

**FORMULATION AND EVALUATION OF MUCOADHESIVE
BILAYER BUCCAL TABLET OF SUMATRIPTAN SUCCINATE****Manisha R. Pundge*, Prafull P. Patil, Dr. Shashikant D. Barhate**Shree Sureshdada Jain Institute of Pharmaceutical Education and Research, Jamner,
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Author****Manisha R. Pundge**Shree Sureshdada Jain
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Pharmaceutical Education
and Research, Jamner,
Dist.Jalgaon Maharashtra,
India 424206.**ABSTRACT**

Objective: To develop mucoadhesive bilayer buccal tablet of Sumatriptan succinate as controlled release tablet to enhance its bioavailability and reduce its frequency of dose. **Method:** Sumatriptan succinate tablets were prepared with natural mucoadhesive polymer Sodium alginate, alone had the bioadhesive forces suitable for buccal bioadhesive tablets, with slightly reducing its strong mucoadhesive property by addition of HPMC, to prevent from damaging of skin due to strong mucoadhesive property of Sodium alginate. 50mg backing layer compressed to control the release of drug from tablet. Ideal batch shows maximum mucoadhesive time and maximum mucoadhesive strength of 13.10g. **Results :** The selected batch F3 and F6 shows maximum release up to 99% and 98% in 6hrs. **Conclusion:** Mucoadhesive bilayer buccal tablet of Sumatriptan succinate improve

bioavailability. A combination of polymer Sodium alginate: HPMC shows good drug release as compared to other batches. The ratio of both polymer was taken as 2:1 showing maximum drug release. These both polymer combinations show good mucoadhesive strength, good permeation also.

KEYWORDS: Bilayer buccal tablet of Sumatriptan succinate, mucoadhesive strength, Sodium alginate, in vitro permeation study.

INTRODUCTION

There are various dosage forms for buccal drug delivery like buccal tablet. Buccal delivery of drug, as an alternative to the oral route of drug administration, is a subject of growing interest because of its numerous advantages such as good accessibility, robustness of epithelium,

facile removal of dosage form in case of need, relatively low enzymatic activity, prevent drug degradation in gastrointestinal tract and avoid hepatic first-pass metabolism. buccal patches, buccal patch, adhesive gels etc.. A suitable buccal drug delivery system should possess good bioadhesive properties, so that it can be retained in the oral cavity for desired duration. Bioadhesive polymers have been used extensively for use in buccal drug delivery systems like polyacrylic acid, polycyanoacrylate, various grades of Hydroxypropyl methyl cellulose, etc. This unidirectional drug release can be achieved by using bilayer devices using polymers like Ethyl cellulose, carbopol, magnesium separate, polycarbophil, etc.^[2,3]

Sumatriptan succinate is 5-HT₁ receptor agonist used in the treatment of migraine. Sumatriptan succinate is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methylindole-5-methanesulfonamide succinate. The physicochemical properties of sumatriptan succinate include its half life about 2.5 hours, molecular weight about 413, bioavailability 15%(oral), 96%(subcutaneous), metabolism by MAO-A enzyme.

Migraine is a mysterious disorder characterised by pulsating headache, usually restricted to one side, which comes in attacks lasting 4-48 hours and is often associated with nausea, vomiting, sensitivity to light and sound, vertigo, loose motion and other symptoms. Migraine attacks consist of an initial visual disturbance in which a flickering pattern followed by a blind spot (a scintillation scotoma) progress gradually across an area the visual field. The visual disturbance is followed, about 30 minutes later, by a severe throbbing headache, starting unilaterally, often accompanied by photophobia, nausea, vomiting and prostration. In fact the visual aura occurs only in about 20 % of migraine sufferers, although many experience other kind of premonitory sensation. Sometimes attacks are precipitated by particular food or by visual stimuli, but more often they occur without obvious cause. The oral formulation offers convenience and ease of use but produces unreliable blood levels and inconsistent response. Recurrence (rebound) occurs with these formulations. 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. 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. Other advantages are non-invasive administration, rapid-onset of action, convenient and easily accessible site, self administrable, low enzymatic activity, etc.

