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Buccal Mucoadhesive Tablets of Sumatriptan Succinate for Treatment of Sustainable Migraine: Design, Formulation and *In Vitro* Evaluation

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Abstract
The objective of present studies were to develop a Sumatriptan succinate buccal mucoadhesive tablet using mucoadhesive polymers such as HPMC K4M, Carbopol 934P, ethyl cellulose and guar gum in alone and in combination as release retarding agent to prolong the drug release, to increase mucoadhesive strength and to avoid first pass metabolism. The mucoadhesive buccal tablets were prepared by direct compression method. The dry blend of drug and polymers were evaluated for precompression parameters to ensure flow properties during tablet punching. The prepared mucoadhesive buccal tablets were evaluated for physicochemical parameters such as hardness, thickness uniformity, weight variation, and moisture absorption studies. The prepared buccal tablets were also evaluated for mucoadhesive strength, *in vitro* drug release and ex vivo drug permeation through goat buccal mucosa. The drug excipients compatibility was evaluated by FTIR and DSC studies. *Ex vivo* mucoadhesive strength, and *in vitro* release studies showed that formulation SMF_{12} containing 12.5% of each polymer combination showed satisfactory bioadhesive strength and exhibited optimum drug release (99.33 % after 10hrs). FTIR and DSC results showed no evidence of interaction between the Sumatriptan succinate and mucoadhesive polymers. The Stability of Sumatriptan mucoadhesive buccal tablets was determined in artificial human saliva and it was found that both Sumatriptan succinate and buccal tablets were stable in human saliva. Hence different mucoadhesive polymers (HPMC K4M, Carbopol 934P, ethyl cellulose and guar gum) in various proportions can be used to prepare mucoadhesive buccal tablets of Sumatriptan succinate having prolonged therapeutic effect with enhanced patience compliance by avoiding first pass metabolism.

Keywords: *Sumatriptan Succinate, Mucoadhesion, HPMC K4M, Carbopol 934P, Migraine*

Introduction
Oral route has been the most popular and successfully used for controlled delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design (possible because of versatility of g.i. anatomy and physiology) and ease of production and low cost of such a system. 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. Moreover, the buccal cavity is easily accessible for self medication and drug absorption is terminated in case of toxicity by removing the dosage form from the buccal cavity. Buccal drug delivery system utilizes mucoadhesive polymers which become adhere to the buccal mucosa upon hydration and hence act as targeted or controlled/sustained release system. Various mucoadhesive dosage forms suggested for oral drug delivery which include adhesive tablets, adhesive patches, adhesive gels, strip, ointment and discs. Other advantages are non-invasive administration, rapid-onset of action, convenient and easily accessible site, self-administrable, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly, damages or irritates the mucosa, painless administration, easy drug withdrawal, cheap and have superior patient compliance.[1,2] Migraine headache are the most common disease described as vascular headache that causes a throbbing and pulsating pain around the head. It involves abnormal sensitivity of arteries within the brain resulting in triggers that often lead to rapid changes in the diameter of artery, resulting from spasm. As a result of this other arteries in the brain and scalp dilate resulting in terrible pain in the head. Sumatriptan is structurally similar to serotonin and is a 5-HT agonist. Sumatriptan stimulates 5-HT receptors of the 1D subtype; most likely presynaptic receptors resulting in selective vasoconstriction of inflamed and dilated cranial blood vessels in the carotid circulation. Sumatriptan succinate is 1-[3-(2-dimethylaminoethyl)-1H-indol-5-yl]-N-methyl-methane sulphonamide succinate. It is a 5-HT1

receptor agonist used in the treatment of migraine. Sumatriptan has low bioavailability after oral administration (about 15%), with a large inter-individual variation, although not affected by concomitant food intake. The dose is 50-100 mg orally. T_{max} is reached at approximately 2 h and is slightly delayed by the presence of food and during an acute migraine attack. The pharmacokinetics of Sumatriptan is linear over the dose range 25-200 mg, with the exception of rate of absorption. Sumatriptan is extensively metabolized in the liver predominantly by monoamine oxidase type A and is excreted mainly in the urine as the inactive indole acetic acid derivative and its glucuronide. Total plasma clearance is 1160 ml/min, of which 20% is renal. The elimination half-life is about 2 h. By designing a buccal mucoadhesive sustained release dosage form of Sumatriptan succinate, the therapeutic effectiveness as well as bioavailability of the drug can be increased as the drug absorbed from the buccal route can bypass the fast pass metabolism because it directly accesses to the systemic circulation through the internal jugular vein.[3,4]

Hence, in the present work an attempt was made to formulate mucoadhesive buccal tablet for Sumatriptan succinate using different combination of polymers in order to avoid first pass metabolism, for prolonged effect and to obtain greater therapeutic efficacy for improving patient compliance.[5]

Materials and Methods

Materials

Sumatriptan Succinate was procured as a gift sample from Aurobindo Pharma Ltd, Hyderabad, India. The polymers like HPMC K4M, and Ethyl cellulose were also obtained as a gift sample from Dr. Reddy's laboratories Pvt. Ltd. The mucoadhesive polymer like Carbopol 934P and Guar gum were purchased from Indian Drugs, Hyderabad. Lactose, PVP K30, Titanium dioxide, Saccharin, Talc and magnesium Stearate were purchased from S.D. fine chemicals Pvt. Ltd' Mumbai, India. All the ingredients were of laboratory grade. The distilled water used in the process of research work was prepared by double distillation process in the laboratory.

Methods

Determination of λmax of pure Sumatriptan Succinate and preparation of calibration curve in phosphate buffer P^H 6.8

Primary stock solution of Sumatriptan Succinate having concentration of 1000 µg/ml was prepared using phosphate buffer P^H 6.8. From the primary stock solution after necessary dilution secondary stock solution having concentration of 10µg/ml was prepared using same phosphate buffer P^H 6.8. The prepared secondary stock solution was then scanned by a UV spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at wavelengths ranging from 400nm to 200nm. The λmax for Sumatriptan in this solution was determined and it was found to be 227nm. The secondary stock solution was then diluted using same phosphate buffer P^H 6.8 to form a series of concentration of 2, 4, 6, 8, and 10 µg/ml and corresponding absorbance were measured at λmax of 227nm. For obtaining the calibration curve of pure Sumatriptan Succinate, the measured absorbance were plotted against corresponding concentrations.[5]

