WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 14, 385-410. Research Article ISSN 2277–7105

FORMULATION DEVELOPMENT AND EVALUATION OF FAST DISSOLVING BIOADHESIVE SUBLINGUAL FILM OF SUMATRIPTAN

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Article Received on
11 Sept. 2017,

Revised on 01 October 2017,
Accepted on 21 October 2017

DOI: 10.20959/wjpr201714-9873

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ABSTRACT

The fast dissolving sublingual films are more beneficial in comparison to the tablets and capsules because sublingual films tend to dissolve within a minute/ second after placing below the tongue. Sumatriptan succinate is a drug of choice used in the treatment of migraine, which is very common problem for the travellers. The aim of the study was formulation development and evaluation of Fast dissolving Bio-adhesive sublingual film of Sumatriptan. Films were prepared by using solvent casting method. Administering the drug by sublingual route enhances the bioavailability and fast dissolving films bypasses the first pass metabolism of the drug. Fast dissolving films are the advancement in the solid dosage forms and having more patient compliance. Fast dissolving sublingual films were prepared using HPMC E5/PVP K30 in the combination, mannitol and glycerine in different concentrations of polymers i.e. 50/10mg, 200/10mg, 400/10mg and 450/10mg. The formulation containing 400/10mg i.e. formulation code F3 which show high dissolution and permeation were selected as best formulation.

KEYWORDS: Sumatriptan succinate, Fast dissolving sublingual films, Migraine.

INTRODUCTION

Delivery System

In the last two decades, there has been enormous effort towards the development of novel drug delivery systems (NDDS). The reason for this development in technology is the relatively low development cost and time required for introducing a NDDS as compared to a new chemical entity. Moreover, in the form of NDDS, an existing drug molecule can get a 'new life' there by increasing its market value, competitiveness and patent life. The conventional or classical therapy also have certain limitations such as in case of oral dosage form it has a problem of swallowing tablets, problem associated with patient compliance among pediatric and geriatric, it is difficult to take these dosage forms without water while travelling and these systems also shows less absorption which leads to slow onset of action. To overcome these problems, a novel drug delivery system is one of a better solution such as designing a sublingual drug delivery system. Sublingual mucosa due to their thin membrane and large veins is relatively permeable. Due to high blood flow, the sublingual mucosa provides rapid absorption and instant bioavailability of drugs.[1] Quick onset of action may therefore be observed as the rapid absorption is possible.[2]

Fast dissolving films are the advanced form of solid dosage form due to their flexibility. Fast dissolving sublingual films are dissolved by itself when placed below the tongue, these are dissolved due to the presence of saliva. Films are used in case of migraine attack, asthma, nausea etc.[3]

Advantages of fast dissolving sublingual drug delivery

Provides better patient compliance
Taste masking of the drug
Improved stability
No need of water
Rapid onset of action
Improve bioavailability
Accurate dosing

Disadvantages of fast dissolving sublingual drug delivery

Fast dissolving films are hygroscopic in nature so kept in dry places
Special packaging should be required for the product stability and safety

Composition of fast dissolving sublingual films

Table. 1: Components of fast dissolving films.[4]

Substances	Composition
Drug	1-30%
Film forming polymer	40-50%
Plasticizer	0-20%
Flavouring agent	q.s.

Migraine

Definition

Acute migraine is a disabling disorder characterized by moderate to severe pain often associated with photophobia, phonophobia, nausea and vomiting. It worsens with day to day activity of patient.[5] An untreated migraine attack can last for 4 hours to 72.[6] Sexual dimorphism is reported in migraine i.e. prevalence ratio among men and women is 3:7.[7]

Causes

Changes in brainstem and their interaction with trigeminal nerve

Variation in brain chemicals which includes serotonin

Hormonal changes in women

Food products, Stress, Changes in wake sleep pattern, Physical factors, Medications

Symptoms: Throbbing, Nausea, Vomiting, Moderate to severe pain, Photophobia (afraid of light), Phonophobia (afraid of sound).

Treatment

1) First line therapies

- Combination analgesics
- Triptans
- NSAIDS

2) Other therapies

- Anti- emetics
- Ergotamin

Pathophysiology of migraine and mechanism of action of triptans

Main goal of acute migraine therapy is to treat the disorder in less time with low cost of treatment and to regain the functional ability as soon as possible. Current approach of anti-

migraine therapy involves the use of potent serotonin 5-HT1B/1D receptor agonists, collectively termed as triptans. There are seven triptans available in market viz. Sumatriptan, Zolmitriptan, Naratriptan, Rizatriptan, Eletriptan, Almotriptan and latest triptan come into the scene is "Frovatriptan".[8] Although all triptan share same pharmacological mechanism of action but they have distinct pharmacokinetic profiles which makes each of the triptan a unique one. Main basis of determining efficacy of a triptan is "pain free response at 2nd hour" of drug administration. Based on this, triptans are broadly classified into two categories viz. "high efficacy" triptans having faster onset of action, high potency and high reoccurrence rate. It includes Sumatriptan, Zolmitriptan, Rizatriptan, Almotriptan and Eletriptan. Another group involves "low efficacy" triptans having slower onset of action, low potency and lower reoccurrence rate. It includes Naratriptan and frovatriptan.

Sumatriptan

Sumatriptan is a synthetic drug belonging to the triptan class which is used in the treatment of migraine. Sumatriptan is structurally similar to the 5-hydroxy tryptamine and it is 5-HT1D receptor agonists.

Sumatriptan present at receptor 1D. It located at CNS and Blood vessels and showing effects such as cerebral vasoconstriction.

Methods for the development of fast dissolving sublingual films

Rolling method: - Solution or suspension of the drug is prepared with film forming polymers and this is subjected to the roller. The rheological properties for solution or suspension of the drug should be considered before processing them. The solvent which is mainly used is water or mixture of water with alcohol. The film which is placed on the roller is dried and then after drying film is cut into specific pieces of desired shapes and sizes.[9]

Hot melt extrusion: - In this method heating is used to convert the polymeric solution into film. In this method API and other ingredients are mixed in a dry state and then subjected to heating process. The mixture is then extruded out in the molten state without using any solvent. The molten mass is thus used to cast the film and then film is cut into desired size and shape. This process is not suitable for the thermolabile ingredients. Optimization of speed of casting and drying time are important from the commercial scale output. E.g. of formulation of FDFs using hot melt extrusion is piroxicam film with maltodextrin plasticizer.[10]

Solid dispersion extrusion: - In this technique immiscible components are extruded with drug and then solid dispersion is prepared. Finally solid dispersion is shaped into the films.

Spray drying: - A solvent system containing film former and other excipients are sprayed or coated on suitable carrier material, dried and peeled off to get the film. The carrier materials used for the film are glass, non siliconized kraft paper or polyethylene film etc.

Solvent casting technique: - In this method the film forming agents are soaked into the solvent overnight. Other ingredients and drug are added to the solution and thoroughly mixed. Then liquid is poured over a suitable casting mold (petri dish) to get a film of desired thickness. The selection of the solvent depends specefically upon active pharmaceutical ingredients.

Ingredients used in the fast dissolving films

Film forming polymers: - These are the agents which are used as film formers. It is used as the base of the FDF's. It helps in the rapid disintegration and provides mechanical properties to the FDF's. It provides good mouth feel also. The disintegration rate of the polymer is decreased by increasing the molecular weight of the polymer film base. Polymers which are mainly used in the FDF's are HPMC (Hydroxyl Propyl Methyl Cellulose), PVA (Polyvinyl Alcohol), pullulan, eudragit, sodium alginate, gelatin, Pectin etc.[11]

Plasticizer:-These plasticizers are important for providing the mechanical properties to the FDF's. Mechanical properties which are mainly improved by using these plasticizers are percentage elongation and tensile strength. Optimized amount of plasticizers are used to get a better FDF's. The commonly used plasticizers are Polyethylene Glycol (PEG 400, 4000 etc.), and glycerol's.