The rationale of this research work is to develop a new mucoadhesive bilayer buccal tablet of

sumatriptan succinate to counteract the problems associated with the conventional available marketed preparation of sumatriptan succinate that they have low bioavailability, frequent dosing as a limitation.^[3,4,6]

MATERIAL AND METHOD

Sumatriptan succinate (Wockhardt limited MIDC, Cidco, Aurangabad), sodium alginate and HPMC (BASF Ltd, Mumbai) were obtained as gift sample. All other chemicals and reagents used in the work were of analytical grades.

METHODS

Drug identification and drug- excipients compatibility study Melting Point: Melting point of Sumatriptan Succinate was determined by taking a small amount of sample in a capillary tube closed at one end and placed in Digital melting point apparatus. (Veego Digital Melting point apparatus) The melting point was recorded. UV Spectrum and Calibration curve of Sumatriptan Succinate The UV spectrum of Sumatriptan succinate was obtained by using Shimadzu UV1800. Accurately weighed 100 mg of the drug was dissolved in sufficient quantity of buffer pH 6.8 and volume made up to 100 ml known as stock solution (1000 µg/ml) . 1ml of aliquot was withdrawn and volume was made up to 100 ml using buffer pH 6.8 to obtain the concentration of 10µg/ml (stock 2). Subsequently aliquots were removed from stock 2 to give 2-10µg/ml. The resultant solution was scanned from 400 to 200 nm.

Compatibility Studies

Fourier Transform Infrared Spectroscopy (FTIR): IR spectra of Sumatriptan succinate and Sumatriptan succinate + sodium alginate, 1-5 mg of the powder samples was triturated with approximately 300 mg of dry KBr and compressed as pellet ,were recorded using SHIMADZU: IRAffinity-1FTIR spectrophotometer.

The FTIR spectra of drug sample were recorded. Similarly, the procedure repeated by dispersing a sample {drug, drug and polymer (1:1) as well as mixture of drug and polymers (1:1:1:1) in FTIR cuvette.

Differential Scanning Calorimetry (DSC): DSC thermogram of Sumatriptan succinate and Sumatriptan succinate + sodium alginate, 2-6 mg of samples in aluminum pans hermetically sealed and subsequently scanned at 10°C/min under nitrogen gas purge, were recorded using a thermal analysis instrument (SSIO 6300 Japan) with a liquid nitrogen sub ambient

accessory. The DSC thermogram was recorded. The physical mixture of drug with polymers for compatibility studies were prepared by triturating drug and drug polymer (1:1) in a dried mortar for 5 min and kept as it for 24 hrs.

Preparation of of Mucoadhesive bilayer buccal Tablet Blend: Core tablet

Shifting: Sumatriptan, HPMC, Sodium alginate, crosscarmellos sodium, MCC 102, SLS Weighed. Mixed in mortar pestle and triturated for 15 minute to obtained homogeneous mixture without addition of magnesium stearate. Addition of magnesium stearate and triturated till get fine powder. Mixed above mixture properly in polythene bag. Ready for direct compression.

Backing membrane: Ethyl cellulose weigh (50mg for each tablet) and transfer in mortar. Ethyl cellulose granules were prepared by wet granulation method using isopropyl alcohol as the granulating solvent. The wet mass was passed through mesh #8 and dried at 40°C for 1 hour. The granules were passed through mesh #22. Ethyl cellulose granules were added on core tablet to subsequently compressed at constant and maximum compression force. The composition of preliminary trial batches of mucoadhesive bilayer buccal tablet of Sumatriptan succinate. Sumatriptan succinate, Sodium alginate, HPMC, Crosscarmellose sodium, SLS, MCC PH102, Aspartame, magnesium stearate were passed through sieve #100. Firstly, all the ingredients were mixed with the help of mortar and pestle. Magnesium stearate was finally added as a lubricants. The blend was compressed into 150 mg weight of core tablet, and then Ethyl cellulose granules used as a backing membrane, hardness 3-6 kg/cm² using the 12 station rotary tablet compression machine using 9.0 mm round standard concave punches (F1-F3). (F4-F6) using the 12 station rotary tablet compression machine using 8.0 mm for core tablet and for backing membrane 7.0 mm round standard concave punch.^[6,7]

