Original Research Article

# Formulation and evaluation of bucco-adhesive tablets of sumatriptan succinate

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## Abstract

**Background:** A novel aspiration in treatment of migraine, to provide greater therapeutic effect, overcome the side effects by complex therapeutic regimen and to improve patient compliance upon administering bucco-adhesive tablet formulations of sumatriptan succinate which have not been tested literally. **Materials and Methods:** This study was designed to develop a bucco-adhesive tablet containing sumatriptan succinate using blends of different bio-adhesive polymeric combinations such as hydroxy propyl methyl cellulose K4M, sodium carboxy methyl cellulose, and Carbopol 934P with a backing layer of ethyl cellulose by a direct compression technique. Tablets were subjected to physico-chemical parameters, swelling index, surface pH, *ex vivo* bioadhesive force, *in vitro drug* release, *ex vivo* drug permeation, and stability in saliva. **Results:** Good results were obtained in all the evaluated parameters. The drug release of all formulation follows zero-order kinetics by a diffusion mechanism type. Stability studies in human saliva, *ex vivo* buccal permeation studies by using sheep and porcine buccal mucosa were carried out for the optimized formulation (S4 CP:HPMC 3:1). **Conclusion:** The developed buccal drug delivery system containing sumatriptan succinate might be the alternative routes available to bypass the first pass metabolism and might be a milestone in the therapy of migraine and among all formulations S4 shows good controlled release results correlated with *ex vivo* permeation studies.

**Key words:** Bucco-adhesive tablet, Carbopol 934P, ethyl cellulose, *ex vivo* permeation studies, HPMC K4M, migraine, sodium carboxy methyl cellulose, sumatriptan succinate

## INTRODUCTION

Sumatriptan succinate is 1-[3-(2-dimethylaminoethyl)-1*H*-indol-5-yl]-*N*-methyl-methane sulfonamide succinate. It is a 5-$HT_1$ receptor agonist used in the treatment of migraine.[1]

Migraine is a condition that affects approximately 10% of the adult population worldwide, yielding approximately 600 million people with about 28 million in the USA alone.[2] In addition to headache, migraine can be associated with a variety of other symptoms, including diarrhea, cold extremities, facial pallor, nausea, vomiting, and sensitivity to external stimuli such as light, sound, or odor. Such migraines typically last for up to 24 h, but can range from 4 to 72 h and patients often experience migraine attacks one to two times per month.[3,4]

The oral formulation offers convenience and ease of use but produces unreliable blood levels and inconsistent response. Recurrence (rebound) occurs with these formulations.[5] This common problem with recurrence is likely due to persistence of the original event with a time course exceeding the duration of action from the currently available formulations.

This is particularly so because sumatriptan has a serum elimination half-life of only 2 h and most of the active drug is eliminated within 4–6 h in the majority of patients. Thus, an optimal product would seek to provide the advantages of rapid, systemic administration of sumatriptan succinate.

Buccal drug delivery system has the potential to fill an unmet need in migraine care by providing direct access to the systemic circulation through the internal jugular vein bypassing the first pass metabolism leading to high bioavailability.[6-8] Other advantages are noninvasive administration, rapid-onset of action, convenient and easily accessible site, self-administrable, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly

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damages or irritates the mucosa, painless administration, easy drug withdrawal, cheap and have superior patient compliance.

In this work, it is designed to develop 9 h bucco-adhesive tablets of sumatriptan succinate with the following objectives to avoid hepatic first pass metabolism, to reduce the frequency of administration, overcome the side effects, simplify the treatment regimen, and to obtain greater therapeutic efficacy to improve patient compliance.

## MATERIALS AND METHODS

### Materials

Sumatriptan succinate (S), micro crystalline cellulose (MCC grade 102) is obtained from Sri Raghavendra Chemicals and Suppliers, Bangalore. Carbopol 934P (CP), hydroxyl propyl methyl cellulose (HPMC K4M), sodium carboxyl methyl cellulose (SCMC), sodium lauryl sulfate (SLS), ethyl cellulose (EC), and magnesium stearate are obtained from Indian Drugs, Hyderabad. All other chemicals used for this study were of analytical grade.

### Preformulation studies

#### *Drug–excipient interaction study*

The pure drug, sumatriptan succinate and a mixture of it with the polymers, HPMC, SCMC, CP, EC and excipients, MCC, SLS were mixed separately with IR grade KBr in the ratio of 100:1 and corresponding pellets were prepared by applying 5.5 metric ton of pressure in a hydraulic press.[9] The pellets were scanned over a wave number range of 4000–400 $cm^{-1}$ in a Thermo Nicolet USA, FTIR instrument.

#### *Solubility studies*

The solubility of drug was determined in phosphate buffer solution pH 6.8 and pH 7.4 by a phase equilibrium method. An excess amount of drug was taken into 50 mL conical flasks containing 20 mL of phosphate buffers (pH 6.8 and 7.4). Conical flasks were closed with aluminum foil and constantly agitated at room temperature for 24 h using rotary shaker.[10] After 24 h, the solution was filtered through a filter paper. The amount of drug solubilized was then estimated by UV spectroscopy.

#### *Determination of partition coefficient*

The partition coefficient of the drugs was determined using a *n*-octanol:water system. The *n*-octanol–water partition coefficient serves as a parameter of lipophilicity. *n*-Octanol and water were presaturated with each other for at least 24 h before the experiment. An accurately weighed quantity of drug was dissolved in 10 mL of the *n*-octanol phase and shaken at 37 °C for 24 h against the 10 mL aqueous phase in a sealed container. The separated *n*-octanol phase was assayed by UV spectroscopy to determine its residual concentration, and hence, the amount partitioned into the aqueous phase.[10] The partition coefficient was expressed as the concentration of drug in the *n*-octanol phase (% w/v) divided by the concentration in the aqueous phase.