Flavors: - Flavors are added to provide taste to the film. There are various flavors which are added to the film formation. Any flavor can be added i.e. intense mint, sour fruits flavor, or other sweet confectionary flavors are also added to the fast dissolving film formulation. Optimized amount of flavor was added to the FDF's. These flavoring agents should be compatible with the drug and other ingredients. The choice of flavors changes with the conditions like age i.e. geriatric patients like mint or orange flavor, while youngsters like fruit flavors.

Coloring agents: - The coloring agents are added to the film formation to impart color to the FDF's. Coloring agents should be compatible with the drug and other ingredients.[12]

Sweetening agents: - It is the most important part of the oral pharmaceutical product. Sweetening agents helps in the taste masking of the bitter drugs. There are varieties of sweetening agents which are used in the formulation of FDF's i.e. sucrose, dextrose, fructose, glucose, etc. There are also polyhydric alcohols such as sorbitol, mannitol and isomalt. These are preferably used in the combination for having less carcinogenic activity and also used as cooling agents.[13]

List of marketed products of fast dissolving film

Table. 2: Marketed products.

S.No.	Name	Manufacturer	API	Uses
1	ZomigFastmelt	Novartis	Zolmitriptan	Anti-migraine
2	Listerine	Pfizer	Cool mint	Mouth fresheners
3	Benadryl	Pfizer	Diphenhydramine HCL	Anti-allergic
4	Theraflu	Novartis	Dextromethorphan HBR	Anti-allergic

MATERIAL AND METHODS

List of Chemicals used

Table. 3: List of chemicals used.

Chemicals	Manufacturers
Sumatriptan Succinate	Azakem Labs Pvt. Ltd., Hyderabad
Hydroxy propyl methyl cellulose E 5 LV	Loba chemicals, Mumbai, India
Glycerin	Cental drug house (P) Ltd, New Delhi
Mannitol	Qualikems Fine Chem Pvt. Ltd
Chitosan	Cental drug house (P) Ltd, New Delhi
Polyvinyl pyrrolidone k-30	Loba Chemicals Mumbai, India
Sodium Hydroxide Pellets	Cental drug house (P) Ltd, New Delhi
Potassium Dihydrogen Orthophosphate	Loba chemicals, Mumbai, India
Hydrochloric acid (HCL)	Cental drug house (P) Ltd, New Delhi

Equipments used

Table. 4: List of equipments used.

Name	Source
Digital pH Meter	Systronics, pH system, India
Digital Vernier Calliper	Mitutoyo, corporation, Japan
Digital Melting Point Apparatus	Popular Traders, Ambala Cantt, India
Double Beam UV Spectrophotometer	Shimadzu Co. Ltd., Japan
Electronic Balance	Shimadzu Co. Ltd., Japan
FTIR Spectrophotometer	Shimadzu Co. Ltd., Japan
Hot Plate	Popular Traders, Ambala Cantt, India
Hot Air Oven	Navyug, Mumbai, India
Magnetic Stirrer	Remi, Pvt. Ltd. Mumbai, India
Scanning electron Microscope	JEOL, JSM 6510 LV, Japan
Vaccum Oven	NAVYUG, India
Differential scanning calorimetry	Pyris diamond, U.S.A

METHODOLOGY

Characterization of SS (Sumatriptan Succinate)

Physical appearance test

SS was observed for colour, odour and physical state.

Melting point

Melting point of SS was determined using capillary method. Drug was filled into the capillary tube sealed at one end Upto the height of 3 mm from the sealed end. Capillary was introduced into the digital melting point apparatus. Melting point was noted from the temperature at which drug starts melting to the temperature at which entire sample melts.

FTIR spectra analysis

A FT-IR spectrum of SS was recorded by Potassium bromide (KBr) palletization method. Drug was mixed with KBr and was compressed into small thin disk, which was subsequently analyzed by FT-IR spectrophotometer. Obtained spectra were analyzed for characteristic peaks corresponding to specific functional groups present in the drug molecule. These peaks were considered as a reference for further drug-excipient compatibility studies.

Analytical method development

Determination of absorption maxima (λ_{max}).

Sumatriptan Succinate (10mg) was accurately weighed and transferred to a 100 ml volumetric flask. To this pH 6.8 phosphate buffer was added to dissolve the drug and make up the volume Upto 100 ml. The resultant solution was having concentration of 100 µg/ml. Then take the scan to get the absorption maxima by using double beam UV-visible spectrophotometer.

Calibration plots of Sumatriptan succinate (SS) in pH 6.8 phosphate buffer

The calibration plot of Sumatriptan Succinate was prepared in pH6.8 phosphate buffer. From the 100µg/ml solution 0.5, 1.5, 2.5, 3.5, 4.5, 5.5 and 6.5 ml were withdrawn separately into pre calibrated 10 ml volumetric flask and volume was made up to the mark by using phosphate buffer USP (pH 6.8). Absorbance was recorded at 227nm by using double beam UV spectrophotometer. All the measurements were done in triplicate and were statistically analyzed. A calibration plot was constructed between concentration (µg/ml) on X- axis and absorbance on Y- axis. The linear regression equation and linear regression coefficient were then calculated from the calibration plot.

Calibration plots of Sumatriptan succinate (SS) in pH 7.4 phosphate buffer

The calibration plot of Sumatriptan Succinate was prepared in pH 7.4 phosphate buffer. From the 100µg/ml solution 1.5, 2.5, 3.5, 4.5 and 5.5ml were withdrawn separately into pre calibrated 10 ml volumetric flask and volume was made up to the mark by using phosphate buffer USP (pH 7.4). Absorbance was recorded at 227nm by using double beam UV spectrophotometer. All the measurements were done in triplicate and were statistically analyzed. A calibration plot was constructed between concentration (µg/ml) on X- axis and absorbance on Y- axis. The linear regression equation and linear regression coefficient were then calculated from the calibration plot.

Drug Excipients compatibility studies

To test the compatibility of the excipients with SS, they were individually mixed with SS in 1:1 w/w proportion (**Table 5**). Resultant mixtures (along with suitable control samples) were transferred to open glass vials sealed and were exposed directly to the variety of temperature and humidity conditions (5˚C i.e. refrigerator conditions and 40˚C/ 75% RH i.e. accelerated conditions) for 15 days. After that the samples were analyzed for change in their physical appearance i.e. colour change, flow characteristics and lump formation and odour change. Chemical incompatibility was tested by analysing the presence and/or alteration of peak values corresponding to specific functional groups present in drug molecule.

Table. 5: Samples kept for incompatibility studies.

Sr. No.	Composition	Weight ratios
1	Drug	Only drug
2	Drug: Polymer	1:1
3	Drug: Mannitol	1:1
4	Drug: PVP K 30	1:1
5	Drug: Polymer: Mannitol: PVP K 30	1:1:1:1

Differential scanning calorimetry (DSC)

The DSC profile of pure and physical mixtures of Sumatriptan was recorded on Perkin Elmer DSC-4 (Pyris Diamond, U.S.A). Thermal behaviour was studied under normal conditions with perforated and sealed quartz pans and with a nitrogen gas flow of 200ml/min. The samples (100mg for pure drug, 1:1 for Sumatriptan + HPMC E5, 1:1 for Sumatriptan + mannitol, 1:1 for Sumatriptan + PVP K30, 1:1:1:1 for Sumatriptan + HPMC E5 + Mannitol + PVP K30) were heated at 5^{o}C/min over a temperature range of 34-300^{o}C. The reference sample used in all the determinations was alumina with a height of 5mg. Peak temperatures and enthalpies were calculated as a mean of three measurements.