Formulation of Mucoadhesive bilayer buccal Tablet of Sumatriptan succinate

Table no.1: Composition of mucoadhesive bilayer buccal tablet of Sumatriptan succinate

SR.No.	Ingredients	F1	F2	F3	F4	F5	F6
1	Sumatriptan succinate	25	25	25	25	25	25
2	Sodium alginate	25	30	50	20	25	50
3	HPMC	75	38	28	50	53	13
4	Crosscarmellose sodium	-	-	-	20	10	15
5	SLS	2	4	4	2	4	4
6	MCC PH 102	20	50	40	30	30	40
7	Magnesium stearate	2	2	2	2	2	2

8	Aspartame	1	1	1	1	1	1
9	Ethyl cellulose (Backing membrane)	50	50	50	50	50	50
Average weight		200	200	200	200	200	200

All quantity taken in mg

Evaluation of Tablets

Evaluation parameters of tablets mentioned in the Pharmacopoeias need to be assessed, along with some special tests are discussed below.

Weight variation

Twenty tablets were selected randomly from each formulation and weighed individually. The individual weights were compared with the average weight for weight variation. The I.P. allows a little variation in the weight of a tablet.

Thickness

Ten tablets from each formulation were taken randomly and their thickness was measured with vernier caliper (Aerospace digital caliper).

Hardness

The tablet was selected randomly from each batches and hardness was determined by Monsanto tablet hardness tester. It is expressed in kg/cm².

Friability

Friability of the prepared tablets was evaluated as the percentage weight loss of 10 tablets tumbled in a friabilator (Model EF2 ELECTROLAB, INDIA) 4 min at 24 rpm. A maximum loss of weight is not greater than 1.0 per cent is acceptable for most tablets.

$$\% F = \frac{\text{Initialweight} - \text{Finalweight}}{\text{Initialweight}} \times 100$$

Drug content

Drug content of prepared bilayer tablet was determined by UV Spectrophotometric method for more accurate results as follows

Spectrophotometric conditions

Apparatus : UV Spectrophotometer. SHIMADZU (1800).

Wavelength : 226.6nm for sumatriptan succinate mucoadhesive bilayer buccal tablet.

Preparation of sample solution: Take 10 tablets of each batch were accurately weighed and crushed in mortar and pestle. Powder was dissolved in ethyl alcohol and filtered through a 0.45- μ m filter paper. The filtered was diluted with phosphate buffer (pH 6.8). The drug content was analyzed spectrophotometrically at 226.6nm. using an UV spectrophotometer using a reference standard curve of Sumatriptan succinate. Absorbance carried out against respective reagent blanks (6.8pH buffer).^[5,6]

In vitro drug release study of Mucoadhesive bilayer buccal of Sumatriptan succinate

The *in vitro* drug release studies of tablets were performed by employing the USP XXVIII paddle method at $37\pm 0.5^\circ\text{C}$ and at 50 RPM and phosphate buffer (pH 6.8) as dissolution media. The samples (5 ml) were removed at an interval of 0, 1, 2, 3, 4, 5, 6; hrs interval and replacing same volume by freshly prepared dissolution media of phosphate buffer pH 6.8 for maintaining sink condition. The aliquots were filtered through 0.45 μ filter and were analyzed by UV - spectrophotometer (Shimadzu 1800) at 226.6 nm for estimation of sumatriptan succinate.^[6,7]

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 and 50 RPM, using a magnetic stirrer. Sheep's 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 and the donor compartment was maintained by stirring with a magnetic bead at 50 rpm. The buccal tablet was placed in the donor chamber and 1 mL of buffer solution (pH 6.8) was added. Aliquots (3mL) 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 was then determined by measuring the absorbance at 282 nm using a UV spectrophotometer.



After carried out in vitro dissolution studies for all formulation, the best formulation F2,F3 and F6 having (sodium alginate :HPMC and also sodium alginate: HPMC : crosscarmellose sodium at different ratios) is selected for ex vivo permeation studies.^[8,9]

Evaluation of mucoadhesive strength

Weigh required to pull off the formulation from mucus tissue is recorded as mucoadhesion/bioadhesion strength in g. This parameter for the tablets was measured on a modified physical balance using bovine cheek pouch as model mucosal membrane.