#### *Preparation of bucco-adhesive tablets*

Buccal tablets of sumatriptan succinate were prepared by a direct compression method. Before going to direct compression, all the ingredients (drug, polymers, and excipients) were screened through sieve no. 100, except magnesium state. All the ingredients were thoroughly blended in a glass mortar with pestle for 15 min.[11,12] After sufficient mixing magnesium stearate was added and again mixed for additional 2–3 min. The mixture is compressed using 11 mm punch on a 16 stages rotary tablet compress machine and EC was used as a backing layer. The composition of bucco-adhesive tablet formulation was mentioned in Table 1.

### Physico-chemical evaluation of the prepared bucco-adhesive tablets

#### *Thickness and weight variation*

The thickness of buccal tablets was determined using a digital Vernier caliper[13] and the tablets were then weighed individually using a digital balance to determine the weight of each tablet. The tablets were subjected to weight variation by individually weighing 10 randomly selected tablets. Such determinations were carried out for each formulation.[14]

#### *Hardness*

Hardness was conducted for three tablets from each batch using a Monsanto hardness tester.[13]

#### *Friability*

A sample of 10 tablets was selected. The sample was accurately

**Table 1: Composition of bucco-adhesive tablet formulation of sumatriptan succinate**

| Ingredients | Formulation code | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | S1 | S2 | S3 | S4 | S5 | S6 | S7 | S8 | S9 | S10 | S11 | S12 |
| Sumatriptan succinate (mg) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| HPMC K4M (mg) | 100 | – | – | 25 | 50 | 75 | – | – | – | 25 | 50 | 75 |
| Carbopol 934 (mg) | – | 100 | – | 75 | 50 | 25 | 25 | 50 | 75 | – | – | – |
| SCMC (mg) | – | – | 100 | – | – | – | 75 | 50 | 25 | 75 | 50 | 25 |
| SLS (%) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| MCC (mg) | 39 | 39 | 39 | 39 | 39 | 39 | 39 | 39 | 39 | 39 | 39 | 39 |
| Magnesium stearate (mg) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| EC (mg) (backing layer) | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |

weighed and placed in the drum of tablet friability apparatus. The samples underwent 25 rpm, for 4 min, and were then reweighed.[15] This process was repeated for all formulations, and the percentage friability was calculated using Eq. (1)

$$F = \frac{(W_1 - W_2)}{W_2} \times 100 \quad \text{..... Eq. (1)}$$

where $F$ represents the percentage weight loss; and $W_1$ and $W_2$ are the initial and final discs weights, respectively.

### Drug content

Ten tablets were weighed and grounded in a mortar with pestle to get fine powder. Powder equivalent to the mass of one tablet was dissolved in ethyl alcohol and filtered through a 0.45-$\mu$m filter paper.[16] The filtrate was diluted with phosphate buffer (pH 6.8). The drug content was analyzed spectrophotometrically at 282 nm using an UV spectrophotometer using a reference to a standard calibration curve of the sumatriptan succinate.

### Swelling index

Buccal tablets were weighed individually ($W_1$) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37 ± 1 °C.[17,18] At regular 1-h time intervals until 9 h, the tablet was removed from the Petri dish, and excess surface water was removed carefully with a filter paper. The swollen tablet was then reweighed ($W_2$) and the swelling index (SI) was calculated using Eq. (2).

$$\text{Swelling Index} = \frac{(W_1 - W_2)}{W_2} \times 100 \quad \text{.... Eq. (1).}$$

where $W_2$ is the weight of the tablet after time '$t$' and $W_1$ is the weight of the tablet before placing in the petri dish.

### Surface pH studies

The bioadhesive tablet was allowed to swell by keeping it in contact with 1 mL of distilled water for 2 h at room temperature.[19] The pH was measured by bringing the pH-meter electrode, in contact with the surface of the tablet and allowing it to equilibrate for 1 min.

### Measurement of bioadhesive force

Bioadhesive force of the tablets was measured on a modified physical balance[20] like shown in Figure 1. The apparatus consisted of a modified double beam physical balance in which a lighter pan had replaced the right pan and the left pan had been replaced by a glass slide (4 cm length and 2.5 cm width) with plastic hang suspended by Teflon rings and copper wire. The left-hand side of the balance was exactly 5 g heavier than the right side. The height of the total set-up was adjusted to accommodate a glass container of 6.6 cm height. In order to find out the bioadhesion strength first buccal tablet ($n = 3$) was stacked to the glass slide with the help of the knob, which was situated at the base of the physical balance. Five grams weight from the right pan was then removed. This lowered the glass slide along with the tablet over the membrane with a weight of 5.0 g. This was kept undisturbed for 5 min. Then, the weights on the right-hand side were slowly added in increments of 0.1 g till the tablet just separated from the membrane surface. The excess weight on the right pan, i.e. total weight minus 5 g was taken as a measure of the bio-adhesive strength.[14] By using this weight calculate the bio-adhesive force using following Eq. (3)

Bio adhesive force (N) = weight in grams × $G$/1000 …Eq. (3)

where $W$ is the weight required for the detachment of two vials in grams, and $G$ is the acceleration due to gravity

The protocols for all animal studies were approved by Institutional Ethical Committee (1220/a/08/CPCSEA/ANCP/06).

### Determination of the ex vivo residence time

The *ex vivo* residence time was determined using a locally modified USP disintegration apparatus, based on the apparatus[21] shown in Figure 2. The disintegration medium was composed of 800 mL pH 6.8 phosphate buffer maintained at 37 °C. The sheep buccal tissue was glued to the surface of a glass slab, vertically attached to the apparatus. The buccal tablet was hydrated from one surface using 0.5 mL of pH 6.8 phosphate buffers, and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to run in such a way that the tablet was completely immersed in the buffer solution at the lowest point and was out at the highest point.[14] The time necessary for complete erosion or detachment of the tablet from the mucosal surface was recorded. The experiments were performed in triplicate ($n = 3$) and mean of triplicate was determined. The protocols for all animal studies were approved by Institutional Ethical Committee (1220/a/08/CPCSEA/ANCP/06).