Formulation of Sumatriptan Succinate mucoadhesive tablet matrix tablets

Sumatriptan Succinate mucoadhesive matrix tablets were formulated by direct compression method. The formulation composition of different batch is shown in **table 1**. All the powders passed through 40 mesh sieve. The required quantity of Sumatriptan Succinate, various polymers and fillers were mixed thoroughly by process of trituration. The dry blends were dried at 40^o C for 5 minutes to reduce moisture content upto 2-5 %. Magnesium stearate and talc were finally added as a lubricant and glidant respectively. The dry blends were tested for various pre compression parameters like bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio etc. The evaluated mixture of powder was directly compressed (8 mm diameter, circular flat faced punches) on a 10 station rotary tablet punching machine (SHAIMAC Technology Pvt. Ltd, Hyderabad, India). Each tablet contained 50 mg of Sumatriptan Succinate. All the tablets were stored in airtight containers for further study.[5, 6]

Table 1: Different formulations of Sumatriptan Succinate buccal mucoadhesive matrix tablets

Formulations (mg)	SMF_1	SMF_2	SMF_3	SMF_4	SMF_5	SMF_6	SMF_7	SMF_8	SMF_9	SMF_{10}	SMF_{11}	SMF_{12}
Sumatriptan	50	50	50	50	50	50	50	50	50	50	50	50
HPMC K4M	50	50	50	50	50	50	-	-	75	75	75	25
Carbopol 934P	50	-	-	25	25	-	25	50	25	-	-	25
Ethyl cellulose	-	50	-	-	25	25	50	25	-	25	-	25
Guar gum	-	-	50	25	-	25	25	25	-	-	25	25
Lactose	32	32	32	32	32	32	32	32	32	32	32	32
PVP K30	10	10	10	10	10	10	10	10	10	10	10	10
Mg stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Titanium dioxide	2	1	1	1	1	1	1	1	1	1	1	1
Saccharine	1	1	1	1	1	1	1	1	1	1	1	1
Total	200	200	200	200	200	200	200	200	200	200	200	200

Evaluation of pre-compression parameters of dry powder blend of all formulations (SMF_1-SMF_{12})

Angle of Repose (θ):

Angle of repose is an important parameter that is used to find out the flow properties of powder and that is indicated as maximum angle possible between the surface of a pile of powder and the horizontal plane. The dry powder blends from different formulations were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius (r) of the heap of powder formed.

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

According to the specifications the angle of repose value less than 25^0 indicates excellent flow whereas angle "between" 25^0-30^0 indicates good flow. The angle "between" 30^0-40^0 indicates passable flow and angle greater than 40^0 indicates very poor flow. [5]

Bulk density:

Both the loose bulk density (*LBD*) and tapped bulk density (*TBD*) of prepared dry powder blends of all the formulations were determined. The quantity of 2 gm of powder blends from each formulation, previously lightly shaken to break any agglomerates formed; were introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface form the height of 2.5cm at second interval. The tappings were continued until no further changes in volume were noted. *LBD* and *TBD* of prepared powder blends of all Sumatriptan mucoadhesive formulations were calculated using the following formulas. [6, 7]

$$LBD = \frac{weight\ of\ the\ granule}{volume\ of\ the\ packing}$$

$$TBD = \frac{weight\ of\ the\ granule}{tapped\ volume\ of\ the\ packing}$$

Compressibility Index (Carr's index):

Compressibility index (Carr's index) is important parameters to determine the flow properties of powder and granules. Carr's index of prepared Sumatriptan mucoadhesive dry powder blends were calculated by following formula

$$Carr's\ index\ (\%) = \frac{TBD-LBD}{TBD} \times 100$$

According to the specification the Carr's index values "between" 5-15 indicates excellent flow where as "between" 12-16 indicates good flow. Values "between" 18-21 indicate fare-passable where as "between" 23-25 indicates poor and "between" 33-38 indicates very poor and greater than 40 indicates extremely poor. [6, 7]

Hausner's ratio:

Hausner's ratios are also another parameter to determine the flow properties of powder and granules. The Hausner's ratios of prepared Sumatriptan mucoadhesive dry powder blends were determined by following formula.

$$Hausner's\ ratio = \frac{TBD}{LBD}$$

According to specifications values less than 1.25 indicate good flow (=20% of Carr's index), where as greater than 1.25 indicates poor flow (=33% of Carr's index). Between 1.25 and 1.5, added glidant normally improves flow. [6, 7]

Evaluation of postcompression parameters of all formulations (SMF_1-SMF_{12})

Thickness

Ten tablets from each formulation of Sumatriptan mucoadhesive sustained release tablets were randomly selected and used for thickness determination. Thickness of each tablet was measured by using digital Vernier Callipers (Mitutoyo dial Thickness Gauge, Mitutoyo,Japan) and the results were expressed as mean values of ten readings, with standard deviations. According to specification tablet thickness should be controlled within a ± 5% variation of standard value.[7]

Tablet Hardness

Hardness of all the formulations of Sumatriptan mucoadhesive sustained release tablets were measured by using Monsanto hardness tester (Cad Mach). From each formulation the crushing strength of ten tablets with known weights were recorded in kg/cm^2 and average were calculated and presented with standard deviation. According to specifications of USP hardness values of 4-5 Kg for tablet is considered as acceptable limit.[8]

Friability

Previously weighed ten Sumatriptan mucoadhesive sustained release tablets from each batch were taken in Roche friabilator (Roche friabilator, Secor India). After100 revolutions of friabilator tablets were recovered. The tablets were then made free from dust using a soft muslin cloth and the total remaining weight was recorded. Friability was calculated from the following formula.

$$\%F = \frac{(Wi - Wf)}{Wi} \times 100$$

Where W_i and W_f were the initial and final weight of the tablets before and after friability test. For any compressed tablet that the lose less than 0.1 to 0.5

% and maximum upto 1% of the tablet weigh are consider acceptable.[9]

Weight variation test

All formulated Sumatriptan mucoadhesive sustained release tablets were evaluated for weight variation as per USP monograph. Twenty tablets were weighed collectively and individually using an electronic balance. The average weight was calculated and percent variation of each tablet was calculated. According to USP monograph, the weight variation tolerance limit for the uncoated tablet having average weight 130mg or less is 10% whereas for average weight between 130-324mg is 7.5% and for average weight more than 324mg is 5%. For the tablet to be accepted, the weight of not more than two tablets deviate from the average weight by not more than 7.5% and no tablet deviates by more than 15%.[9, 10]

Content uniformity

Twenty Sumatriptan mucoadhesive sustained release tablets were taken and triturated to form powder and powder equivalent to one tablet was taken and dissolved in 100 ml of phosphate buffer P^H 6.8 and heated at 37 ^{0}C for 15 to 20 minutes with stirring. The solution was filtered, suitably diluted and the Sumatriptan content was measured by using UV Spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at 227nm. Each measurement was carried out in triplicate and the average drug content in each Sumatriptan mucoadhesive sustained release tablets was calculated.[7]