Swelling behavior of mucoadhesive tablets

The extent of swelling was measured in phosphate buffer pH 6.8 at the end of 0.5, 1, 2,4, 5, 6 hrs tablets were withdrawn, soaked on tissue paper and weighed, and then percentage weight gain by the tablet and with the help of below given formula.^[7,8]

Swelling Index = Final weight - Initial weight / Initial weight x 100

RESULTS AND DISSCUSSION

Drug Identification and drug-excipients compatibility study

Melting Point

The melting point Sumatriptan succinate was determined on Digital melting point apparatus was found to be 169-172°C which is good agreement with reported melting point.

UV Spectrum and Calibration curve of Sumatriptan Succinate

The UV spectrum of Sumatriptan Succinate solution (10µg/ml) exhibited wavelength of absorbance maximum at 226.6nm which complies with reported and calibration curve shows $r^2=0.997$.

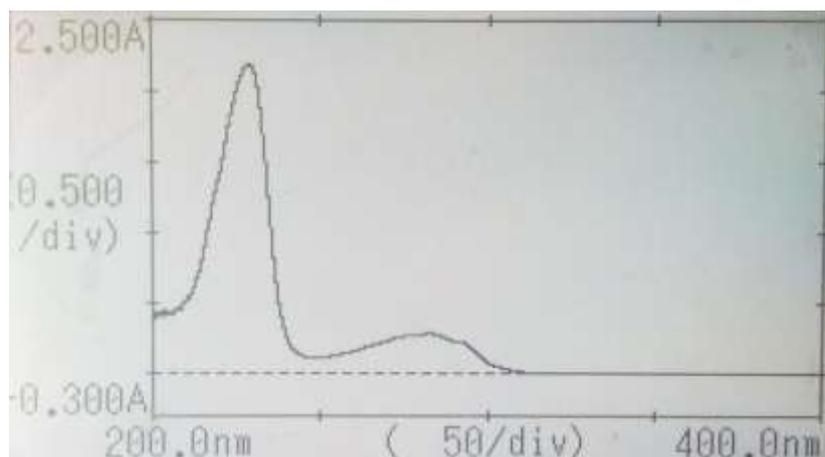


Figure no.1: UV spectrum of Sumatriptan succinate in 6.8 PH buffer

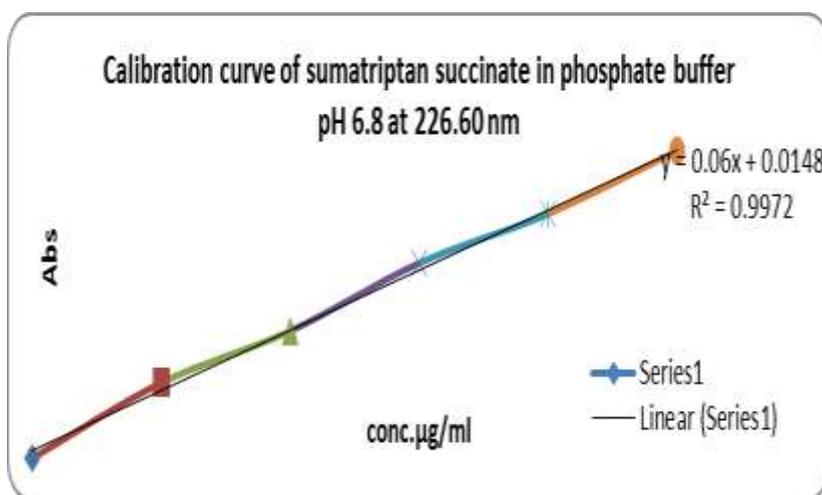


Figure no.2: Calibration curve of Sumatriptan succinate in phosphate buffer in pH 6.8 at 226.60 nm

Fourier Transform Infra Red Spectrophotometer (FTIR)