### In vitro drug release studies

The *in vitro* drug release of buccal tablets of sumatriptan succinate was done by using the United States Pharmacopeia Type (II)

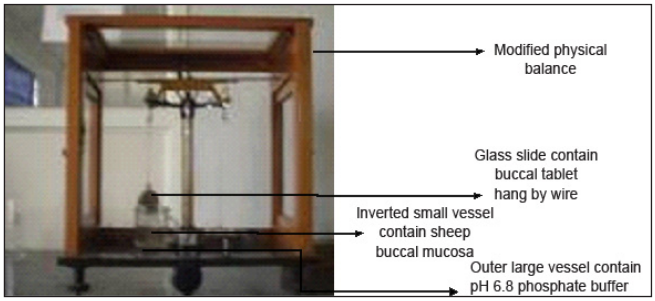


**Figure 1:** Measurement of bioadhesive force

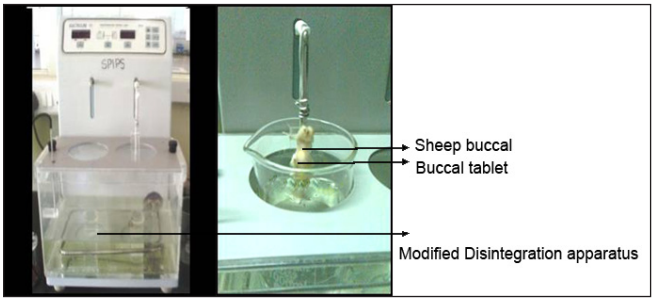


**Figure 2:** Determination of the *ex vivo* residence time

rotating paddle method. The dissolution medium consisted of 500 mL of phosphate buffer pH 6.8. The release was performed at 37 ± 0.5 °C, with a rotation speed of 50 rpm.[17,18,22] The backing layer of the buccal tablet was attached to the glass slide with instant adhesive (cyanoacrylate adhesive). The slide was placed in the bottom of the dissolution vessel. Samples (5 mL) were withdrawn at predetermined time intervals and replaced with a fresh medium. The samples were filtered through a filter paper and analyzed after appropriate dilution by a UV spectrophotometer at 282 nm.

### *Ex vivo permeation studies*

*Ex vivo* permeation study of buccal tablets through the buccal mucosa was performed using a Chien diffusion cell at 37 °C ± 0.2 °C and 50 rpm, using a magnetic stirrer.[17,18] Sheeps and pigs are easier to maintain and considerably less expensive and their buccal mucosa is non-keratinized and is similar to that of the human buccal mucosa.

Buccal mucosa was obtained from a local slaughterhouse and used within 2 h of slaughter. The epithelium was separated from underlying connective tissues with surgical scissors and clamped between donor and receiver chambers of the Chien diffusion cell. After the buccal membrane was equilibrated for 30 min with phosphate buffer pH 6.8 between both the chambers, the receiver chamber was filled with fresh pH 7.4 buffer solution which mimics the pH of blood stream[23] and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 50 rpm that is shown in Figure 3. The buccal tablet was placed in the donor chamber and 1 mL of buffer solution (pH 6.8) was added.[24] Aliquots (5 mL ) were collected at predetermined time intervals and replaced with the same quantity of fresh solution. The collected aliquots filtered through a filter paper, and the amount of drug permeated through the sheep buccal mucosa and porcine buccal mucosa was then determined by measuring the absorbance at 282 nm using a UV spectrophotometer. The protocols for all animal studies were approved by Institutional Ethical Committee (1220/a/08/CPCSEA/ANCP/06).

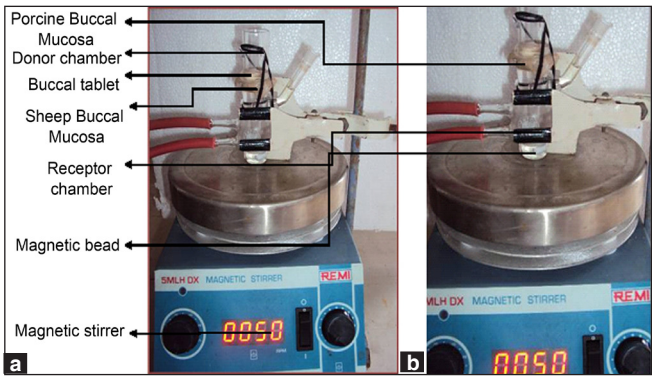


**Figure 3:** *Ex vivo* permeation studies: (a) sheep buccal mucosa; (b) porcine buccal mucosa

### *Stability in human saliva*

Stability studies of the buccal tablet were performed for optimized formulation in normal human saliva. The human saliva was collected from humans and filtered through a filter paper. The buccal tablet was placed in separate petri dishes containing 5 mL of human saliva and placed in a temperature controlled oven for 9 h at 37 °C ± 0.2 °C at regular intervals (0, 3, 6, and 9 h), the buccal tablet was examined for change in color, surface area, and integrity.[10]

## RESULTS AND DISCUSSION

In this work efforts have been made to prepare bucco-adhesive tablets of sumatriptan succinate using various blends of polymers such as HPMC K4M, CP, and SCMC. SLS was used as permeation enhancer. EC was used as a backing membrane.