Swelling index study

The extent of swelling was measured in terms of percentage weight gain by the tablet. The swelling index of all formulation was studied. One tablet from each batch was kept in a Petridis containing 2% agar gel plates with the core facing the gel surface and incubated at 37±1 °C. The tablet was removed every two hour interval up to 12 hour and excess water blotted carefully using filter paper. The swollen tablets were re-weighed (W_t). The swelling index (SI) of each tablet was calculated according to the following equation.[9, 10]

$$SI = \frac{(W_t - W_0)}{W_0} \times 100$$

Where W_0 = initial weight, W_t = weight after time t

Measurement of bioadhesive force

Bioadhesive force of the tablets was measured on a modified physical balance that is shown in **figure 1**.[12] 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.[11, 13] By using this weight, bio-adhesive force for all the formulations of Sumatriptan buccal mucoadhesive tablets were calculated using following equation

$$N = (W \times g)/1000$$

Where N is bio adhesive force, W is the weight required for the detachment of two vials in grams, and g is the acceleration due to gravity.

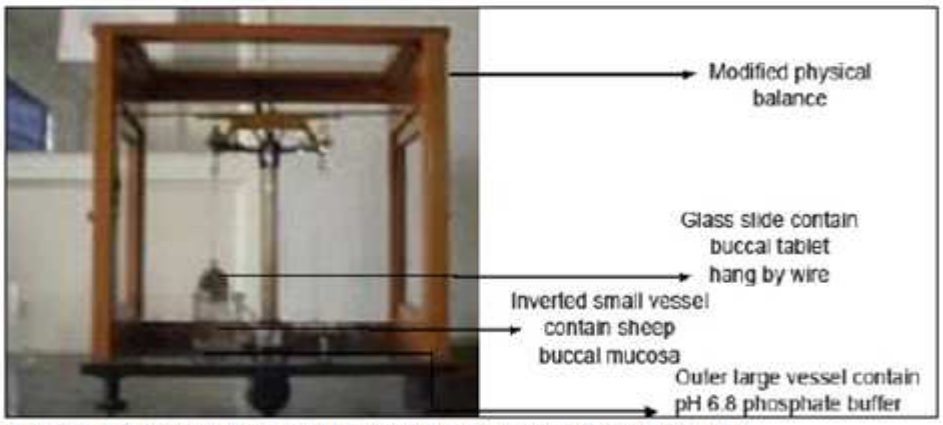

Figure 1: Modified physical balance for mucoadhesive studies

***In-vitro* drug release study**

The *in-vitro* dissolution study was conducted for all the formulations using an eight station USP dissolution rate test apparatus type-II (LABINDIA DS 8000, Mumbai, India.). A total volume of 900 ml of phosphate buffer P^H 6.8 was taken as dissolution medium, which was maintain at 37°C ± 0.5°C at 50 rpm. 5ml of aliquots were periodically withdrawn and the same volume was replaced with an equal volume of fresh dissolution medium. Samples were collected at 1 hour intervals and after filtering by Whatmann filter paper, were analyzed spectrophotometrically at 227nm for determination of Sumatriptan that were released from mucoadhesive sustained release tablets.[12]

Ex vivo permeation study of buccal mucoadhesive tablets

Ex vivo permeation study of Sumatriptan mucoadhesive buccal tablet was carried out on goat buccal mucosa membrane (as semi permeable membrane) using modified Franz diffusion cell with a diffusion area of 17.35 cm^2 with the acceptor compartment volume capacity of 45 ml and maintained at 37 ± 0.5°C. Fresh goat buccal mucosa was mounted between the donor and receptor compartments. The mucoadhesive tablet was placed into the donor compartments and clamped together. The donor compartment was filled with 1 ml of phosphate buffer P^H 6.8. The receptor compartment was filled with phosphate buffer P^H 6.8 and the hydrodynamics in the compartment was maintained by stirring with a magnetic bead at uniform slow speed. 5 ml samples were withdrawn at pre-determined time intervals and replaced with 5ml of same fresh buffer. Then the sample were analyzed using an UV spectrophotometer at 227 nm for the amount of Sumatriptan absorbed through buccal mucosa.[14]

Characterization of the _in vitro_ drug release profile

The rate and mechanism of release of Sumatriptan from prepared buccal mucoadhesive tablet were analyzed by fitting the dissolution data into following exponential equations.

Zero order release equation:

$$Q = K_0 \, t$$

Where Q is the amount of drug released at time t and K_0 is the zero order release rate constant.

The first order equation:

$$\log(100 - Q) = log100 - K_1 \, t$$

Where, K_1 is the first order release rate constant.

The dissolution data was fitted to the Higuchi's equation:

$$Q = K_2 t^{1/2}$$

Where, K_2 is the diffusion rate constant.

The dissolution data was also fitted to the Korsmeyer-Peppas equation, which is often used to describe the drug release behaviour from polymeric systems:

$$\log\left(\frac{M_t}{M_\infty}\right) = \log K + n \, logt$$

Where M_t is the amount of drug released at time *t*, M_∞ is the amount of drug release after infinite time, *K* is a release rate constant and *n* is the diffusion exponent indicative of the mechanism of drug release.

For matrix tablets, if the exponent $n < 0.5$, then the drug release mechanism is quasi-fickian diffusion (If $n = 0.5$ then fickian diffusion and if the value is $0.5 < n < 1$, then it is anomalous diffusion coupled with erosion. An exponent value of 1 is indicative of Case-II Transport or typical zero-order and $n > 1$ non-fickian super Case II). The diffusion exponent was based on Korsmeyer-Peppas equation.

