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Formulation and *in-vitro* evaluation of mucoadhesive buccal films of zolmitriptan

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ABSTRACT

The zolmitriptan is a serotonin (5-HT_1) agonist used for the treatment of migraine with or without aura. The absolute oral bioavailability is about 40 to 50%. The half-life of zolmitriptan is 2.5 to 3 hrs and it undergoes hepatic metabolism. So, in order to improve the bioavailability and efficacy, we have developed buccal patches of zolmitriptan, using mucoadhesive polymers like NaCMC, HEC, HPMC (5cps), chitosan and PVP by solvent casting technique. The developed buccal films were characterized for various parameters like physicochemical, mechanical and drug release characteristics. All the prepared patches were smooth surface and elegant texture. All the prepared patches were weighing in between 22.66 to 29.33 mg. The thicknesses of the patches were in the range of 0.243 to 0.306 mm. Folding endurance was in the range of 272 to 298. Surface pH was in the range of 6.33 to 6.86 pH. Swelling index was in the range of 31.62 to 44.26 %.The *in-vitro* residence time for all the patches in between 3.16 to 6.33 hrs. The tensile strength was in the range of 5.166 to 7.664 Kg/cm^2. Drug content uniformity study showed uniform dispersion of the drug throughout the formulation in the range of 94.33 to 98.63 %. *In-vitro* drug release studies in the range of 81.93 to 96.85 at the end of 8^{th} hrs. Stability studies were suggesting that there was no significant change in drug content and *in-vitro* drug release. FTIR studies revealed that, there was no incompatibility of the drug with the excipients used.

Keywords: Zolmitriptan, buccal films, mucoadhesion /bioadhesion, i*n-vitro* drug release.

INTRODUCTION

Mucoadhesive drug delivery, system has become highly interesting in the last 10-15 years. The lack of efficacy of certain drugs due to decreased bioavailability, unpredictable and erratic absorption, GI intolerance, or pre-systemic elimination of other potential route for administration. The recent development in the drug delivery has intensified investigation of mucosal delivery of drug such route includes oral, buccal, ocular, nasal and pulmonary routes etc [1]. Mucoadhesive drug delivery systems are delivery systems, which utilized the property of bioadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting a drug to particular region of the body for extended period of time. Problems such as high first pass metabolism and drug degradation in gastrointestinal environment can be circumvented by administering the drug via the buccal route [2]. A drug can be easily applied and localized to the application site and can be removed from there if necessary. Attempt has been made earlier to formulate various mucoadhesive buccal device including films, patches, disks, strips, ointments, and gels [3].

An ideal buccal patch should be flexible, elastic and soft yet adequately strong to withstand breakage due to stress from mouth activities. Moreover, it must also exhibit good mucoadhesive strength so that it can be retained in the mouth for a desired duration. As such, the mechanical, mucoadhesive, and swelling properties of buccal patches are critical and essential to be evaluated. The buccal route has high acceptance due to avoidance of 1st pass metabolism and possibility of being accessible for controlled drug release [4-6]. Various bioadhesive mucosal dosage forms have been developed which include adhesive tablets, gels, ointments, films and more recently patches. Buccal patches are preferred over adhesive tablets in terms of flexibility and patients comforts. Now day's bioadhesive polymers received considerable attention as platforms for buccal controlled delivery due to their ability to localize the dosage form in specific regions to enhance drug bioavailability. Chitosan is composed of glu-cosamine and N-acetylglucosamine, which are also constituent of mammalian tissue. It is non toxic, biocompatible and biodegradable polymer [7]. This polymer is known for its film as well as matrix forming abilities. In addition chitosan has enzyme inhibitor as well as permeation enhancer properties [8- 10].