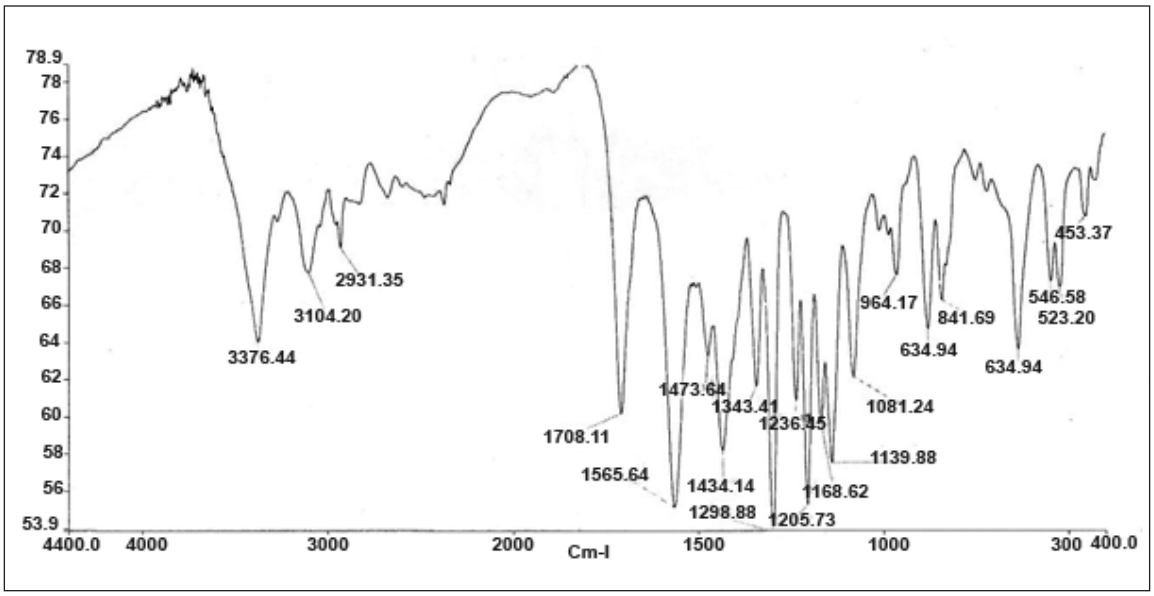


**Figure 4:** IR spectra of pure Sumatriptan succinate.

**Table 2: Physico-chemical parameters of formulations S1–S12**

| Formulation code | Thickness (mm ± SD) | Weight variation (g ± SD) | Friability (% ±*SD*) | Hardness (kg/cm² ±SD) | Drug content (% ±SD) |
|---|---|---|---|---|---|
| S1 | 2.51 ± 0.39 | 0.196 ± 0.29 | 0.045 ± 0.005 | 4.46 ± 0.05 | 98.96 ± 0.3 |
| S2 | 2.41 ± 0.23 | 0.195 ± 0.26 | 0.027 ± 0.007 | 5.1 ± 0.5 | 99.16 ± 0.45 |
| S3 | 2.29 ± 0.36 | 0.192 ± 0.58 | 0.142 ± 0.004 | 4 ± 0.05 | 98.49 ± 0.29 |
| S4 | 2.50 ± 0.21 | 0.195 ± 0.3 | 0.052 ± 0.003 | 4.76 ± 0.05 | 98.53 ± 0.32 |
| S5 | 2.52 ± 0.30 | 0.192 ± 0.59 | 0.048 ± 0.005 | 4.17 ± 0.2 | 99.11 ± 0.17 |
| S6 | 2.42 ± 0.25 | 0.191 ± 0.87 | 0.127 ± 0.008 | 4.13 ± 0.03 | 99.1 ± 0.11 |
| S7 | 2.41 ± 0.23 | 0.191 ± 0.88 | 0.043 ± 0.007 | 4.26 ± 0.05 | 98.23 ± 0.5 |
| S8 | 2.57 ± 0.19 | 0.192 ± 0.56 | 0.039 ± 0.005 | 4.46 ± 0.07 | 98.13 ± 0.59 |
| S9 | 2.38 ± 0.22 | 0.194 ± 0.24 | 0.062 ± 0.008 | 4.67 ± 0.05 | 97.73 ± 0.62 |
| S10 | 2.18 ± 0.12 | 0.196 ± 0.29 | 0.047 ± 0.006 | 4.1 ± 0.1 | 98.73 ± 0.4 |
| S11 | 2.46 ± 0.28 | 0.194 ± 0.3 | 0.025 ± 0.005 | 4.66 ± 0.05 | 98.41 ± 0.39 |
| S12 | 2.24 ± 0.19 | 0.194 ± 0.57 | 0.047 ± 0.004 | 4.57 ± 0.04 | 97.73 ± 0.64 |

**Table 3: Swelling index profile for all formulations S1–S12**

| Formulation code | Time (h) | | |
|---|---|---|---|
| | 3 | 6 | 9 |
| S1 | 42.7 ± 0.06 | 62.6 ± 0.08 | 120.5 ± 0.05 |
| S2 | 56.7 ± 1.04 | 85.4 ± 1.02 | 142.2 ± 1.04 |
| S3 | 62.7 ± 0.06 | 95.7 ± 0.02 | 150.2 ± 0.07 |
| S4 | 58.2 ± 0.01 | 85.2 ± 0.02 | 132.2 ± 0.05 |
| S5 | 49.3 ± 0.05 | 90.2 ± 0.02 | 126 ± 0.06 |
| S6 | 48.3 ± 0.04 | 85.3 ± 0.04 | 130.2 ± 0.06 |
| S7 | 57.6 ± 0.06 | 88.6 ± 0.05 | 136 ± 0.08 |
| S8 | 48.7 ± 0.07 | 77.7 ± 0.05 | 128.8 ± 0.12 |
| S9 | 55.7 ± 0.12 | 90.7 ± 0.01 | 138.5 ± 0.06 |
| S10 | 52.3 ± 0.05 | 84.5 ± 0.12 | 118.5 ± 0.05 |
| S11 | 56.2 ± 0.06 | 86.7 ± 0.32 | 114.5 ± 0.04 |
| S12 | 56.3 ± 0.04 | 85 ± 0.05 | 112.6 ± 0.12 |

## Preformulation studies

### *Drug–excipient interaction study*

The physicochemical compatibility of the drugs and the polymer was established through FTIR studies. sumatriptan succinate gave peaks at respective wave numbers i.e. S=O stretching (1081 $cm^{-1}$), tertiary amine (3104 $cm^{-1}$), C–N stretching (1298 $cm^{-1}$, 1236 $cm^{-1}$), C–S stretching (634 $cm^{-1}$), N–H stretching (3376 $cm^{-1}$)

However, additional peaks were absorbed in physical mixtures which could be due to the presence of polymers and indicated that there was no chemical interaction between sumatriptan succinate and other excipients which are shown in Figures 4–6.