Hixson-Crowell recognized that area of the particle is proportional to the cubic root of its volume, and derived an equation as follows

$$W_0^{1/3} - W_t^{1/3} = K_s t$$

Where *Wo* is the initial amount of drug, *Wt* is the remaining amount of drug in dosage form at time *t*, and K_S is a constant incorporating the surface volume relation. The graphs are plotted as cube root of percent drug remaining versus time.[17, 18]

Drug excipients compatibility studies

Drug excipients compatibility studies were done by FTIR and DSC

Fourier Transform Infrared (FTIR) spectroscopy:

Fourier transform infrared (FTIR) study was performed to verify any physical or chemical interaction between the pure drug and the excipients used. The FTIR studies of pure drug Sumatriptan, HPMC K4M, carbopol 934P, Ethyl Cellulose, guar gum and the formulation that contains all those ingredients (SMF_{12}) were carried out. It was performed by potassium bromide (*KBr*) pellet method. The samples were triturated with *KBr* and pellet was prepared by setting the pressure to 100 kg/cm^2 for 2 min. The obtained pellet was analyzed in FTIR 8400S, Shimadzu, Japan. The peaks that were obtained for the pure drug, polymers and formulation, characterised for the presence of different functional group and ensured that there was no extra peaks formed which usually indicates formation of new functional group.[19, 20]

Differential Scanning Calorimetric (DSC) analysis:

Another method of estimating the physical interaction between drug and polymers used for the formulation of different dosage form is thermal analysis by DSC or TGA techniques. In the present studies the DSC analysis of Sumatriptan and formulation that contains all the ingredients used for preparation buccal mucoadhesive tablets (SMF_{12}) were carried out using a Shimadzu DSC 60, Japan; to evaluate any possible polymer drug

thermal interaction. Exactly weighed 5 to 6 mg samples were hermetically sealed in aluminium crucible and heated at constant rate of 10° C/min over a temperature range of 40 to 300°C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.[21]

Stability in human saliva

Stability studies of the buccal tablet were performed for optimized formulation in artificial human saliva. The artificial human saliva was prepared by using following material listed in **table 2** and filtered through a filter paper. The buccal tablet was placed in separate Petri dishes containing 5 ml of artificial saliva and placed in a temperature controlled oven for 10 hour at 37 °C ± 0.2 °C at regular intervals (0, 3, 6, and 10 h), the buccal tablet was examined for change in colour, surface area, and integrity.[10]

Table 2: Composition of artificial saliva Materials

Composition	Amount (gm/lit)
Sodium chloride (NaCl)	0.4
Potassium chloride (KCl)	0.4
Calcium chloride($CaCl_2.2H_2O$)	0.8
Sodium di hydrogen phosphate ($NaH_2PO_4.2H_2O$)	0.78
Sodium sulfide ($NaS.9H_2O$)	0.005
Urea	1

Results and Discussion

Evaluations of precompression parameters were usually carried out to ensure the tyre of flow properties of dry powder and granules during tablet punching. The bulk densities of dry powder blends of all formulations were found to be in the range of 0.248 to 0.292 g/cm^3 and the tapped densities were found to be in between 0.320 to 0.367 g/cm^3. This indicates good packing capacity of powder blends. Bulk density and tapped density measurements found that density of a powder depends on particle packing and that density changes as the powder consolidates. Values of Carr's index below 16 usually show good flow characteristics, but readings above 23 indicate poor flowability. Carr's indexes of all the formulations were found "between" 11.65 to 23.79 that indicate excellent to passable flow properties. Formulations SMF_5 and SMF_8 having Carr's index more 23 which indicates pore flow properties and presences of more fine particles. Hausner's ratio is simple method to evaluate stability of powder column and to estimate flow properties. Low range was observed of Hausner's ratio that indicates good flow ability. In all formulations the Hausner's ratios were found "between" 1.13 to 1.31 that indicates good flow and the formulation having Hausner's ratios more than 1.25 requires adding glidant to improve flow properties. Angle of repose is suited for particle > 150μm.Values of angle of repose ≤ 25 generally indicates the free flowing material and angle of ≥ 40 suggest a poor flowing material. The angle of repose is indicative of the flowability of the material. The angle of repose of all formulations fell within the range of 18.46 to 25.40 *i.e.* dry powder blends were of good flow properties. The evaluation results of all precompression parameters for the formulation SMF_1 to SMF_{12} were shown in the **table 3**.

Table 3: Precompression parameters of dry powder blends of Sumatriptan mucoadhesive matrix tablet formulations SMF_1- SMF_{12}

F. No.	Bulk density (gm/cc)	Tapped density (gm/cc)	Angle of repose	Carr's index	Hausner's ratio
SMF_1	0.265±0.08	0.332±0.07	22.45±0.16	20.18	1.25
SMF_2	0.286±0.07	0.367±0.09	25.08±0.12	22.07	1.28
SMF_3	0.274±0.04	0.345±0.09	22.94±0.09	20.57	1.25
SMF_4	0.288±0.05	0.326±0.09	18.46±0.15	11.65	1.13
SMF_5	0.269±0.09	0.353±0.10	25.40±0.17	23.79	1.31
SMF_6	0.274±0.04	0.344±0.08	21.35±0.11	20.34	1.25
SMF_7	0.285±0.07	0.361±0.07	22.66±0.16	21.05	1.26
SMF_8	0.248±0.09	0.324±0.09	22.73±0.12	23.46	1.31
SMF_9	0.267±0.09	0.339±0.06	23.28±0.12	21.24	1.26
SMF_{10}	0.292±0.06	0.358±0.05	21.46±0.14	18.44	1.23
SMF_{11}	0.258±0.10	0.320±0.08	22.14±0.09	19.38	1.24
SMF_{12}	0.270±0.11	0.322±0.06	20.25±0.11	16.15	1.19

All values are expressed as average± SD; (n=3)

Table 4: Evaluation of post-compression parameters of Sumatriptan mucoadhesive matrix tablets formulation *SMF_1- SMF_{12}*

F. No.	Average hardness (kg/cm^2)	Average Weight Variation (mg)	Average friability (% w/w)	Average thickness (mm)	Content uniformity (%)	Bioadhesive strength (N)
SMF_1	4.63±0.7	202±2.43	0.52±0.05	3.43±0.14	98.84±1.6	0.268±0.007
SMF_2	4.82±0.4	201±2.28	0.47±0.06	3.39±0.11	99.52±1.2	0.312±0.002
SMF_3	4.44±0.6	200±2.35	0.56±0.02	3.35±0.14	100.4±1.7	0.196±0.004
SMF_4	4.89±0.3	203±2.46	0.53±0.05	3.28±0.15	99.44±1.5	0.216±0.002
SMF_5	4.75±0.3	198±2.82	0.45±0.06	3.29±0.09	98.56±1.2	0.269±0.001
SMF_6	4.49±0.5	201±2.54	0.52±0.03	3.31±0.16	99.63±1.4	0.225±0.006
SMF_7	4.40±0.6	200±2.24	0.48±0.06	3.36±0.12	98.22±1.8	0.288±0.004
SMF_8	4.58±0.4	199±2.51	0.41±0.04	3.38±0.15	102.6±1.4	0.257±0.006
SMF_9	4.42±0.6	202±2.42	0.40±0.05	3.40±0.13	99.75±1.5	0.214±0.007
SMF_{10}	4.56±0.3	199±2.41	0.54±0.06	3.32±0.12	99.18±1.4	0.229±0.003
SMF_{11}	4.68±0.6	200±2.52	0.39±0.07	3.38±0.09	98.46±1.5	0.182±0.002
SMF_{12}	4.76±0.4	202±2.62	0.42±0.04	3.39±0.10	99.61±1.2	0.273±0.006