The zolmitriptan is a serotonin (5-HT_1) agonist used for the treatment of migraine with or without aura. The absolute oral bioavailability of zolmitriptan is about 40 to 50%, and half-life is 2.5 to 3 hrs, it undergoes hepatic metabolism [11-14]. Because of poor bioavailability of zolmitriptan by oral route, there is a need to increase its bioavailability by formulating it into buccal dosage forms. Hence, zolmitriptan is a suitable drug for buccal dosage forms and may provide a better therapeutic profile than oral route. In the present investigation, zolmitriptan buccal films were prepared using different mucoadhesive polymers like sodium carboxy methyl cellulose (NaCMC), hydroxy ethyl cellulose (HEC), hydroxy propyl methylcellulose (HPMC 5cps), chitosan and polyvinyl pyrrolidone (PVP) by solvent casting technique. The prepared films were evaluated for various parameters related to delivery system like weight uniformity, thickness, folding endurance, surface pH, swelling index, *in-vitro* residence time, tensile strength, drug content estimation, i*n-vitro* release study, stability study, and drug polymer interaction. In the proposed research work, we have prepared buccal films with the aim to achieve: Greater therapeutic efficacy, avoidance of gastrointestinal disturbances and improve the bioavailability of zolmitriptan by avoiding hepatic metabolism, and improve patient compliances. The goal of the present study was an attempt to design and evaluate mucoadhesive buccal films of Zolmitriptan with different polymers viz. Na CMC, HEC, HPMC, and Chitosan and PVP.

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MATERIALS AND METHODS:

Zolmitriptan was obtained as gift sample from Cipla Pvt. Ltd., Mumbai. Sodium CMC, HEC, and PVP were purchased from Loba Chemical Pvt. Ltd., Mumbai. HPMC (5cps) was obtained as gift sample from Astra Zeneca Pvt. Ltd, Bangalore. Chitosan were purchased from Sangam Lab. Ltd, Tarapur. Propylene glycol was purchased from SD Fine Chem, Mumbai.

Preparation of zolmitriptan mucoadhesive films [15, 16]:

Buccal films of zolmitriptan were prepared by solvent casting technique employing mercury as substrate. Composition of circular cast films of various formulations is mentioned in **Table 1.** The mucoadhesive films were prepared using polymers like NaCMC, HEC, HPMC (5cps), chitosan and PVP. Propylene glycol was used as plasticizer. The calculated amount of polymer was dispersed in three fourth volume of water with continuous stirring using magnetic stirrer and the final volume was adjusted with distilled water. In case of chitosan films, the polymeric solution was prepared using 1.5% acetic acid in distilled water under continuous stirring for 48 hrs. The resulting viscous chitosan solution was filtered through nylon gauze to remove debris and suspended particles. The calculated amount of zolmitriptan was incorporated in the polymeric solutions after levigation with 30% propylene glycol of polymer weight. The solution was casted onto mercury substrate then kept in hot air oven at 40°C, (in case of chitosan kept at room temperature) for 24 hrs. The films were punched into size 10 mm in diameter containing 2.5 mg of zolmitriptan. The prepared films packed in aluminum foil and stored in an airtight glass container to maintain the integrity and elasticity of the films.

Table 1: Composition of zolmitriptan mucoadhesive buccal patches.

FC	Polymer and its concentration (% w/v)					Plasticizer* Concentration (%w/w) PG
	NaCMC	HEC	HPMC (5cps)	Chitosan	PVP	
F1	3%	—	—	—	0.3%	30
F2	—	3%	—	—	0.3%	30
F3	—	—	8%	—	0.3%	30
F4	—	—	—	1.5%	0.3%	30
F5	3%	—	—	—	0.5%	30
F6	—	3%	—	—	0.5%	30
F7	—	—	8%	—	0.5%	30
F8	—	—	—	1.5%	0.5%	30

FC= Formulation Code, Percentage of polymer weight.Each 10 mm* film *contains 2.5 mg of zolmitriptan.PG =Propylene glycol*

Evaluation of zolmitriptan mucoadhesive buccal films.
The prepared buccal films were evaluated for following properties like weight uniformity, thickness, folding endurance, surface pH, swelling index, *in-vitro* residence time, tensile strength, drug content, *in-vitro* release study, stability study.