Preparation of Fast Dissolving Sublingual Films (FDSF'S)

FDSF'S were prepared by solvent casting method. Firstly HPMC E 5/PVP K 30 was dissolved in 10ml distilled water and stirred until the solution becomes clear. The solution was allowed to stand for 1 hr so that the air bubbles were cleared completely. Another solution was prepared by dissolving drug, plasticizer and mannitol in required distilled water. Both the prepared solutions were mixed together and were stirred for 1.5 hrs. After stirring, solution was poured into a 9cm petri plate and was dried in hot air oven at 45^{o}C for overnight. A film of 2×2 cm^{2} dimensions was cut down from the petri plate. Prepared film were valuated for thickness, tensile strength, percent elongation, disintegration time, dissolution study and mucoadhesion study.[14]

Table. 6: Composition of films.

Formulation code	HPMC E5/PVP K 30 (mg)	Plasticizer(mg)	Sweetener (mg)	Drug (mg)	Remarks
F1	50/10	80	20	35	Film was not formed
F2	200/10	80	20	35	Film was formed but breakage was their
F3	400/10	80	20	35	Uniform film was formed
F4	450/10	80	20	35	Film formed but do not sustain its integrity

Evaluation of Sublingual films

Physical evaluation

- **Film forming capacity**

It is the ability of film formers to form desired films. It is categorized according to film forming capacity such as very poor, poor, average, good, very good and excellent.[15]

- **Appearance of films**

It is evaluated by visual observation such as transparent or opaque.[16]

- **Weight variation**

The film of dimension 2×2 cm^{2} was cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated.

- **Thickness**

The thickness of the patch was measured using digital Vernier Calliper with a least count of 0.01 mm at different position of the film. The thickness was measured at five different positions of the film and average was taken and standard deviation was calculated.

Mechanical evaluation

- **Folding endurance**

To determine folding endurance, a film was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance.[17]

- **Tensile strength**

The Tensile strength (psi) is the property of the film that requires a load to cause load deformation failure of film. Film strips in special dimension and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the strips were pulled by the top clamp at a rate of 100 mm/min; the force and elongation were measured when the film broke. Tensile strength was obtained by following equation:

Tensile strength = Force at break / Initial cross-sectional area of the sample

- **Percent elongation**

The percent elongation is measured when the film snaps as sufficient force applied so as to exceed the elastic limit. Percentage elongation was obtained by following equation.[18]

% Elongation = Increase in length at breaking point (mm) / original length (mm) × 100

- **Surface pH**

The surface pH of fast dissolving film was determined in order to investigate the possibility of any in vivo side effect. As an acidic or alkaline pH may cause irritation of the mucosa, so the surface pH of the films was determined to check whether its neutralising or not. A pH electrode was used for this purpose. The film was allowed to swell in closed petri dish for 30 min. The pH was measured by bringing the electrode in contact with the surface of the sublingual film. The procedure was performed in triplicate and average with standard deviation was reported.

- **In-vitro Disintegration**

The disintegration time is the time when the film starts to break or disintegrates. In *vitro* disintegration time was determined in a petri dish containing 25ml of pH 6.8 phosphate buffer at 37±0.5^{0}C with swirling every 10 sec.[19]

- **Drug Content**

Drug content determination of the film was carried out by dissolving the film of 4 cm^2 in 100 ml of pH 6.8 phosphate buffer using magnetic stirrer for 1 hour. The drug concentration was then evaluated spectrophotometrically at λ_{max} of 227 nm. The determination was carried out in triplicate and average with standard deviation was recorded.

- **Dissolution test**

I*n vitro* dissolution test was carried out according to the USP type II dissolution apparatus. 900ml of pH 6.8 phosphate buffer was taken as dissolution media, the temperature was maintained at 37±0.5°C with a rotation speed of 50rpm. Five ml of sample was taken at regular intervals which were replaced with same volume of fresh pH 6.8 phosphate buffer and take the absorbance at 227 nm with the help of double beam UV-Visible spectrophotometer.

- **Scanning electron microscopy (SEM)**

The morphological characteristics of the Sublingual films were studied by scanning electron microscopy (JEOL, JSM-6510 LV SEM). The film sample was placed in the sample holder and the SEM micrographs were taken at 10,000x and 3000 magnification using tungsten filament as an electron source. Films were fixed onto a metallic stub with double sided conductive tape (diameter 12 mm, Oxon, Oxford Instruments, UK).

RESULT AND DISCUSSION

Characterization of SS

Physical appearance test

Result of physical characterization of SS is listed in **Table.7**. No variations were found in its specification in Certificate of Analysis (COA) and observations recorded at the time of experimentation.

Table. 7: Physical characterization of SS.

Sr.No.	Parameter	Observation
1.	Odour	Odourless
2.	Colour	White
3.	Appearance	Powder

Melting point

Experimentally observed melting point (**Table.8**) complies with reported melting point in literature.[20]

Table. 8: Melting point of SS.

Sr.No.	Parameter	Specification in literature	Melting point
1.	Melting point	168.22^0C	168^oC

FTIR spectra analysis

The FT-IR spectra of procured sample show comparable principle absorption bands with that of FT-IR spectra of working standard of SS obtained from industry (**Fig.1 and Table.9**). Compliance between the values of characteristic peaks indicates the purity of drug.

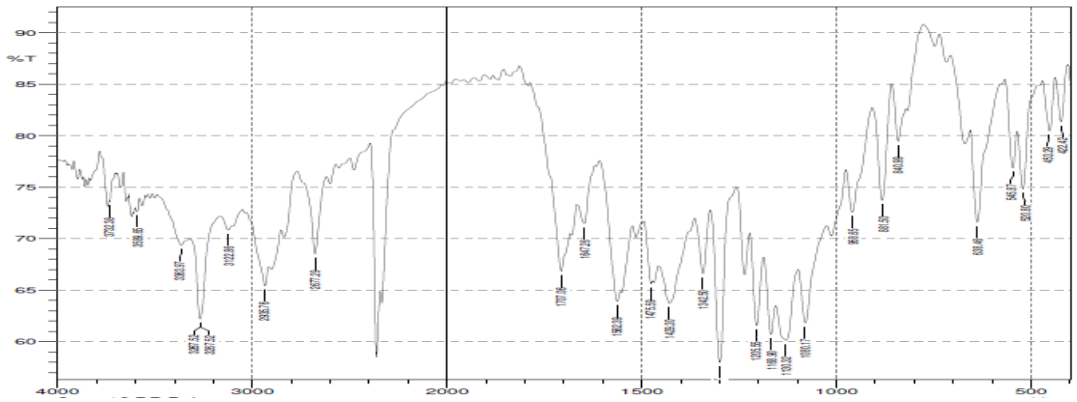


Fig. 1 IR spectra of Sumatriptan succinate.

Table. 9: FTIR spectra analysis of SS.

Sr.No.	Standard value range (cm^{-1})	Observed value	Interpretation
1.	3395-3180	3363.97	N-H stretch
2.	1081-1030	1080.17	S=O stretch
3.	700-600	638.46	C-S stretch
4.	3000-2840	2935.76	C-H stretch

The IR spectra of the given sample show comparable principle absorption band. This matching for characteristic peak of drug with that of standard confirms the purity of drug.

Analytical method development

Determination of absorption maxima

Irrespective to the nature of media the λmax of SS was found to be 227nm (**Fig.2**).