All values are expressed as average± SD; (n=3)

All the physical parameters evaluated after compression of Sumatriptan mucoadhesive matrix tablets were found to be satisfactory. Typical tablet defects, such as capping, chipping and picking, were not observed. The physicochemical characterizations of different batches of Sumatriptan mucoadhesive tablets are given in **table 4**. The average thickness of the tablets were ranged between 3.28±0.15 to 3.43±0.14 mm and all the formulations were within acceptable limits. All the batches showed uniform thickness. Weight variations for different formulations were found to be 198±2.82 to 203±2.46mg. The average percentage deviation of all tablet formulations was found within the limit, and hence all formulations passed the test for uniformity of weight as per official requirement. The hardness of all the Sumatriptan mucoadhesive matrix tablets formulations were ranged from 4.89±0.3 to 4.40±0.6 kg/cm^2 that were according to the specification. The percentage friability of all the formulations were ranged from 0.40±0.05% to 0.56±0.02% and found within the prescribed limits. The percentages of drug content of the entire formulations of Sumatriptan mucoadhesive matrix tablet (SMF_1 to SMF_{12}) were found "between" 98.22±1.8 to 102.60±1.4 which were within the acceptable limits.

Determination of bioadhesive force is important parameters for mucoadhesive formulation as it decides to what extend the formulation will adhere to the mucosa membrane. Bioadhesive forces were determined for all the formulations (SMF_1-SMF_{12}). The formulations that contained higher concentration of ethyl cellulose showed more bioadhesive force then other formulations. Formulation SMF_2 having 25% of ethyl cellulose had highest bioadhesive force. Next to ethyl cellulose, the formulations that contained higher concentration of carbopol 934P showed better bioadhesive force that was noticed in case of SMF_1 and SMF_8. Lower bioadhesive force was noticed for the formulations containing higher concentration of natural polymer 'guar gum' that was observed in case of formulation SMF_3 and SMF_9.

Swelling study was performed on all the formulations (SMF_1 to SMF_{12}) for 10 hours. The result of swelling index was shown in **figure 2**. The formulation that contains HPMC K4M, carbopol 934P and guar gum showed higher swelling indices due to higher hydrophilicity and more water uptake of the polymers. But reverse is observed with the formulations containing higher percentage of ethyl cellulose as it is a hydrophobic polymer. The formulation SMF_4 that contains 25% of HPMCK4M, 12.5% of carbopol and 12.5% of guar gum showed higher swelling indices then other formulations. The formulation SMF3 that contains 25% of HPMCK4M and 25% of guar gum showed higher swelling indices but after 7 hour, the formulation started bulk erosion as guar gum is a natural polymer. Formulation SMF_2, SMF_7, and SMF_{10}, that contain more % of ethyl cellulose had lower swelling index in comparison to other formulation as ethyl cellulose is a hydrophobic polymer.

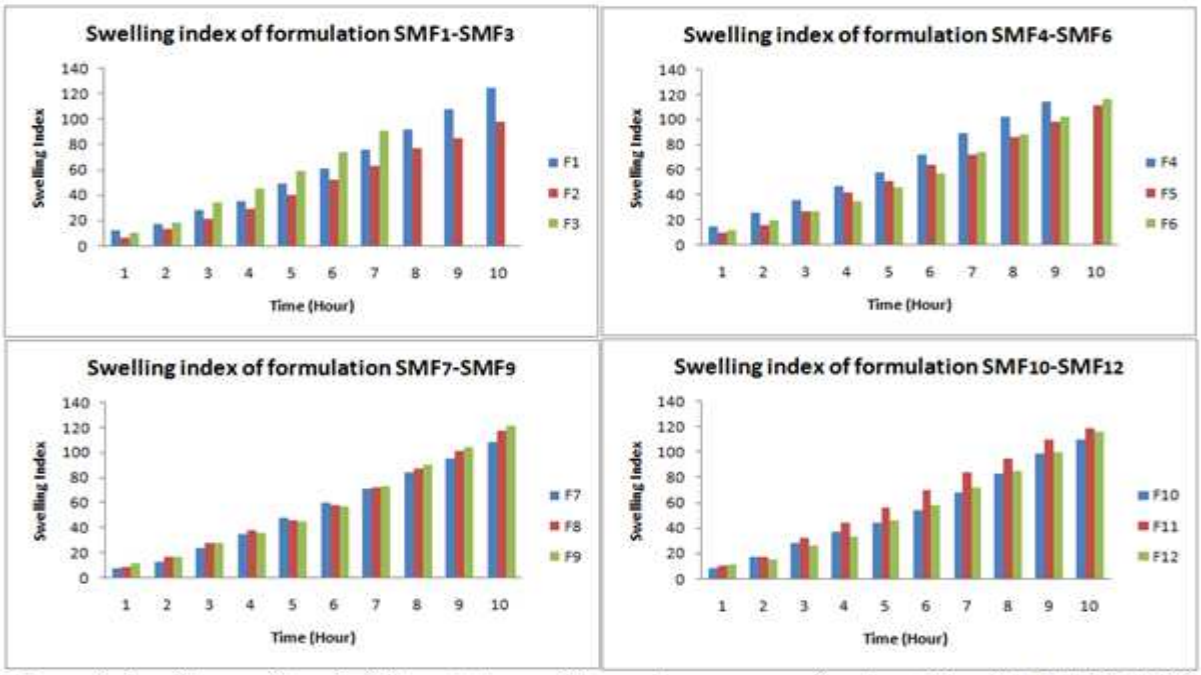

Figure 2: Swelling studies of all formulations of Sumatriptan mucoadhesive tablets (SMF1-SMF12)