Weight uniformity of films [17]:
For evaluation of films weight, three films of 10 mm from each formulation were taken and weighed individually on a digital balance. The results were analyzed for mean and standard deviation.

Thickness of films [18]:
For evaluation of thickness, three films of 10 mm from each formulation were taken and thickness was measured by screw thickness gauze. The results were analyzed for mean and standard deviation.

Folding endurance of films [19]:
Folding endurance of the film was determined by repeatedly folding one film at the same place till it broke or folded upto 300 times manually, which was considered satisfactory to reveal good films properties. The number of times of films could be folded at the same place without breaking gave the value of the folding endurance. This test was done on randomly selected three films from each formulation.

Surface pH of films [20, 21]:
For determination of surface pH three films of each formulation were allowed in contact with 1ml of distilled water for 1 hrs at room temperature. The surface pH was measured by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 minute. A mean of three reading was recorded.

Swelling Index of films [22, 23]:
For the determination of swelling index the preweighed (W_1) three films 10 mm diameter from each formulation were placed in Petri dishes (containing 20 ml of water). After 5, 10, upto 30 min. intervals, the patches were removed and the excess water on their surface was carefully removed using filter paper. The swollen patches were weighed (W_2) accurately.
The percentage of swelling index calculated by,

$$\% \text{ Swelling Index} = \frac{W_2 - W_1}{W_1} x100$$

***In-vitro* residence time of zolmitriptan films [24, 25]:**
The *in-vitro* residence time was determined using IP disintegration apparatus. The disintegration medium was 800 ml of pH 6.8 phosphate buffer maintained at 37 ± 2ºC. The segments of rat intestinal mucosa, each of 3 cm length, were glued to the surface of a glass slab, which was then vertically attached to the apparatus. Three mucoadhesive films of each formulation were hydrated on one surface using pH 6.8 phosphate buffers and the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down. The patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time required for complete erosion or detachment of the films from the mucosal surface was recorded (n=3).

Tensile strength of films [26-27]:
Tensile strength of the films was determined with digital tensile strength tester (Tinius-Olsen). The sensitivity range of the machine is 1-10 Newton's. It consists of two load cell grips. The lower one was fixed and upper one was movable. The test patch of size (1x4 cm^2) was fixed between these cell grips and force was applied till it breaks. The tensile strength of the patch was directly taken from the dial reading in Newton's, which was converted into kilogram.

Tensile Strength Tester

Drug content uniformity study of films [28, 29]:
The films were tested for drug content uniformity by UV-Spectrophotometric method. Films of 10 mm diameter were cut from three different places from the casted films. Each film was placed in 100 ml volumetric flask and dissolved in pH 6.8 phosphate buffer and 0.2 ml is taken and diluted with pH 6.8 phosphate buffer upto 10 ml. The absorbance of the solution was measured at 222 nm using UV/visible spectrophotometer (Shimadzu UV-1700). The percentage drug content was determined using the standard graph and the same procedure was repeated for three films of each formulation.

***In-vitro* release studies of zolmitriptan films in pH 6.8 phosphate buffer [30]:**
For *in-vitro* release study, cellophane membrane was used as a barrier membrane with pH 6.8 phosphate buffer as a medium. The cellophane membrane was soaked for 24 hrs in pH 6.8 phosphate buffer. The films were evaluated for drug release using diffusion cells; cellophane membrane was attached between the donor and receptors compartments. The prepared buccal films containing drug was placed inside donor compartment and maintained at 37 ± 2°C. The receptor compartment was filled with 100 ml pH 6.8 phosphate buffer and hydrodynamics was maintained by stirring with a magnetic bead at 100 r/min. 2 ml sample was withdrawn and replaced with 2 ml fresh pH 6.8 phosphate buffer to maintain the sink condition. The drug release was analyzed in UV/ visible spectrophotometer at 222 nm.