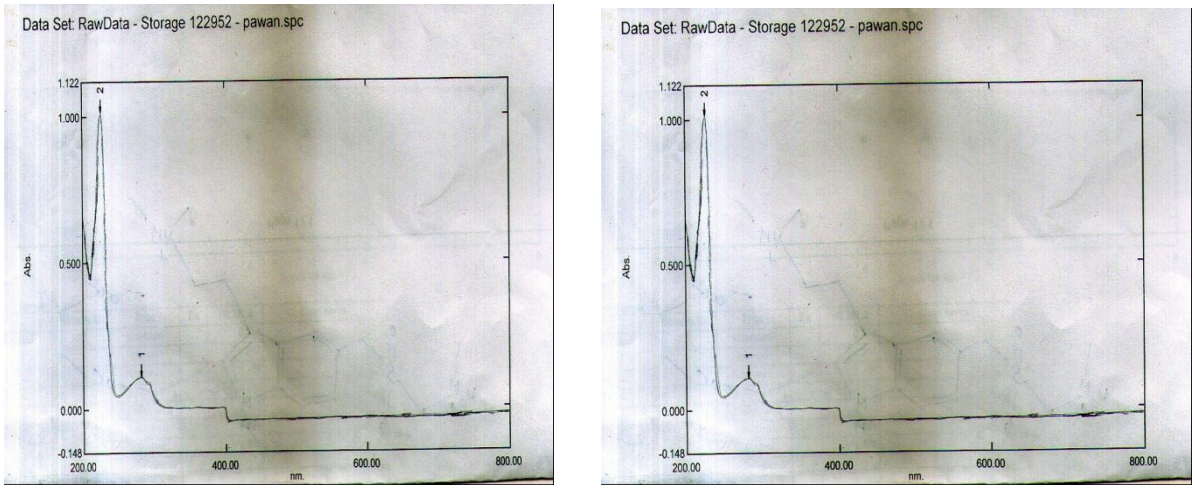


Fig.2 Determination of λmax of SS in different media (A) phosphate buffer USP (pH 6.8) and (B) phosphate buffer USP (pH 7.4).

Construction of calibration plots for SS

Calibration plots of SS were developed in phosphate buffer USP (pH 6.8) and phosphate buffer USP (pH 7.4). Reason behind selecting above mentioned buffers comprises the resemblance of their pH with characteristic sites within the body that are required to be considered for the development of sublingual dosage form.

Table. 10 Calibration curve of Sumatriptan succinate in pH 6.8 phosphate buffer.

Sr.No.	Conc.	Abs.
1	0.5	0.148±0.000577
2	1.5	0.231±0.000577
3	2.5	0.334±0.001
4	3.5	0.434±0.002
5	4.5	0.549±0.001528
6	5.5	0.667±0.002
7	6.5	0.775±0.0157

Data are represented as mean ± S.D (n=3).

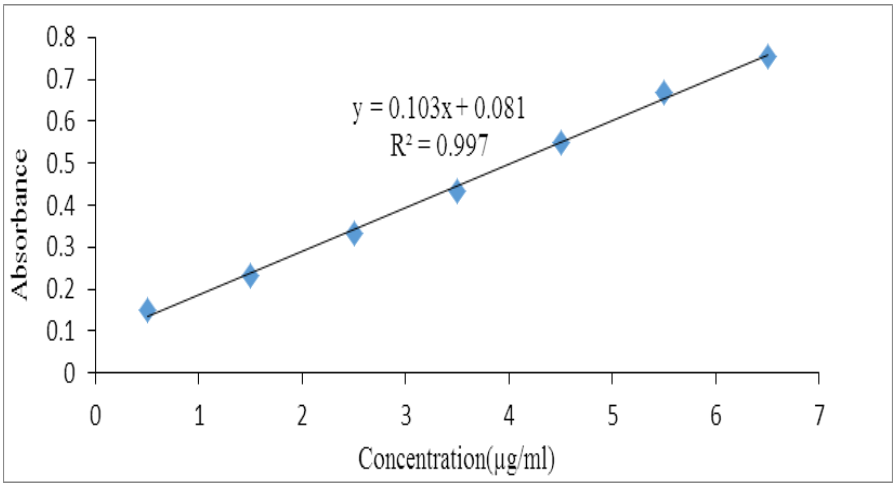


Fig. 3 Calibration curve of Sumatriptan succinate in 6.8 pH phosphate buffer.

Table. 11 Calibration curve of Sumatriptan succinate in pH 7.4 phosphate buffer.

Sr.No.	Conc.	Abs.
1	1.5	0.212±0.000577
2	2.5	0.311±0.001
3	3.5	0.421±0.000577
4	4.5	0.534±0.001528
5	5.5	0.623±0.001

Data are represented as mean ± S.D (n=3).

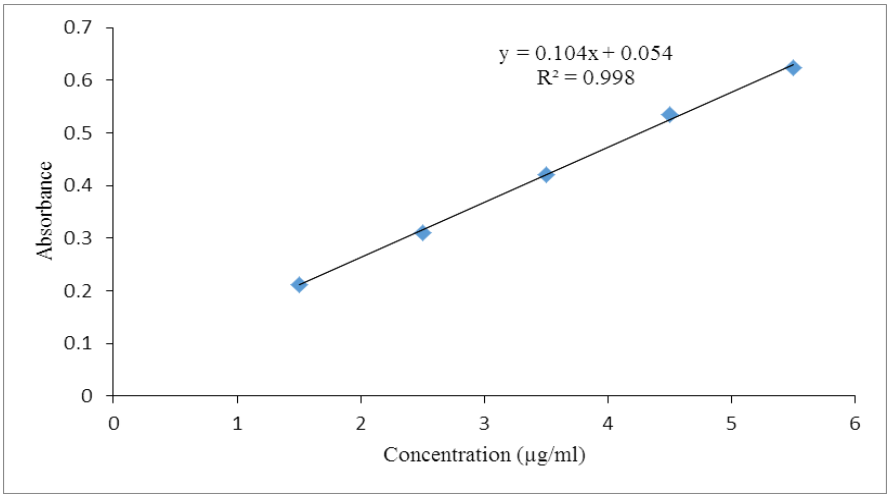


Fig. 4 Calibration curve of Sumatriptan succinate in 7.4 pH phosphate buffer.

Drug excipients compatibility studies

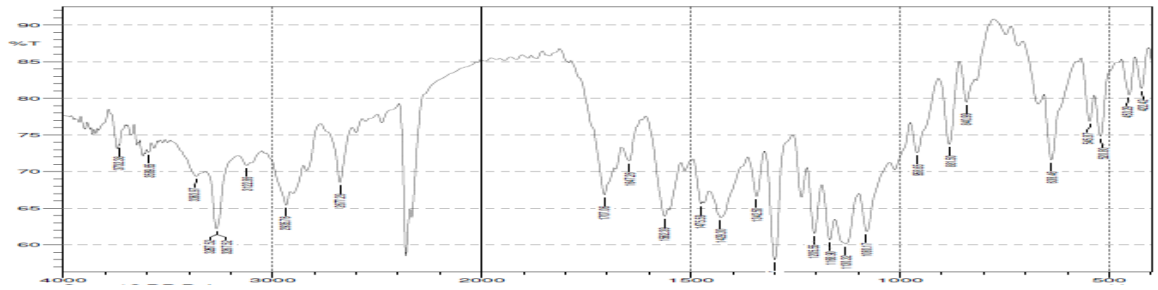
Physical drug excipient compatibility studies concluded that there was no lump formation, flow change, colour change or odour change during the time of storage at specified storage conditions. The DSC results and the IR spectra revealed that no interaction between the drug and the used polymers occurred as there was no change in the melting endothermic peaks and

no shift in the IR peaks of the drug.There was no shifting in IR peaks of the samples kept at different environmental conditions with respect to initial sample and control samples as shown in **Fig. 5 & 6** and **Table. 12** which confirm the compatibility of drug with different excipients.