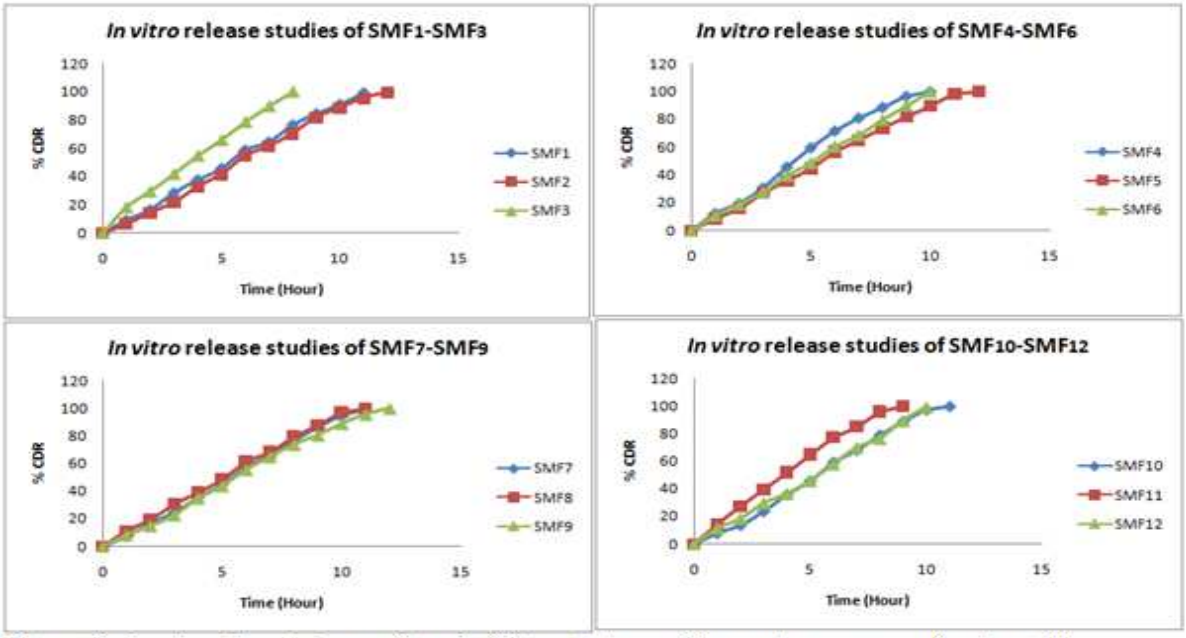

Figure 3: *In vitro* dissolution studies of all formulations of Sumatriptan mucoadhesive tablets

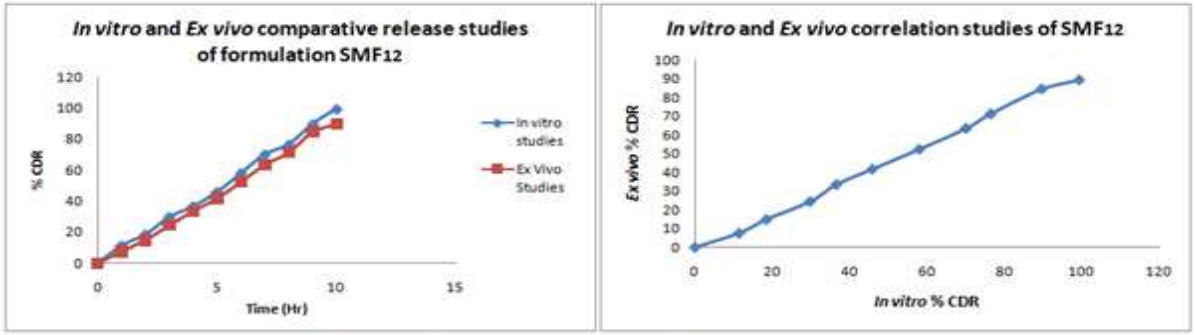

Figure 4: Comparative release profile of In vitro and Ex vivo release studies and correlation

In order to optimise the *in vitro* drug release along with bioadhesive force, different hydrophilic matrix polymers *viz.*, HPMC K4M, Carbopol 934P, guar gum and hydrophobic matrix polymer *viz.*, ethyl cellulose were used for 12 different formulations of Sumatriptan mucoadhesive matrix tablets. The drug release profiles of different formulations were shown in **figure 3**. In these studies HPMCK4M was usually used for sustained release effect with bioadhesive strength to some extent. It was observed that using hydrophilic polymer alone caused initial burst release because drug is hydrophilic in nature and maximum release upto 8 to 9 hour. So one more hydrophobic polymer *i.e* ethyl cellulose was added to reduce the initial burst release and also it had remarkable bioadhesive strength. SMF_2 formulation that contained 25% of HPMC K4M and 25% of ethyl cellulose, released the drug upto 12 hour but initial release was very low to elicit therapeutic action. Among all the formulations, SMF_{12} could be considered as optimised formulation as the initial release was 11% and maximum release upto 10 hours and had remarkable bioadhesive strength that may be adequate criteria for bioadhesive formulation. Formulation SMF_3 containing 25% of HPMC K4M and 25% of guar gum showed an initial burst release with maximum release upto 8 hour and also had lowest bioadhesive strength.

Ex vivo permeation studies (diffusion studies) were carried out for optimised formulation (SMF_{12}) using goat buccal mucosa and compared with *in vitro* drug release studies (dissolution studies). From the above studies, the cumulative percentage of drug release for *in vitro* dissolution studies was 99.09% within 10 hour where it was 89.36% within 10 hour for ***ex vivo*** studies. The difference in drug release profiles may be attributed due to low permeability of the drug. Both the release profile were correlated on point to point basis and shown in **figure 4**.

The *in vitro* dissolution data of optimised formulation SMF_{12} were fitted in different kinetic models viz. zero order, first order, Higuchi, Hixon-Crowell and Korse-Meyer Peppa's kinetic model equation and the graphs were plotted and shown in **figure 5**. The zero-order plots were found to be fairly linear as indicated by their highest regression values. The release exponent 'n' for optimised formulation SMF_{12} was found to be 0.95 ($0.5 < n < 1$), which appears to indicate a coupling of the diffusion and erosion mechanism so-called anomalous diffusion. So in present study *in vitro* drug release kinetic of optimised formulation of Sumatriptan mucoadhesive matrix tablets followed zero order release kinetic models and drug release mechanism is anomalous diffusion coupled with erosion. The regression values of kinetic studies were noted in **table 5**.