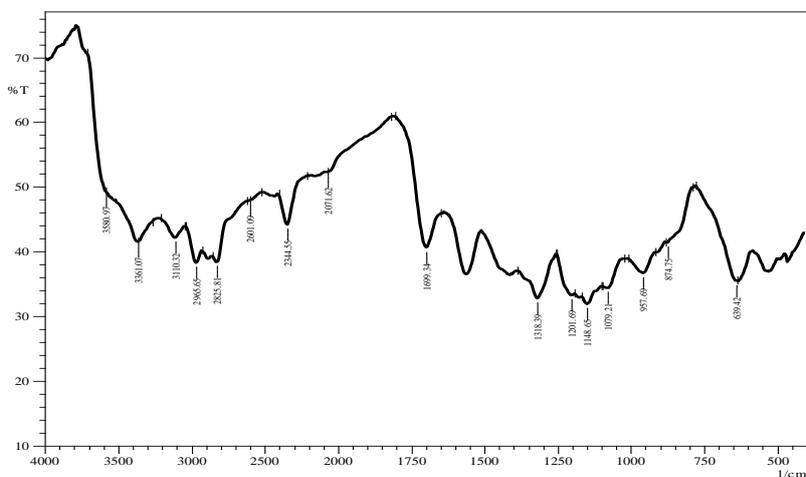


Figure no.3: FTIR Spectra of sumatriptan succinate

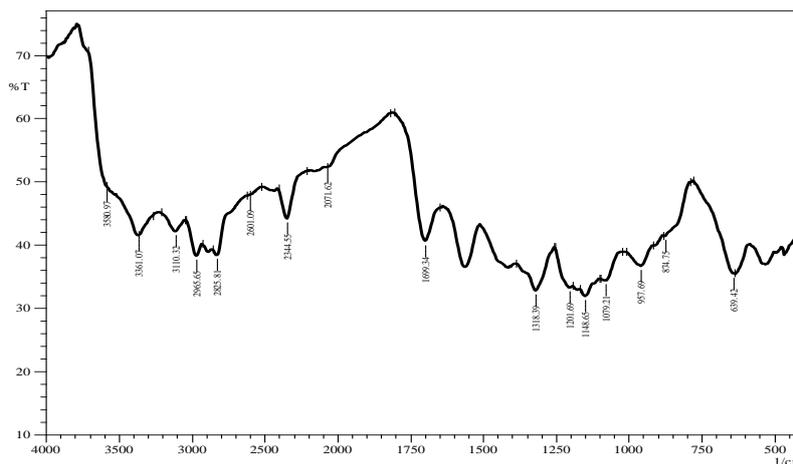


Figure no.4: FTIR Spectra of Sumatriptan succinate + Sodium alginate + HPMC
Differential Scanning Calorimetry (DSC)