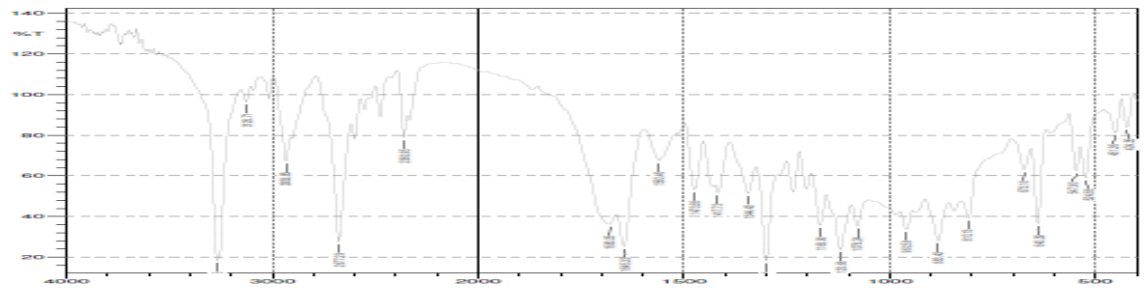
Table. 12 Physical compatibility study of the Sumatriptan Succinate with different excipients.

Composition	Control (RT)	5^0C		45^0C/75% RH	
		Initial	15^{th}day	Initial	15^{th} day
Drug	–	–		–	
Drug: Polymer	–	–		–	
Drug: Mannitol	–	–		–	
Drug: PVP K30	–	–		–	
Drug: Polymer: Mannitol: PVP K30	–	–		–	

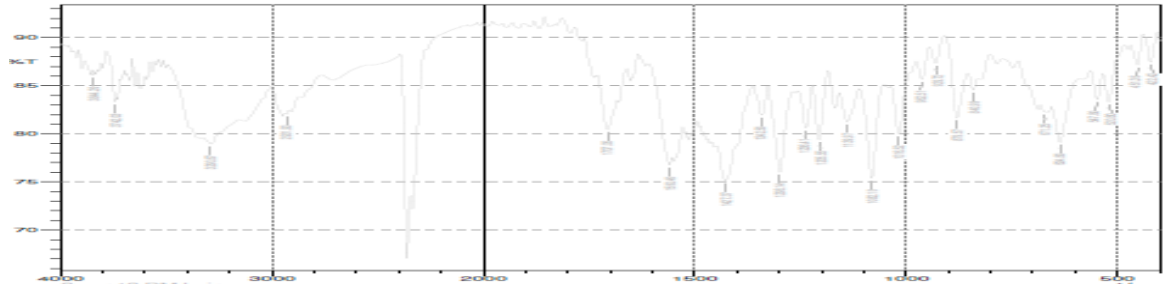
Refers to the same as original.



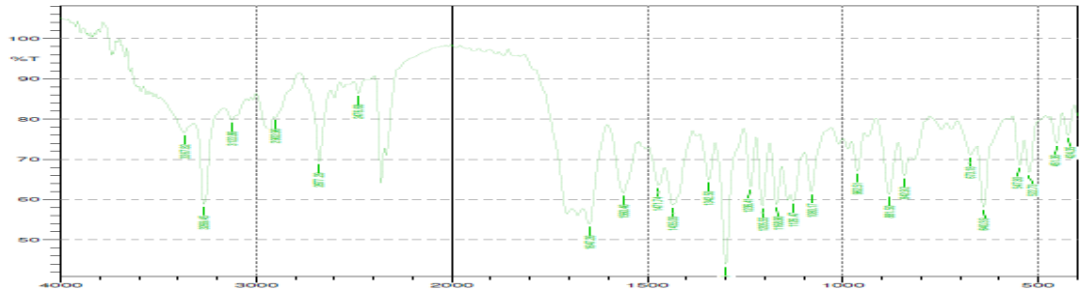
(A) Sumatriptan succinate.



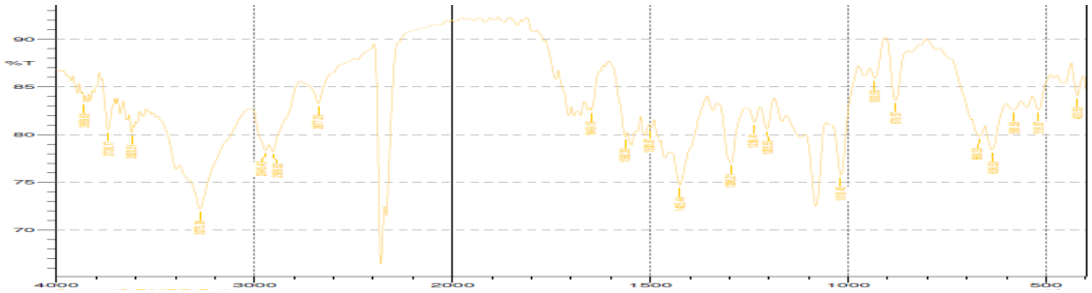
(B) Sumatriptan succinate:HPMC E 5.



(C) Sumatriptan succinate: Mannitol.

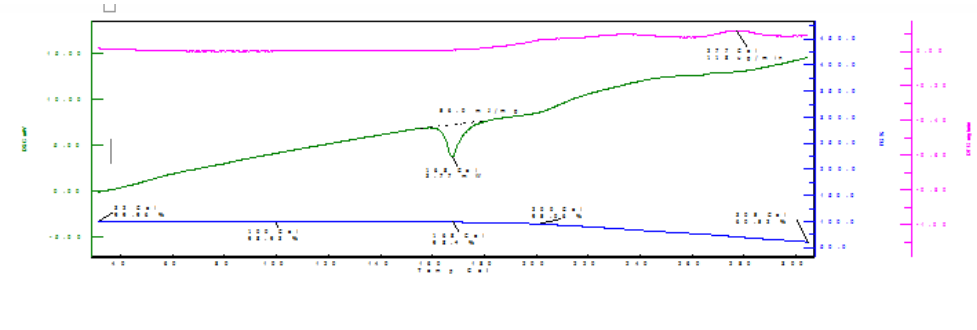


(D) Sumatriptan succinate:PVP K 30.

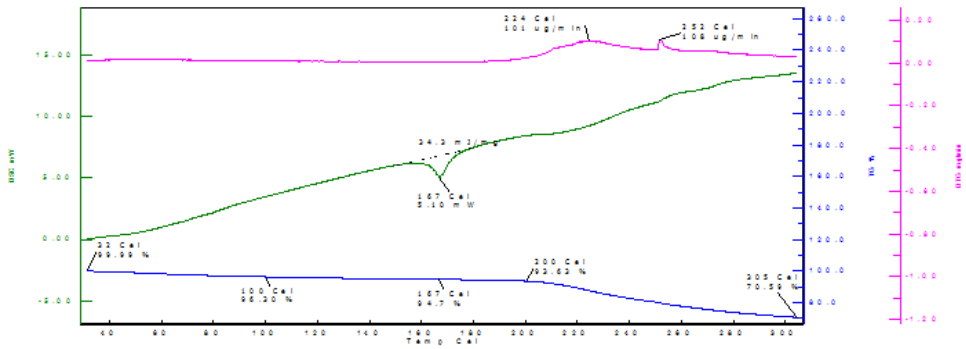


(E) Sumatriptan succinate: HPMC E 5: PVP K 30: Mannitol.