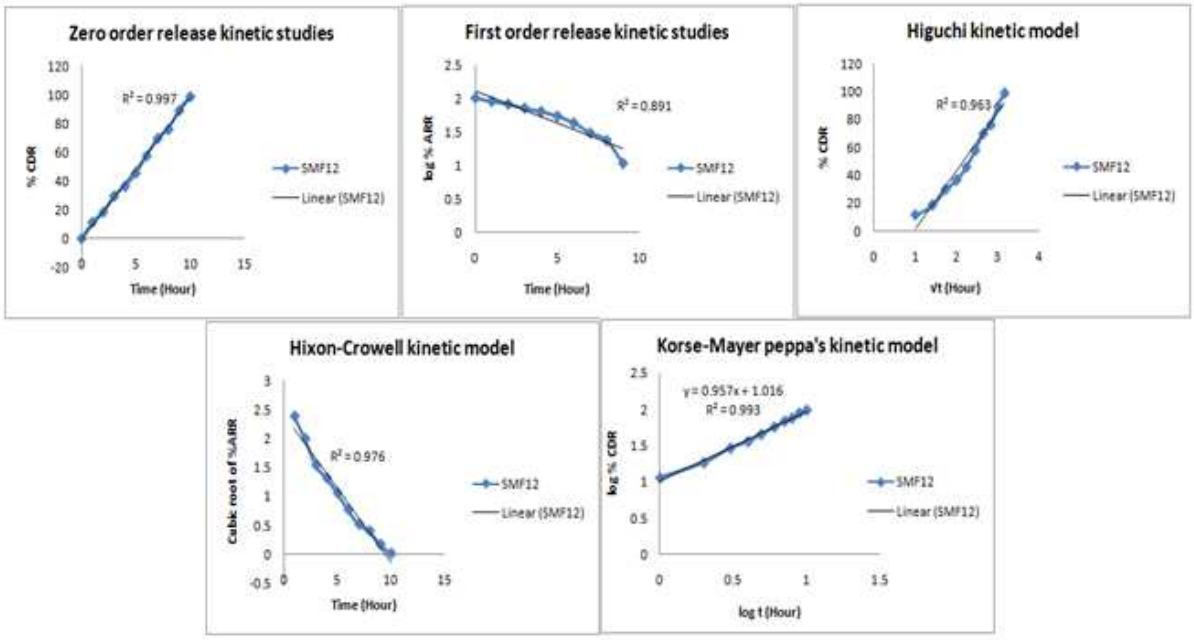

Figure 5: *In vitro* release kinetic profile of optimised formulation SMF12

Table 5: Regression values of *in-vitro* release kinetic study optimized Sumatriptan mucoadhesive matrix tablet (SMF_{12}**)**

Formulation	R^2value of Zero order	R^2 value of 1st order	R^2value of Higuchi model	R^2value of Hixon-Crowell model	R^2value of Peppa's model	'n' value of Peppa's model
SMF_{12}	0.997	0.891	0.963	0.976	0.993	0.957

The physicochemical compatibility of the pure drug (Sumatriptan succinate) and the polymer that used for the formulations was established through FTIR studies. Sumatriptan succinate exhibits characteristics peaks at respective wave numbers i.e. S=O stretching (1079 cm^{-1}), tertiary amine (3094 cm^{-1}), C–N stretching (1296 cm^{-1}, 1233cm^{-1}), C-S stretching (634 cm^{-1}), N–H stretching (3376 cm^{-1}). Thus it was evident that all the characteristic peaks that were present in the spectra of pure drugs replicated in the same region in the spectra of optimised formulations of Sumatriptan mucoadhesive matrix tablet (SMF_{12}) indicating that there is no significant interaction between the drugs and the polymers. However, additional peaks were absorbed in optimised formulation which could be due to the presence of polymers. The FTIR spectra of drug and optimised formulations were shown in **figure 6**.