### *Solubility studies*

The solubility study was conducted in pH 6.8 and pH 7.4 phosphate buffer because these are average pH values of oral cavity and blood, respectively. Solubility of sumatriptan succinate in the pH 6.8 and 7.4 was found to be 100 ± 2.85 mg/mL, 106 2.3 mg/mL, respectively.

### *Partition coefficient*

The partition coefficient of the sumatriptan succinate in pH 6.8 phosphate buffer and 1-octanol was found to be 1.2.

### *Physico-chemical evaluation of the prepared bucco-adhesive tablets*

Physico-chemical evaluation data of Table 2 indicate that thickness of tablets varied from 3.18 ± 0.12–3.57 ± 0.19 mm. The drug content analysis and the weight uniformity of the prepared formulation have shown that the process adopted for punching tablets in this investigation is capable of giving films with a uniform drug content and with minimum intrabatch variability.

The percentage friability in the formulation S3 (1% SCMC) has shown the highest value of 0.142 ± *0.004*. The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness. The friability of the tablets was found to be <1%.

### *Swelling index*

SI values of all the formulations were given in Table 3 indicate that the S3 shows a maximum SI of 150.*2* ± *0.07*. The S2 shows a SI of 142.*2* ± *1.04*. The S1 shows a SI of *120.5* ± *0.05*.

Matrices containing S4–S6 demonstrated increase in swelling values as the content of CP was increased. This observation could be due to higher and faster swelling of CP.

Matrices containing S7–S9 exhibited maximum swelling values, which could be attributed to higher hydrophilicity and water uptake of CP and SCMC compared to HPMC. CP is more hydrophilic than HPMC and if it is added in high ratios causes higher swelling from matrices containing different ratios of CP and HPMC.

Matrices containing S9–S12 demonstrated increase in swelling values as the content of SCMC was increased, this could be attributed to higher water uptake of SCMC. Swelling behavior of buccal tablets of all formulations as a function of time is shown in Figure 7.

### *Surface pH*

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was

**Table 4: Bioadhesive force, *ex vivo* residence time and surface pH values for formulations S1–S12**

| Formulation code | Bio adhesive force (N) | *Ex vivo* residence time (h) | Surface pH |
|---|---|---|---|
| S1 | 0.198 ± 0.001 | 8.62 ± 0.10 | 6.41 ± 0.2 |
| S2 | 0.292 ± 0.002 | 8.52 ± 0.25 | 4.56 ± 0.05 |
| S3 | 0.302 ± 0.003 | 8.41 ± 0.15 | 6.46 ± 0.03 |
| S4 | 0.214 ± 0.02 | 10.3 ± 0.15 | 6.83 ± 0.03 |
| S5 | 0.201 ± 0.001 | 10.73 ± 0.10 | 6.26 ± 0.01 |
| S6 | 0.182 ± 0.002 | 11.15 ± 0.35 | 6.28 ± 0.01 |
| S7 | 0.252 ± 0.002 | 8.74 ± 0.14 | 6.88 ± 0.01 |
| S8 | 0.234 ± 0.002 | 10.7 ± 0.25 | 6.81 ± 0.1 |
| S9 | 0.262 ± 0.004 | 9.13 ± 0.35 | 6.83 ± 0.05 |
| S10 | 0.196 ± 0.002 | 9.35 ± 0.27 | 6.41 ± 0.31 |
| S11 | 0.185 ± 0.004 | 8.26 ± 0.31 | 6.61 ± 0.03 |
| S12 | 0.160 ± 0.001 | 8.45 ± 0.16 | 6.55 ± 0.07 |

**Table 5: Data for *in vitro* drug release for all formulations**

| Formulation code | Time (h) | Cumulative percentage release of drug (%) |
|---|---|---|
| S1 | 8 | 89.41 |
| S2 | 8 | 91.25 |
| S3 | 8 | 94.19 |
| S4 | 9 | 96.16 |
| S5 | 9 | 95.17 |
| S6 | 9 | 93.16 |
| S7 | 9 | 93.82 |
| S8 | 9 | 91.68 |
| S9 | 9 | 90.15 |
| S10 | 9 | 93.39 |
| S11 | 9 | 92.19 |
| S12 | 9 | 90.3 |

**Table 6: *Ex vivo* drug permeation profile for formulation S4**

| Time (h) | Cumulative % drug released (sheep mucosa) | Cumulative % drug released (porcine mucosa) |
|---|---|---|
| 1 | 7.2 | 9.8 |
| 2 | 17.5 | 18.7 |
| 3 | 26.3 | 29.2 |
| 4 | 35.1 | 40.1 |
| 5 | 44.3 | 49.8 |
| 6 | 53.2 | 59.1 |
| 7 | 62.7 | 68.9 |
| 8 | 73.1 | 77.9 |
| 9 | 84.2 | 87.1 |

**Table 7: *In vitro* and *ex vivo* cumulative percentage drug release (sheep mucosa) and correlation of formulation S4**

| Time (h) | *In vitro* cumulative percentage drug release | *Ex vivo* cumulative percentage drug released (sheep mucosa) |
|---|---|---|
| 1 | 14.2 | 7.2 |
| 2 | 27.08 | 17.5 |
| 3 | 37.06 | 26.3 |
| 4 | 48.23 | 35.1 |
| 5 | 59.19 | 44.3 |
| 6 | 67.09 | 53.2 |
| 7 | 79.14 | 62.7 |
| 8 | 87.54 | 73.1 |
| 9 | 96.16 | 84.2 |

**Table 8: *In vitro* and *ex vivo* cumulative percentage drug release (porcine mucosa) and correlation of formulation S4**

| Time (h) | *In vitro* cumulative percentage drug release | *Ex vivo* cumulative percentage drug released (porcine mucosa) |
|---|---|---|
| 1 | 14.2 | 9.8 |
| 2 | 27.08 | 18.7 |
| 3 | 37.06 | 29.2 |
| 4 | 48.23 | 40.1 |
| 5 | 59.19 | 49.8 |
| 6 | 67.09 | 59.1 |
| 7 | 79.14 | 68.9 |
| 8 | 87.54 | 77.9 |
| 9 | 96.16 | 87.1 |

**Table 9: Stability profile of optimized formulation (S4) in human saliva**

| Sampling interval (h) | Change in color | Change in surface area ($cm^2$) | Change in integrity |
|---|---|---|---|
| 0 | NO | NO | NO |
| 3 | NO | 1.32 | NO |
| 6 | NO | 2 | NO |
| 9 | NO | 2.5 | NO |

determined to keep the surface pH as close to neutral as possible.