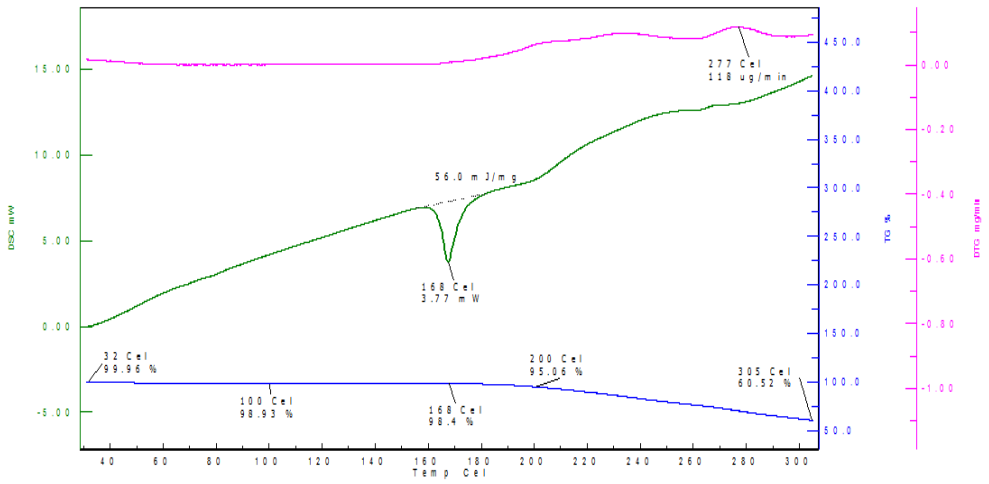
Fig. 8.5 FTIR spectra of (A) Sumatriptan Succinate (B) Physical mixture of Sumatriptan Succinate and HPMC E5 (C) Physical mixture of Sumatriptan Succinate and Mannitol (D) Physical mixture of Sumatriptan Succinate and PVP K 30 (F) Physical mixture of Sumatriptan Succinate: HPMC E 5:Mannitol:PVP K 30.



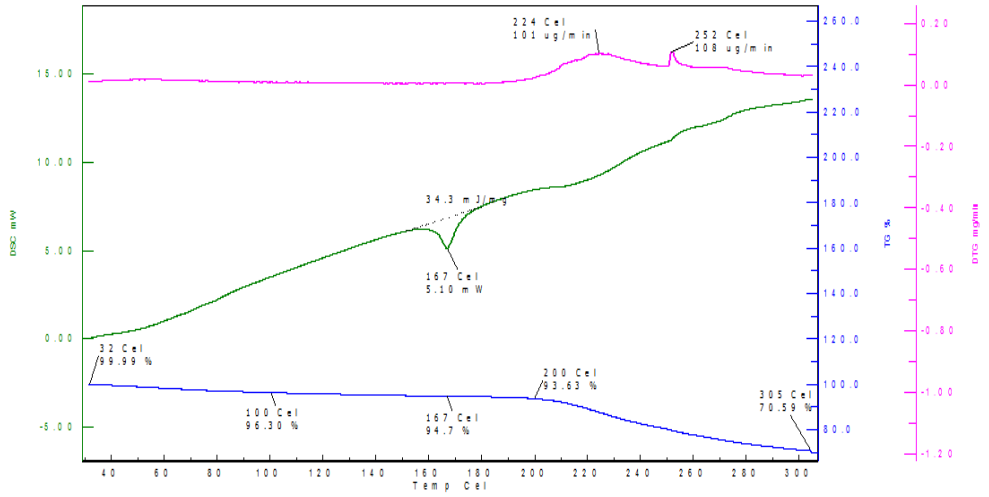
(A) Sumatriptan succinate



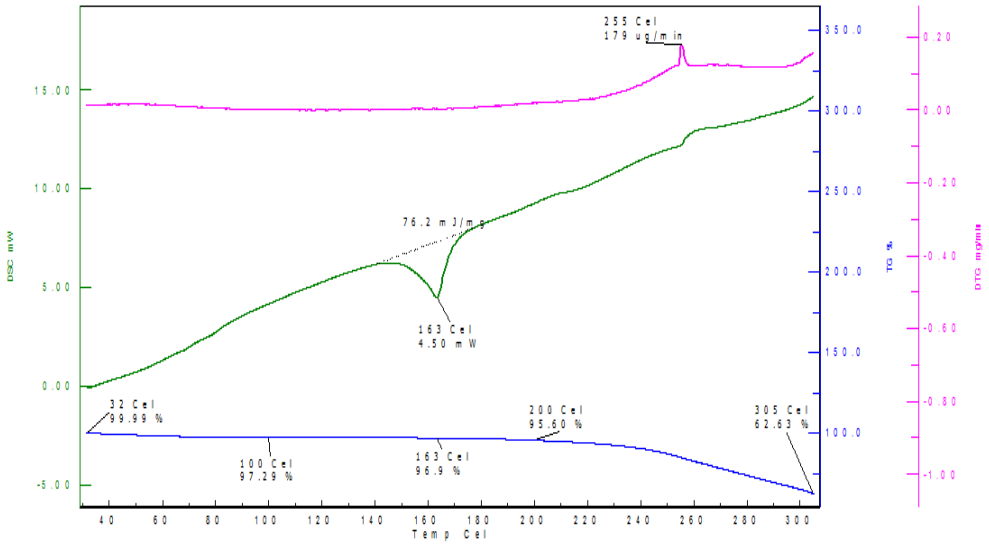
(B) Sumatriptan succinate:HPMC E 5



(C) Sumatriptan succinate: Mannitol.



(D) Sumatriptan succinate:PVP K 30.



(E) Sumatriptan succinate:HPMC E 5:PVP K 30:Mannitol.

Preparation of fast dissolving sublingual films

Initially the film forming polymer i.e. HPMC E5 and permeation enhancer i.e. PVP K30 were used for the preparation of films in different conc. i.e. 50/10mg, 200/10mg, 400/10mg and 450/10mg. Best concentration was further used for the preparation of film (400/10mg) due to their uniformity.

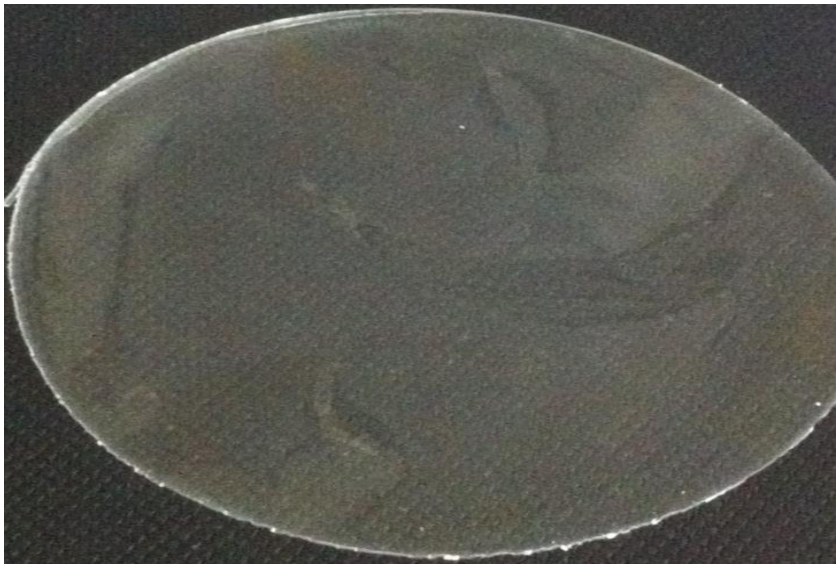


Fig.7 Sumatriptan sublingual film.

Evaluation of sublingual film

- **Film forming capacity**

Table. 13 Results of film forming capacity.

Sr.No.	Formulation code	Film forming capacity
1	F1	Very poor
2	F2	Poor
3	F3	Very good
4	F4	Average

- **Appearance of films**

Table. 14: The results of appearance of films.