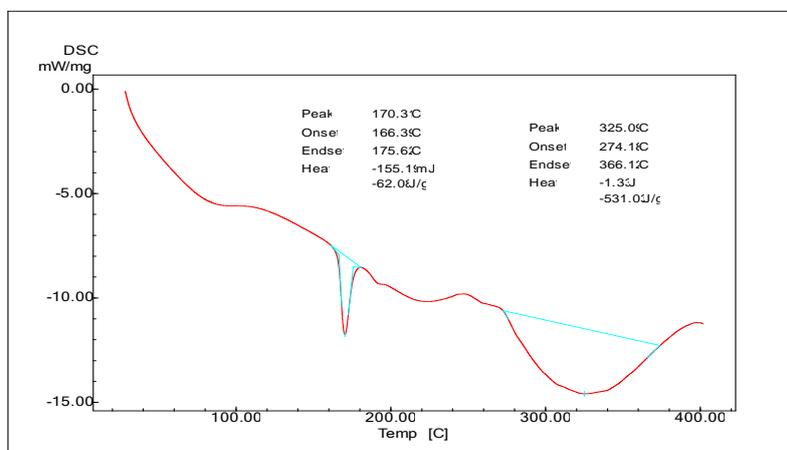


Figure no5: DSC Graph of pure Sumatriptan

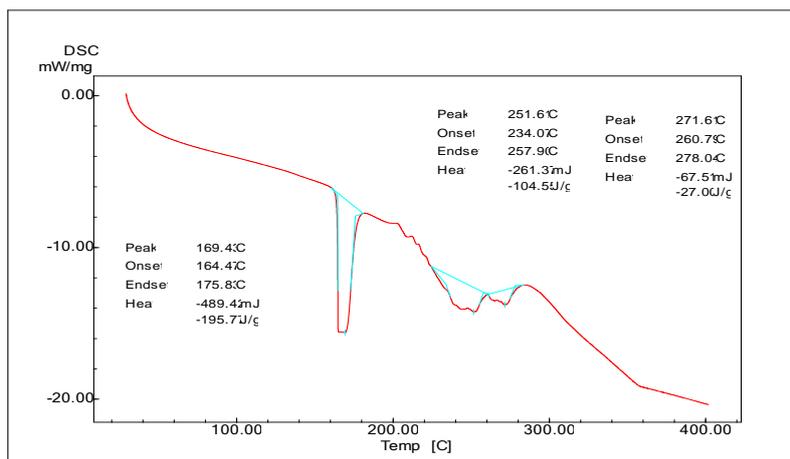


Figure no.6:DSC Graph of pure Sumatriptan + sodium alginate + HPMC

Evaluation of Tablets: The tablets from the factorial batches were evaluated for different evaluation parameters of tablets.

Appearance

The tablets from all factorial batches were white, circular. The surface texture was smooth. The thickness of tablets of factorial batches was 3.12 to 3.24 mm and it was found to be within limit of deviation from average value (not more than 5%).

Weight variation

Fortabletweighing 300 mg or more, not more than two tablets differ from the average weight by 5% deviation. The weight variation within limits indicates uniformity in tablet compression and consequently content of drug in a unit.

Hardness

Thehardness is important characteristics to be evaluated for handling and transportation properties of the tablets. The hardness of tablets was found to be 5.8 to 8.0 Kg/cm² which indicate good handling and transportation characteristics.

Friability

The friability is important characteristics to be evaluated for handling and transportation properties of the tablets. The friability of tablets was less than 0.5% which indicates good handling and transportation characteristics.

Drug content

The drug content of the nine formulations was found to be between 97.2 to 102 % (i.e. variation of $\pm 4\%$).

The value ensures good uniformity of the drug content in the tablet.

In vitro drug release studies

In vitro drug release study was carried out using USP dissolution apparatus II in buffer pH 6.8 for a period of 6 Hrs.

Kinetics analysis of drug release

Summarize the kinetic of sumatriptan succinate release data by linear regression according to zero, first order kinetic and simplified Higuchi model and the release constant k was calculated. The release of sumatriptan succinate from sodium alginate, and HPMC followed, zero and first order release model. All batches form thin film and mechanism of drug release was found to be non fickien.^[25,26]

Table no.2: Powder Characterization of bilayer buccal tablet of Sumatriptan succinate

Formulation Batch	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr' s index (%)	Hausner' s ratio	Angle of repose (degree)
F1	0.474±0.006	0.584±0.02	18.69±0.04	1.232±0.003	24.65±0.03
F2	0.463±0.01	0.695±0.03	33.33±0.04	1.150±0.003	24.75±0.02
F3	0.370±0.002	0.460±0.03	34.43±0.03	1.24±0.02	24.90±0.03
F4	0.460±0.01	0.520±0.03	36.46±0.02	1.13±0.03	28.20±0.01
F5	0.480±0.03	0.580±0.004	24.75±0.02	1.20±0.01	30.22±0.01
F6	0.401±0.008	0.531±0.003	22.47±0.03	1.32±0.01	30.30±0.02

Where, All values are mean ± SD, n=3

Table no.3: Evaluation of Mucoadhesive Buccal Tablet

Formulation code	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	% Drug content	Average weight (mg)
F1	4.28	3.5	0.615	96.22	198.9
F2	4.25	3.8	0.608	98.21	197.1
F3	4.26	3.6	0.590	99.24	195.5
F4	4.24	3.4	0.590	96.54	198.9
F5	4.26	3.8	0.612	97.21	198.9
F6	4.28	4.0	0.408	98.21	197.1

Percent total drug release of formulation F1 to F6

Table no.4: In-vitro drug release profile of Mucoadhesive Buccal Tablet

Time (hours)	% Drug Release					
	F1	F2	F3	F4	F5	F6
1	6.25	7.5	8.1	9.92	8.12	8.31
2	14.12	18.2	20.2	18.21	19.20	20.10
3	35.21	38.23	40.2	39.23	40.01	42.21
4	81.6	84.21	86.2	81.21	84.23	86.32
5	90.12	94.23	98.24	94.23	95.25	96.28
6	96.22	98.21	99.24	96.54	97.21	98.20

