

It was unable to notice any relation between the drug release and polymer composition from the drug release study. The faster drug release can be correlated to the high swelling indices observed in this study. Unlike other patches, sodium alginate-based buccal patches containing hydrophilic polymer PVP- K30 and Carbapol 934P exhibit superior release. All the selected formulations were best fit the Higuchi model. According to this model, micropore diffusion may regulate the drug release from this formulation. The drug release rate from matrixes where the drug loading exceeds the matrix's solubility. Fickian drug release is characterized by a concentration-dependent linear dependence of the released drug on the square root of time. Fick's laws, which depict the macroscopic movement of molecules due to a concentration gradient, form the basis of diffusion. Increased drug: polymer ratio results in Fickian or diffusion-based drug release mechanism. This result may be due to the diffusion of the release medium, which solubilizes the drug and causes the buccal patches to slowly release the drug [17].

There as a good correlation between *in vitro* drug release and *in vitro* drug permeation. The results of permeation studies indicated that SUS was released and permeated through pig buccal mucosa and probably may permeate through the human buccal membrane as well. The stability studies data showed that there was no impact on the chemical and physical stability of the formulations throughout the study period.

The FTIR Spectra indicated the compatibility between the drug and polymers. The DSC confirms that the drug remains intact within the formulation. The XRD denotes the transformation from a crystalline state to an amorphous state.

CONCLUSION

This study effectively developed unidirectional mucoadhesive buccal patches of SUS using polymers such as sodium alginate, Chitosan, Carbapol P934, PVP-K30, and HPMC. The SUS patches demonstrated promising physicochemical and *in vitro* characteristics. The prepared patches are assumed to bypass hepatic first-pass metabolism, enhancing drug bioavailability and patient compliance by potentially reducing side effects.

ACKNOWLEDGEMENTS

The authors thank SciWrite Global (www.sciwriteglobal.com), a medical communications company, for the editorial support.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

LIST OF ABBREVATIONS

SA: Sodium Alginate, PVP K-30: Poly Vinyl Pyrrolidine K-30, HPMC: Hydroxy Propyl Methyl Cellulose, SUS: Sumatriptan Succinate, PG: Propylene Glycol, PEG: Poly Ethylene Glycol, RH: Relative Humidity.

REFERENCES

[1] Mohammed SA, Mohsin K and Muhammed Z. Advances in oral drug delivery. Front. Pharmacol. 2021; 12: 1-21.

[2] Ratnaparkhi M and Gupta Jyoti P. Sustained release oral drug delivery system-an overview. *Terminology.* 2013; 3: 11-21.

[3] Bussone G, Manzoni GC, Cortelli P, Roncolato M, Fabbri L and Benassuti C. Efficacy and tolerability of sumatriptan in the treatment of multiple migraine attacks. Journal of the Neurological Sciences. 2000; 21: 272-8.
[4] Perioli L. Development of mucoadhesive patches for buccal administration of ibuprofen. J. Control.Release. 2004; 99: 73–82.
[5] Guo JH and Cooklok KM. The effects of backing materials and multilayered systems on the characteristics of mucoadhesive buccal patches. J Pharm Pharmacol. 1996; 48: 255.
[6] Peh KK and Wong CF. Polymeric films as vehicle for buccal delivery: swelling, mechanical and bioadhesive properties. J Pharm Pharm Sci. 1999; 2: 53-61.
[7] Davis SS, Daly PB, Kennerley JW, Frier M, Hardy JG and Wilson CG. Design and evaluation of sustained release formulations for oral and buccal administration. Karger, Basle. 1982: 17-25.
[8] Kok KP and Choy FW. Polymeric films as vehicle for buccal delivery: swelling, mechanical, and mucoadhesive properties. J Pharm Pharmaceut Sci. 1999; 2: 53–61.
[9] Zhang H and Robinson JR. *In vitro* methods for measuring permeability of the oral mucosa. Oral mucosal drug delivery. New York: Marcel Decker: 1996; 9: 85-100.
[10] Aarif khan M. Development and *in vitro* evaluation of salbutamol sulphate mucoadhesive buccal patches. Int J Pharm Pharm Sci, 2011; 3: 3944.
[11] Senel S and Hıncal AA. Drug permeation enhancement via buccal route: possibilities and limitations. J. Control. Release. 2001; 72: 133–144.
[12] Christopher AS and Philip WW. Permeability and pathophysiology of oral mucosa. Adv. Drug Deliv. Rev. 1993; 12: 13-24.
[13] Supriya SS, Nilesh SS, Sagar S and Vilasrao K. Mucoadhesive bilayered patches for administration of sumatriptan succinate. AAPS PharmSciTech. 2008; 9: 909-916.
[14] James RL. 'Metaprolol Tartarate', in analytical profiles of drug substances, Klaus Florey academic press, London. 2005; 12: 325.
[15] John GH and Wyka BE. 'Clotrimazole', in analytical profiles of drug substances, Klaus Florey academic press, London. 2005; 11: 225.
[16] Higuchi T. Rate of release of drug medicaments from ointment bases containing drugs in suspension. J.Pharm.Sci. 1961; 50: 874-875.
[17] Korsmeyer RW, Gurny R, Doelker E, Buri P and Peppas NA. Mechanism of potassium chloride release from compressed, hydrophilic, polymeric matrices: Effect of entrapped air. J Pharm Sci. 1983; 72: 1189-1191.