Surface pH of the optimized formulation S4 was found to be 6.83. This pH is near to the neutral, so the formulation does not cause any irritation on the mucosa. Surface pH values for all the formulations are shown in Table 4.

### *Bioadhesive force*

Bioadhesive force depends on molecular weight and swelling behavior of the polymers, contact time with mucus. The bioadhesion characteristics were affected by the type and ratio of the bioadhesive polymers. The bio adhesion force test was conducted for all formulations (S1–S12) of sumatriptan succinate buccal tablets determined by using the sheep mucosa at various mixing ratios of the polymers (HPMC, CP, and SCMC) and evaluation data represented in Table 4.

The highest detachment force was observed with the formulation S3 (SCMC). The optimized tablet (S4) showed 0.214 N of bioadhesive force. The high bioadhesive force of SCMC and CP may be due to the formation of secondary bioadhesion bonds with mucin and interpenetration of polymeric chains in the interfacial region, while the HPMC undergo superficial bioadhesion and the comparison of bioadhesive force of all formulations was

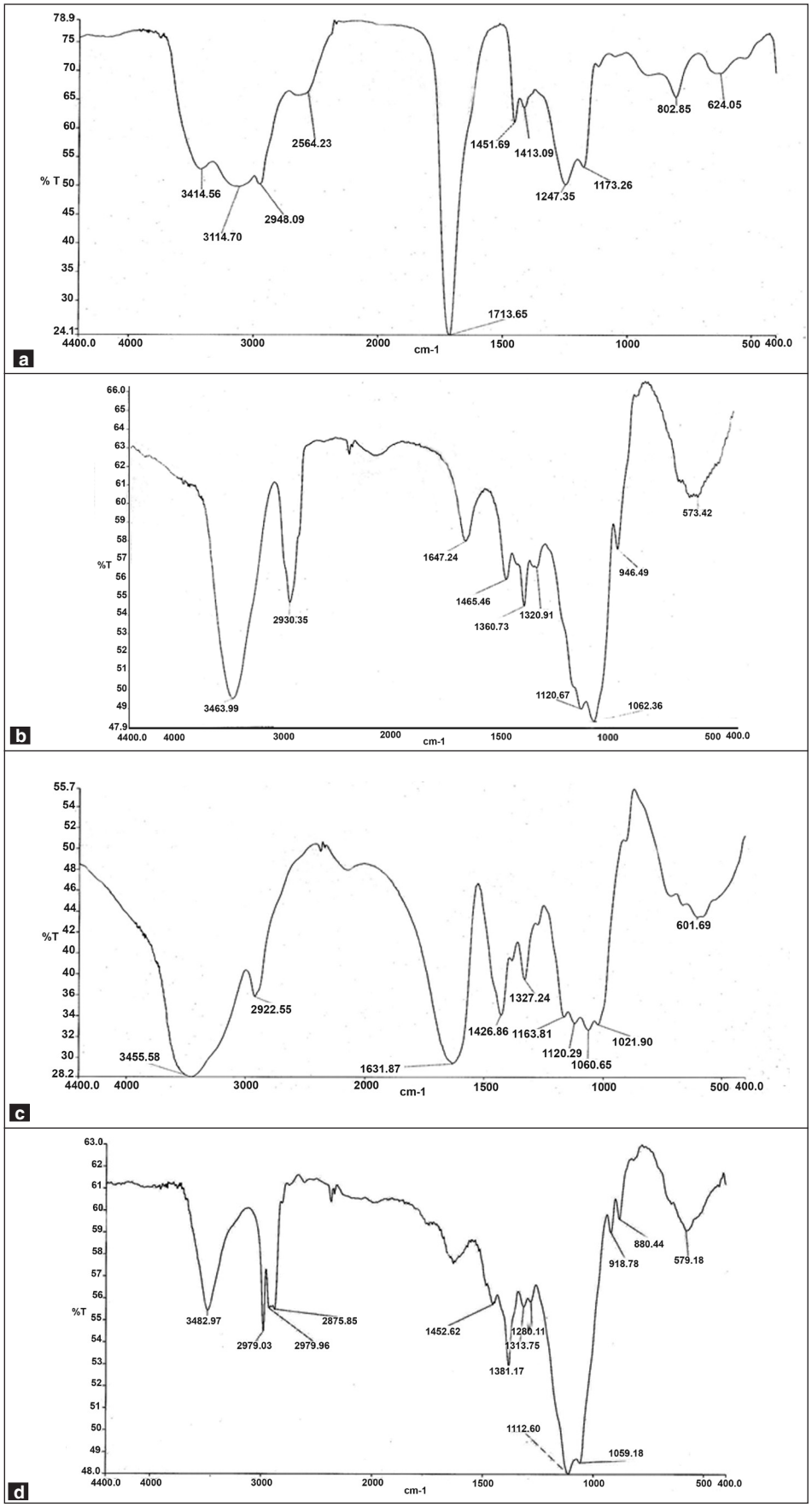


**Figure 5:** IR spectra of (a) Carbopol 934P, (b) HPMC K4M, (c) SCMC, (d) ethyl cellulose

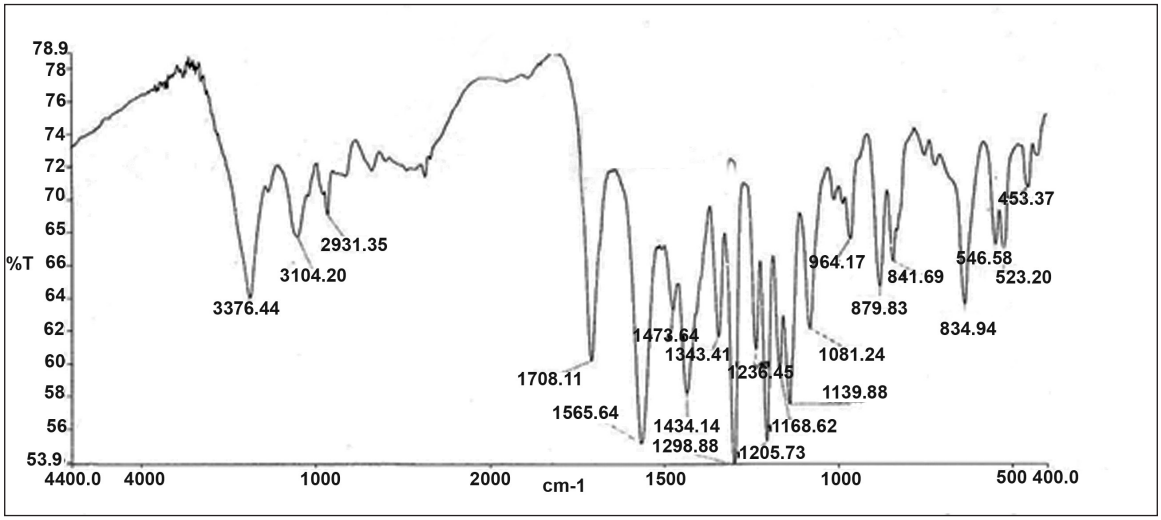


**Figure 6:** IR spectra of sumatriptan succinate with polymers like HPMC K4M, CP 934P SCMC, and ethyl cellulose

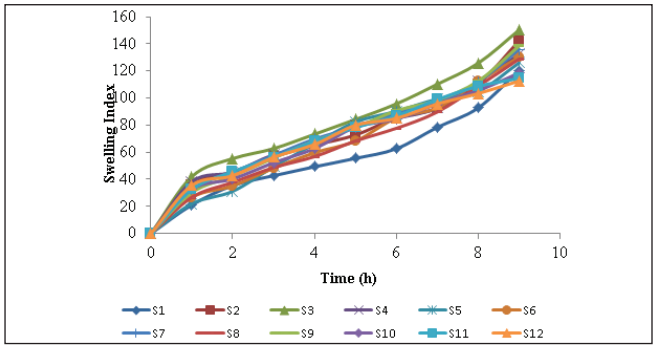


**Figure 7:** Comparative swelling studies for formulations S1–S12

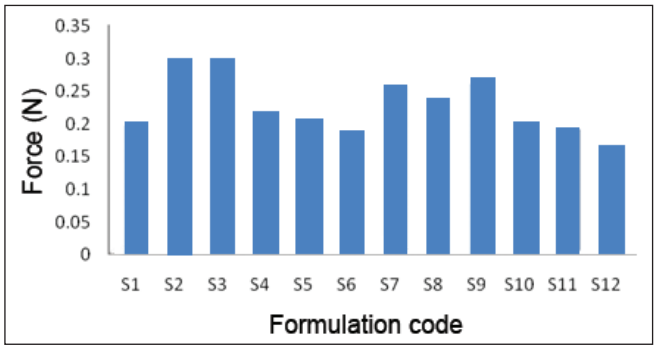


**Figure 8:** Bio-adhesive force for all formulation S1–S12

shown in Figure 8.

### *Ex vivo* residence time

*Ex vivo* residence time for all the formulations varied from 8 to 11 h. The optimized formulation (S4) showed 10.3 ± 0.15 h. The difference could be due to the combination of various amounts of polymers, which affects the bioadhesion. The bioadhesion time is increased as Carbopol is increased. This is because of the high bioadhesive nature of the Carbopol and interpenetration of polymeric chains into the mucus membrane. *Ex vivo* residence time values were given in Table 4.