Table no.5: Ex-vivo permeation result for batches (F2,F3 and F6)

Time (hours)	% Drug permeable		
	F2	F3	F6
1	8.2	8.6	7.2
2	15.5	19.8	17.5
3	49.6	50.2	44.3
4	55.8	60.4	53.5
5	74.63	78.56	72.23
6	82.95	88.88	84.20

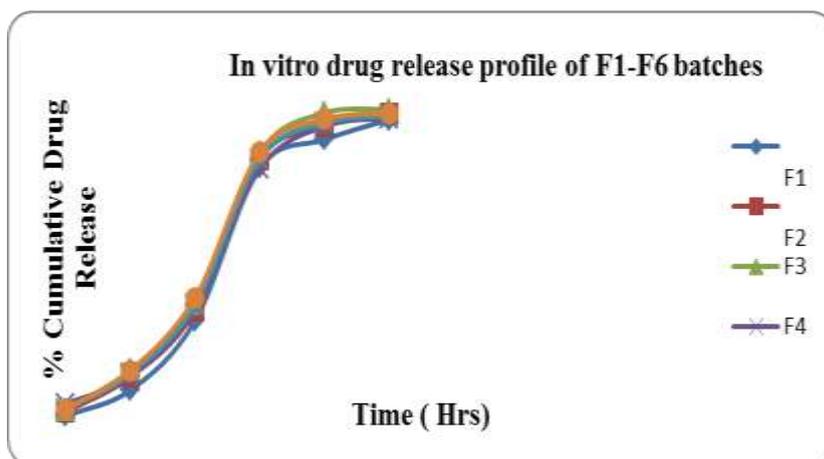


Figure no.6: In vitro drug release profile

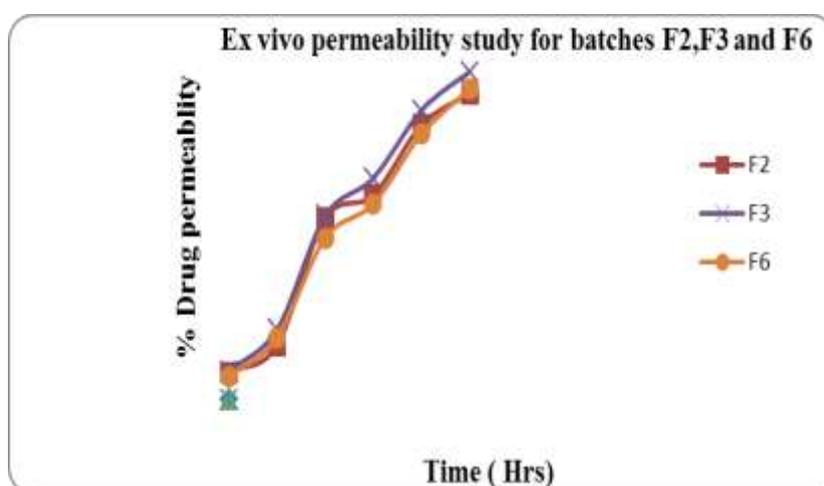


Figure no.7: Drug permeability profile

CONCLUSION

Now a day's migraine is widely increasing disorder find out in population mostly in adult persons due to increasing stress, changing sleep pattern, some unhealthy food etc. Addition of Sodium lauryl sulphate add in the formulation carried out the action of skin penetrant. It show the desired permeation result across the buccal mucosa. The permeation of buccal tablet of sumatriptan succinate shows increase in the bioavailability due to avoiding the hepatic first pass effect. It is also concluded that on mucoadhesion test the batch of [F3 and F6] showing good result. Tablet were attached to sheep mucosa and it stick to the mucosa membrane without collapsed and it could stabilize sumatriptan succinate buccal tablet on human cheek, in saliva for at least 4 hours. The result of mathematical model fitting data indicated that, the best fit model in all cases was found to be Korsmeyer Peppas and release was found to be fickian diffusion.

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