Sr.No.	Formulation code	Appearance
1	F1	Transparent
2	F2	Transparent
3	F3	Transparent
4	F4	Transparent

- **Weight Variation**

Three films each of 4cm^2 were cut at three different places from the casted film and weight variation was determined. The result of weight variation is shown in **Table 15.**

Table. 15: Results of weight variation.

Sr.No.	Formulation code	Mean ± S.D.
1	F3	54.66±2.516611

Data are represented as mean ± S.D (n=3).

- **Thickness**

Thickness of film was done in triplicate and then average and standard deviation was taken. The results of thickness are given in **Table.16.**

Table. 16 Results of thickness.

Sr.No.	Formulation code	Mean±S.D.
1	F3	0.05±0.005774

Data are represented as mean ± S.D (n=3).

- **Folding endurance**

Mechanical strength is an important aspect for any type of dosage forms. It has got very significant prospects as far as industrial requirement is concerned. A good mechanical property is always an indication that the product is going to withstand any cut, wear and tear or damage during handling or transportation. Therefore, this is very critically evaluated. As friability is the official evaluation of tablets to ensure mechanical strength, folding resilience/endurance is the evaluation parameter of films/patches. Folding endurance of film was done in triplicate and then average and standard deviation was taken. The results of folding endurance are given in **Table. 17.**

Table. 17: The results of folding endurance.

Sr.No.	Formulation code	Mean±S.D.
1	F3	286±1

Data are represented as mean ± S.D (n=3).

- **Tensile strength and Percent elongation**

Tensile testing is an indication of the strength or the toughness and elastic behaviour of the film, measured by the parameters tensile strength (TS), percent elongation, sometime denoted by elongation at break (E/B). A soft and weak film is characterized by a low TS and E/B. A

hard and brittle film is defined by a moderate TS and low E/B. Hence it is suggested that a suitable buccoadhesive film should have a relatively moderate TS and E/B. The results of tensile strength and Percent elongation are given in **Table.18.**

Table. 18 Results of Tensile strength and Percent elongation.

Sr.No.	Formulation code	Tensile strength	Percent elongation
1	F3	3.85	20

- **Surface pH**

Surface pH of film was done in triplicate and then average and standard deviation was taken. The results of surface pH are given in Table.19 The results showed that the prepared films were suitable for buccal administration as the pH of buccal region is nearly 6.5.

Table. 19: The results of surface pH.

Sr.No.	Formulation code	Mean ± S.D.
1	F3	6.88 ± 0.051962

Data are represented as mean ± S.D (n=3).

- **In-Vitro Disintegration**

In-Vitro Disintegration of film was done in triplicate and then average and standard deviation was taken. The results of in-Vitro Disintegration are given in **Table. 20.**

Table. 20: The results of in vitro disintegration.

Sr.No.	Formulation code	Mean ± S.D.
1	F3	55 ± 1

Data are represented as mean ± S.D (n=3).

- **Drug content**

The prepared film formulation was assayed for drug content. Actual drug content in the prepared films was in the range of 95-105% of the claimed content. This indicates the even distribution of the drug in the prepared matrix of the films as well as the stability of drug in the procedure used for preparation. It was observed that the formulation was satisfactory in uniformity of drug as given in **Table. 21.**

Table. 21: The results of drug content.

Sr.No.	Formulation code	Mean ± S.D.
1	F3	2.26 ± 0.015275

Data are represented as mean ± S.D (n=3).

- **In-vitro Dissolution**

In-Vitro Dissolution of film was done in triplicate and then average and standard deviation was taken. 91.21% of drug was released from the film within 540 sec. The results of in-Vitro Dissolution are given in **Table. 22 and Fig. 8.**

Table. 22: The results of in vitro dissolution.

Sr.No.	Formulation code	Time (sec.)	Mean ± S.D. (% release)
1	F3	30	21.29 ± 1.713
2	F3	60	27.13 ± 1.713
3	F3	90	32.83 ± 0.790
4	F3	120	35.62 ± 1.160
5	F3	150	38.66 ± 1.334
6	F3	180	39.67 ± 1.334
7	F3	210	41.70 ± 0.580
8	F3	240	43.60 ± 1.160
9	F3	270	45.88 ± 1.795
10	F3	300	46.13 ± 1.334
11	F3	330	49.04 ± 2.010
12	F3	360	51.70 ± 0.658
13	F3	390	57.53 ± 2.092
14	F3	420	65.89 ± 0.956
15	F3	450	74.75 ± 0.956
16	F3	480	76.90 ± 1.160
17	F3	510	88.43 ± 0.956
18	F3	540	91.21 ± 0.759

Data are represented as mean ± S.D (n=3).

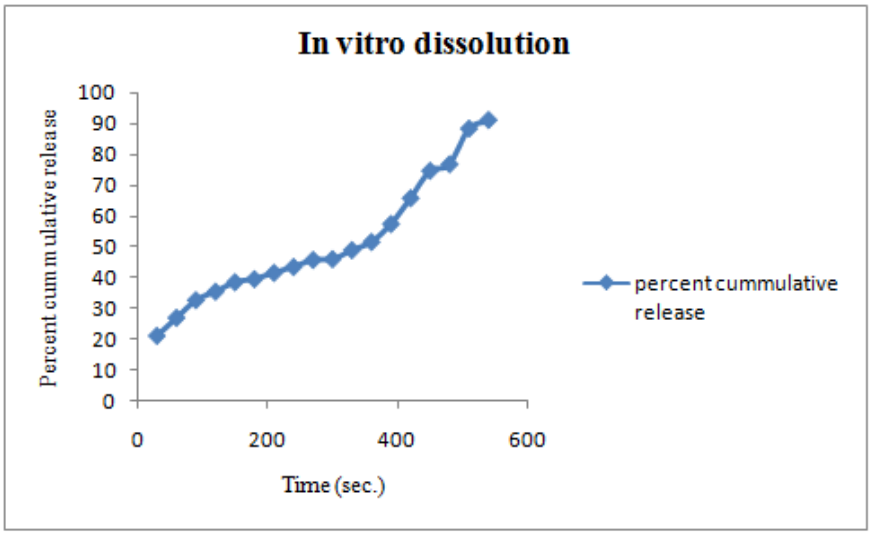
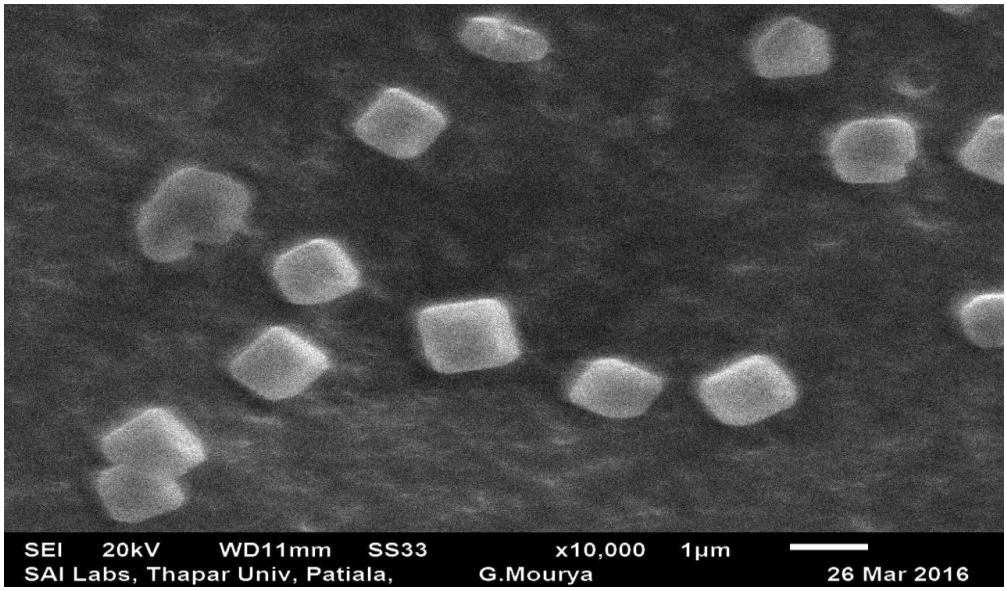