### *In vitro* release studies

The *in vitro* drug release data in Table 5 indicated that formulation S1, S2, and S3 formulated with 1% HPMC, 1% CP, and 1% SCMC has shown release 89.41%, 91.25%, and 94.19% at 8th h. The *in vitro* drug release plot has shown that the drug release followed zero-order kinetics, which was envinced from the regression value of the abovementioned plot. In order to confirm this fact, Peppa's plot was drawn which has shown slope values of 1.032, 0.926, and 0.999, respectively, which confirms that the diffusion mechanism involved in the drug release was of the non-Fickian diffusion type.

The formulation S4 formulated with 1:3 (HPMC:CP) which has shown the highest drug release 96.16% at 9th hour may be due to the short diffusional path length among all formulations. In order to confirm this fact, Peppa's plot was drawn which has shown a slope value of 0.867, which confirms that the diffusion mechanism involved in the drug release was of the non-Fickian diffusion type.

The formulation S5 and S6 formulated with 1:1 and 3:1 (HPMC:CP) has shown release 95.17% and 93.16%, respectively, at 9th h. In order to confirm this fact, Peppa's plot was drawn which has shown slope values of 0.968 and 1.049, respectively, which confirms that the diffusion mechanism involved in the drug release was of the non-Fickian diffusion type.

The formulation S7, S8, and S9 formulated with 1:3, 1:1, and 3:1 (CP:SCMC) has shown release 93.82%, 91.68%, and 90.15%, respectively, at 9th hour. In order to confirm this fact, Peppa's plot was drawn which has shown slope values of 0.853, 0.887, and 0.934, respectively, which confirms that the diffusion mechanism involved in the drug release was of the non-Fickian diffusion type.

The formulation S10, S11, and S12 formulated with 1:3, 1:1, and 3:1 (HPMC:SCMC) has shown release 93.39%, 92.19%, and 90.3%, respectively, at 9th hour. In order to confirm this fact, Peppa's plot was drawn which has shown slope values of 1, 1.075, and 1.14, respectively, which confirms that the diffusion mechanism involved in the drug release was of the non-Fickian diffusion type.