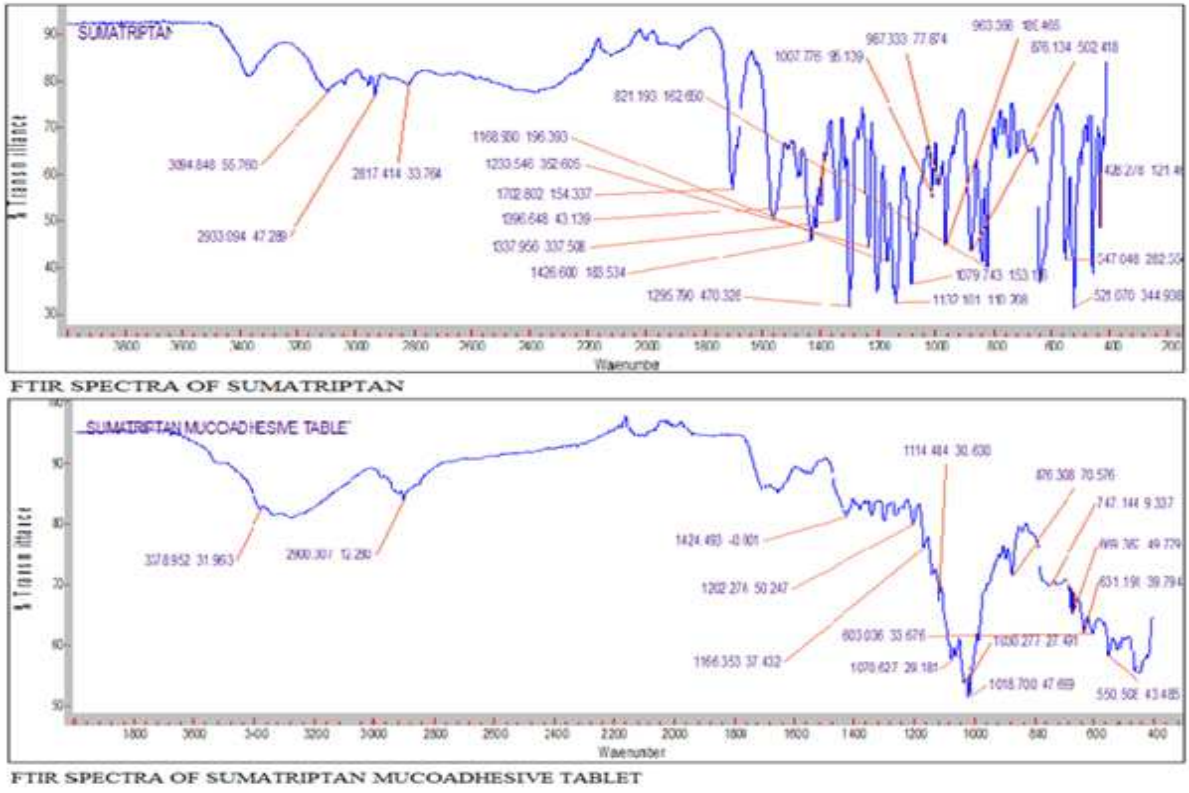

Figure 6: FTIR studies of pure drug and optimised formulation SMF12

DSC studies were conducted on the pure drug and for optimised formulation (SMF_{12}). DSC thermogram of pure Sumatriptan showed sharp endothermic peak at 172.3 °C. Similar endothermic peaks were obtained at 159.1°C for the optimized formulation. The endothermic peak that appears at 76.4 °C for HPMC K4M also appears the similar peaks at 85.6 °C in optimised formulation SMF_{12}. The endothermic peak for ethyl cellulose that appears at 139.5 ^{0}C and 199.4^{0}C also appears at 159.3^{0}C and 217.2 ^{0}C for optimised formulation respectively. The endothermic peak that appears at 247.2 ^{0}C and 246.4 ^{0}C for Sumatriptan and carbopol 934P respectively also appears at 217.2 ^{0}C in optimised formulation without any shifting. It was noticed that the endothermic peaks that appears in optimised formulation is the intermediate of all the polymer and drug used in the formulation. Presence of all peaks indicates that all ingredients are compatible with Sumatriptan succinate and there is no thermal (physical) incompatibility between the selected ingredients. DSC thermogram of optimised formulation, drug and polymers are shown in **figure 7**.

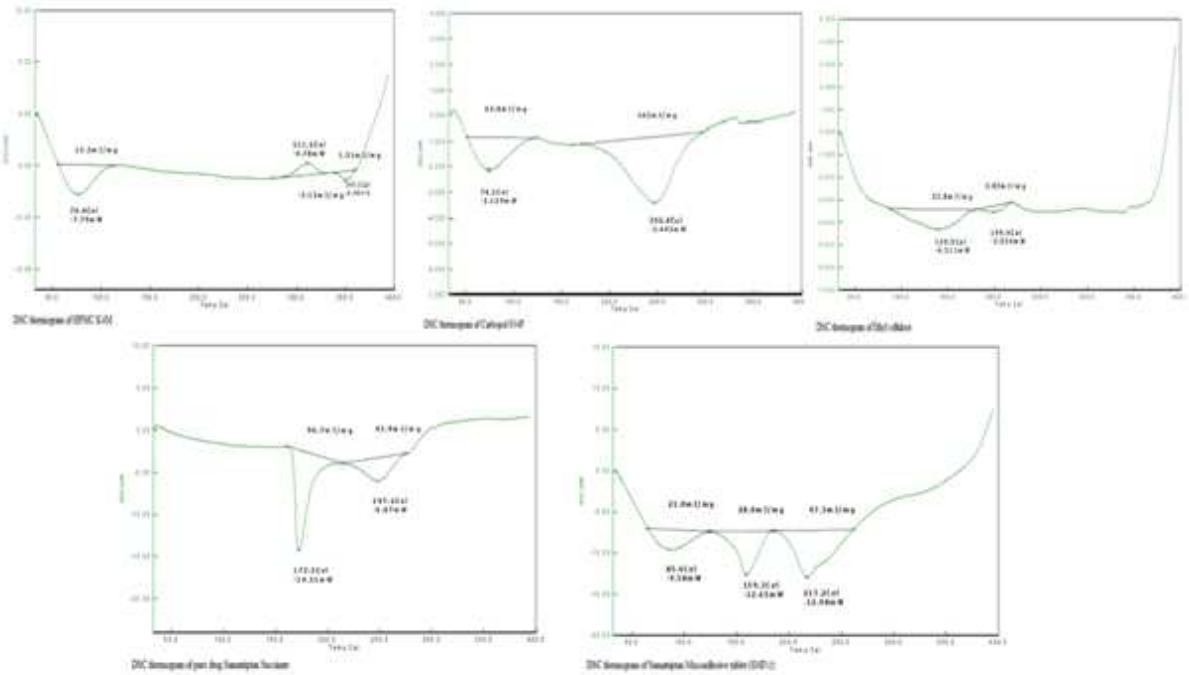

Figure 7: DSC studies of pure drug, polymers and optimised formulation SMF12

The stability studies performed in artificial human saliva that was prepared in the laboratory would be more accurate to mimic the stability of the Sumatriptan succinate mucoadhesive buccal tablet in oral cavity *in vivo*. Based on the results of *ex vivo* mucoadhesion, *in-vitro* release studies, formulation SMF_{12} was selected for stability study. Stability studies in prepared artificial human saliva showed no change in the colour of Sumatriptan succinate buccal tablets, which would have happened if drug was unstable in human saliva. Results reveal that the buccal tablets are having sufficient stability in the prepared artificial saliva. The thickness and diameter of tablets slightly changed due to swelling of the polymers in prepared artificial saliva but buccal tablets did not collapse till the end of studies confirming that the device strength was sufficient.

Conclusion

In the present work Sumatriptan buccal mucoadhesive matrix tablet were successfully developed. The major challenge in this work was to study the effect of various low density polymers on *in vitro* release rate of buccal mucoadhesive of Sumatriptan with adequate bioadhesive strength to contact the buccal mucosa for prolonging the drug residence time. The mucoadhesive and *in vitro* drug release effect of different types of low density matrix forming polymers HPMC K4M, Carbopol 934P, Guar gum and Ethyl cellulose were studied. The main objective of using hydrophobic polymer ethyl cellulose with HPMC was to prevent the burst release effect the hydrophilic drug under study with hydrophilic polymer like HPMC, carbopol, guar gum and it is having good bioadhesive nature which was successfully developed. Formulation $SMFF_{12}$ that contained 12.5% of all the four polymers i.e. HPMC K4M, Carbopol 934P, guar gum and ethyl cellulose showed sustained drug release for 10 hour (99%) and had adequate bioadhesive strength, emerged as optimised formulation. Increase in proportion of hydrophilic polymer caused initial burst release effect. To overcome that effect hydrophobic polymer ethyl cellulose were added. *In vitro* drug release profiles of optimised formulation were compared with *ex vivo* drug diffusion studies and *in vitro-ex vivo* correlation were established. Kinetic of *in vitro* drug release of optimized formulation $SMFF_{12}$ found to be zero order having drug release mechanism as anomalous diffusion coupled with erosion. FTIR studies revelled that there is no chemical interaction between drug and polymers. DSC studies proved that no thermal interaction between the drug Sumatriptan and polymer used in the present studies. The stability studies were carried out in artificial human saliva and the optimised formulation were found to be stable without any remarkable physical changes. Thus from the results of the current study clearly indicate, a promising potential of the Sumatriptan buccal mucoadhesive system as an alternative to the conventional dosage form as it enhance bioavailability of the Sumatriptan by bypassing the first pass metabolism and by producing sustained release effect for sustainable migraine. However, further clinical studies are needed to assess the utility of this system for patients suffering from migraine.

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