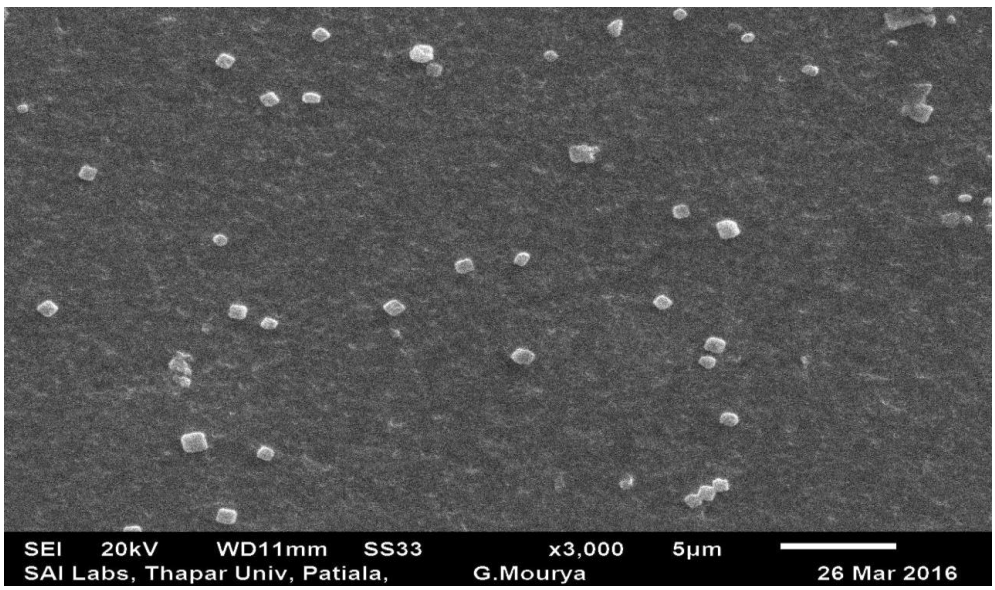
Fig. 8 Plot of in vitro release of sublingual film.

- **Scanning electron microscopy**

Morphological characteristic of sublingual film (F3) was studied by scanning electron microscopy. Study was done at 10,000 and 3000 magnification. Integrity of the structure was analysed and found to be intact with some cuboidal crystals of PVP K30 dispersed on the films. Smooth surface of film also confirms the uniform distribution of drug and polymers. Smooth surface may help in the proper adhesion of film to the site of action i.e., buccal mucosa). The results are given in **Fig.9.**



(A)



(B)

Fig.9 Scanning electron microscopic images of Film (F3) at the magnification of (A) 10,000 and (B)3000.

- **Ex vivo Permeation studies**

The oral mucosa represents a barrier to drug permeation and it is intermediate between skin epidermis and the gut in its permeability characteristics. The permeability study defines the effectiveness of SS to move across this barrier and providing enough evidence that the buccal absorption could provide means for SS administration. Therefore, in vitro permeability experiments of SS were conducted. 72.55% of drug release was found to be permeated after 18 min. confirming appreciable permeation of drug through film. The results are given in **Table. 23 and Fig. 10.**

Table. 23: The results of ex vivo permeation studies.

Sr.No.	Formulation code	Time (min.)	Mean ± S.D.	% Release
1	F3	2	0.102 ± 0.004	8.74
2	F3	4	0.121 ± 0.002	10.19
3	F3	6	0.236 ± 0.010	18.96
4	F3	8	0.356 ± 0.011	28.129
5	F3	10	0.432 ± 0.014	33.93
6	F3	12	0.576 ± 0.008	45.02
7	F3	14	0.751 ± 0.018	58.28
8	F3	16	0.879 ± 0.009	67.05
9	F3	18	0.938 ± 0.010	72.55

Data are represented as mean ± S.D (n=3).

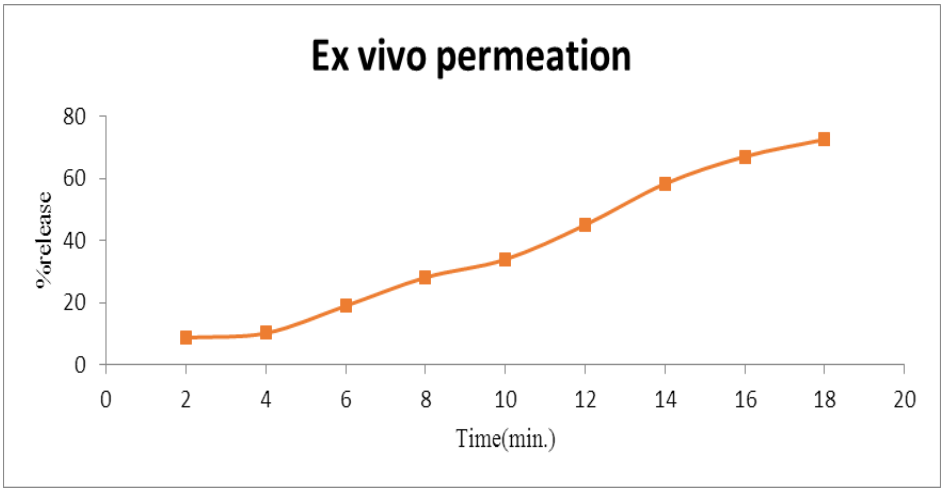


Fig.10 Plot of ex vivo permeation of sublingual film.

CONCLUSION

Fast dissolving films have been introduced in the market recently as they provide convenience and ease of use over other dosage forms such as disintegrating tablets. The use of hydrophilic polymers as means of delivering therapeutically active drug via fast dissolving

films has been the focus of attention in recent years. Drug chosen for study is Sumatriptan succinate which is serotonin 5-HT_1 receptor agonist that potently and selectively binds to 5-$HT_{1B/1D}$ subtype present mainly in brain. It is used mainly in acute attack of migraine. The identification of Sumatriptan succinate was confirmed by melting point and IR spectra. In the present study fast dissolving sublingual films of Sumatriptan succinate were prepared by solvent casting method using polymer HPMC E5/PVP k30 and their combinations along with different concentration of plasticizer. Hydroxy propyl methylcellulose (HPMC E5) and mannitol were used as excipients due to their excellent film forming property and palatable taste. Glycerine was used as a plasticizer. Studies were carried out using different conc of the polymer/pvp k30 i.e. 50/10mg, 200/10mg, 400/10mg and 450/10mg but only in 400/10mg(F3) uniform film was formed and in others film was formed but don't sustain its integrity and in some breakage was there. The high percentage drug release of formulation F3 was observed with approximately 91.25% of Sumatriptan succinate release within 540 sec. The formulation F3 also showed high percentage of drug permeated during *ex vivo* permeation study. Thus it may conclude that these combination systems of HPMC E5 along with PVP K30 have potential for consideration for drug delivery through FDFs.

Therefore, on the basis of the data obtained from the in vitro and ex vivo studies, the formulation F3 is the promising formulation for the immediate release of Sumatriptan succinate through sublingual route since they exhibited maximum drug release and permeation. The present fast dissolving sublingual film containing Sumatriptan succinate is considered to be potentially useful for treatment of acute migraine patients especially for pediatrics and elderly patients due to its convenience.

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