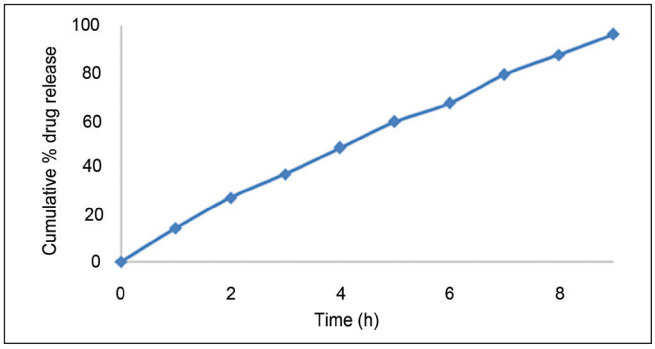


**Figure 9:** *In vitro* drug release of optimized formulation S4

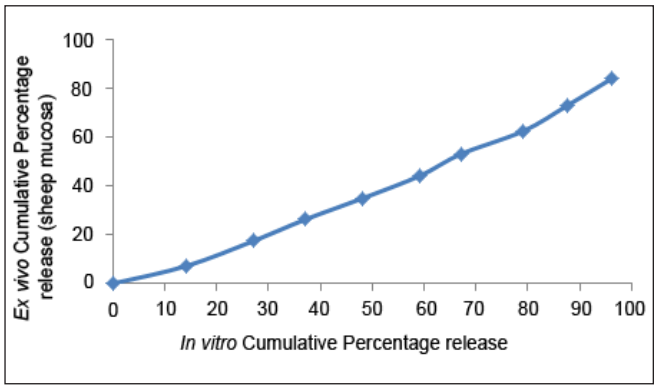


**Figure 10:** *In vitro* and *ex vivo* (sheep mucosa) correlation of formulation S4

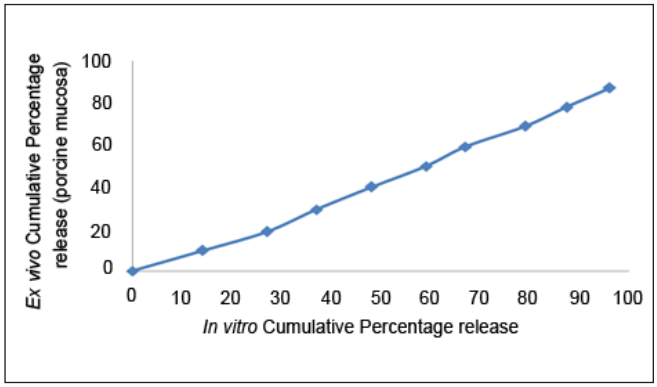


**Figure 11:** *In vitro* and *ex vivo* (porcine mucosa) correlation of formulation S4

The *in vitro* release plots of all other formulations were suggestive of zero-order release and are diffusion mediated which was envinced from the regression value Higuchi's plot. All the formulations undergo non-Fickian type of release which is confirmed from the slope values obtained from the Peppa's plot. Based on the drug release the optimized formulation selected for further study was S4 (CP:HPMC in 3:1). *In vitro* drug release of formulation S4 was shown in Figure 9.

### *Ex vivo permeation of buccal tablets*

After carrying out the *in vitro* dissolution studies for all the formulations, the best formulation S4 (CP:HPMC in 3:1) is selected for the *ex vivo* permeation studies. The *ex vivo* buccal permeation study was carried out by using sheep buccal mucosa, the formulation S4 (CP:HPMC in 3:1) showed drug diffusion for 9 h up to the extent of 84.2%. The studies which were carried out by using porcine buccal mucosa showed drug diffusion of 87.1% and these were mentioned in Table 6. The variation among the used biological membrane could be attributed to the fat content and thickness of the membrane used. As the sheep mucosa has more fat deposition and the thickness compared with porcine mucosa, it might have hampered the drug release through the membrane.

### *In vitro and ex vivo correlation*

*The ex vivo* study was carried out by using sheep mucosa and porcine mucosa revealed that the consistence *in vitro* release pattern of the formulation S4 was reproducible even in biological environment. At the end of 9$^{th}$ hour the *ex vivo* drug release showed 84.2% and 87.1%, respectively, and values were mentioned in Tables 7 and 8. The results which are mentioned in Tables 7 and 8 indicated that the *in vitro* and *ex vivo* techniques correlation was very good. They are well correlated, so the release pattern has followed the predicted zero-order kinetics in biological systems also which are shown in Figures 10 and 11.

### *Stability of buccal tablets in human saliva*

The stability study was conducted only for optimized formulation (S4). There was no change in the color and integrity of the tablets. The data obtained from the study are presented in Table 9. From the stability results it was known that formulation S4 has stability in human saliva. It was reported that no color was changed when it was placed in human saliva. Physical properties of the sumatriptan succinate buccal tablets such as diameter slightly changed owing to swelling of the system in human saliva. Buccal tablets maintained their integrity in the human saliva throughout the study, conforming the sufficient strength of the system.

## CONCLUSION

Development of bioadhesive buccal drug delivery of sumatriptan succinate tablets is one of the alternative routes of administration to avoid first pass effect and provide prolong release by increasing the diffusional path length using bioadhesive polymers. From the results, it was concluded that the *in vitro* drug release, bioadhesive force and *ex vivo* studies, the formulation containing CP and HPMC K4M at the ratio of 3:1 is suitable for buccal delivery. The release pattern followed non-Fickian diffusion with zero-order release. Hence sumatriptan succinate bucco-adhesive tablet could be a promising one as they increase bioavailability, minimize the dose, reduce the side effects, and improve patient compliance and also sumatriptan succinate might be a right and suitable candidate for oral controlled drug delivery via bucco-adhesive tablets.

Further studies are needed to investigate these formulations for its performance in pharmacokinetics, *in vivo* studies on higher animals, and controlled clinical studies on human beings able to bring the product into the market.

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