Stability studies [31]:
The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors. To assess the drug and formulation stability, stability studies were done according to ICH guidelines. The formulated buccal films were wrapped in aluminum foil and stored at 45 ± 0.5ºC for period of three months. After the period of three months films ere tested for drug content and *in-vitro* release profiles.

Characterization of zolmitriptan films:
FTIR Studies:
Infra-red spectra of pure drug zolmitriptan and physical mixture of formulations were scanned by using FTIR spectrophotometer (Jasco 410), with KBr pellets.

RESULTS AND DISCUSSION:

Physical characteristics of plain films and patches containing drug are shown in **Table 2.**

Preparation of standard calibration curve of zolmitriptan in pH 6.8 phosphate buffer:
For standard stock solution 10 mg of zolmitriptan was dissolved in 100 ml pH 6.8 phosphate buffers to give a concentration of 1 µg/ml. From standard stock solution taken 0.1, 0.2, upto 0.5 ml of solution in 10 ml volumetric flask. The volume was made up to mark with pH 6.8 phosphate buffer to produce concentration as, 1 to 5 µg/ml of zolmitriptan respectively. The absorbance of prepared solution of zolmitriptan was measured at 222 nm in spectrophotometer. The absorbance data for standard calibration curve are given in **Table 2** and plotted graphically as shown in the **Fig 1.**

Table 2: Standard calibration data of zolmitriptan pH 6.8 phosphate buffer

Sl. No.	Absorbance	Concentration (µg/ml)
1.	0	0.00
2.	1	0.165
3.	2	0.325
4.	3	0.471
5.	4	0.627
6.	5	0.786

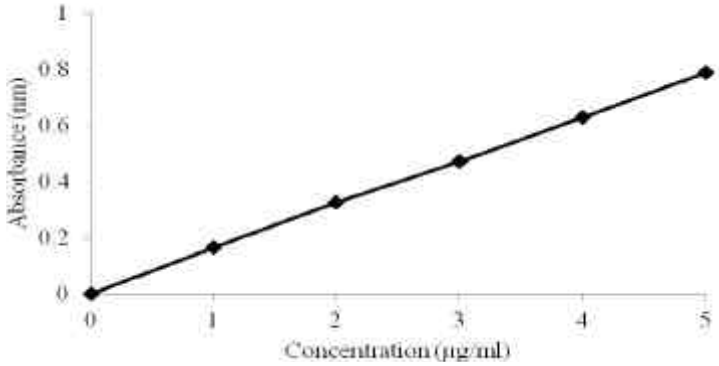

Fig 1: Standard calibration curve of zolmitriptan in pH 6.8 phosphate buffer.

Mucoadhesive films of zolmitriptan were prepared using mucoadhesive polymers NaCMC, HEC, HPMC (5cps), chitosan and PVP. The drug delivery system was designed as a matrix. All the films were shows smooth surface and elegant texture. The physical characteristics of various films are given with mean ± standard deviation in **Table 3.** The weights of (10 mm) films were in the range of 22.66 ± 1.471 to 29.33 ± 1.154 mg and film thickness in the range of 0.243 ± 0.020 to 0.306 ± 0.015 mm. The films were found uniform in weight and thickness. The folding endurance was measured manually, films were folded

Table 3: Physical evaluation of mucoadhesive buccal films of zolmitriptan:

FC	Weight uniformity (mg)± SD, (n=3)	Thickness (mm)± SD, (n=3)	Folding Endurance ± SD, (n=3)	Surface pH ± SD, (n=3)	% Swelling Index ± SD, (n=3)
F1	22.66 ± 1.471	0.273 ± 0.015	278 ± 1.527	6.53 ± 0.152	41.16 ± 1.242
F2	24.33 ± 1.032	0.246 ± 0.015	286 ± 1.527	6.66 ± 0.152	37.64 ± 0.996
F3	23.00 ± 2.880	0.256 ± 0.015	292 ± 2.081	6.60 ± 0.346	40.02 ± 1.416
F4	29.22 ± 1.184	0.300 ± 0.015	272 ± 1.154	6.33 ± 0.152	31.62 ± 0.889
F5	24.34 ± 2.562	0.274 ± 0.020	288 ± 0.286	6.80 ± 0.360	44.26 ± 1.096
F6	25.66 ± 2.401	0.243 ± 0.020	294 ± 0.251	6.72 ± 0.212	41.09 ± 1.608
F7	23.66 ± 2.880	0.286 ± 0.035	298 ± 0.115	6.86 ± 0.057	43.18 ± 0.719
F8	29.33 ± 1.154	0.306 ± 0.015	281 ± 2.333	6.63 ± 0.208	33.22 ± 0.855

FC= Formulation Code.

repeatedly till it broke, and it was considered as the end point. Folding endurance was found to be in the range of 272 ± 1.154 to 298 ± 0.115. The folding endurance was found to be highest for F7 and the lowest for F4 formulation. Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the degree of hydration of polymer, the surface pH of the buccal films was determined to optimize both drug permeation and mucoadhesion. Attempts were made to keep the surface pH as close to salivary pH as possible, the surface pH of all the films was within the range of 6.33 ± 0.152 to 6.86 ± 0.057 pH. No significant difference was found in surface pH of different films. The comparative percentage swelling of various formulations was in order of F5>F7>F1>F6>F3>F2>F8>F4 percentage swelling was highest for F5 and the lowest for F4 formulation, because PVP is freely soluble in water, which enhanced the water uptake capacity in the finished dosage form. As increase in concentration of PVP, increase in swelling index. The swelling behavior and *in-vitro* residence time of the mucoadhesive polymers are observed as given in **Table 3 and 4**. The incorporation of PVP induced significant reduction of *in-vitro* residence time of the studied formulation which may correlate with the increase in swelling behavior due to enhanced erosion rate. The *in-vitro* residence time shown by all formulation was good. The F4 showed maximum *in-vitro* residence time while F5 formulation shows minimum *in-vitro* residence time. The swelling behaviors of polymer in films were shown in **Fig 2.** The percent swelling index and *in-vitro* residence time for the films is in between 31.62 ± 0.889 to 44.26 ± 1.096 % and 3.16 ± 0.057 to 6.33 ± 0.251 hrs respectively. The tensile strengths of films were in the order of F7>F3>F6>F2>F5>F8F1>F4. Among all the films studied F7 showed highest tensile strength and F4 showed lowest tensile strength. This must be due to the hydrogen bonding of drug and polymer. The tensile strength of films is in the range of 5.166 ± 0.200 to 7.664 ± 0.267 Kg/cm^2. The drug content results were shown in **Table 4.** In the entire formulations drug was uniformly dispersed through out the patches in the range of 94.33 ± 1.524 to 98.63 ± 0.224 %. **Fig 3 and 4** shows the *in-vitro* drug release studies were performed for all the prepared formulation by using pH 6.8 phosphate buffer as dissolution medium and measuring drug concentration UV spectrophotometrically at 222 nm. The studies were performed upto 8 hrs.

Table 4: Physical evaluation of mucoadhesive buccal films of zolmitriptan:

FC	*In-vitro* Residence time(hrs) ±SD, (n=3)	Tensile Strength ±SD, (n=3)	%Drug Content ± SD, (n=3)	Drug released in 4 hrs. ±SD, (n=3)	Drug released in 8 hrs. ±SD, (n=3)
F1	3.46 ± 0.115	5.236 ± 0.251	98.33 ± 0.577	46.59 ± 1.170	93.58 ± 0.846
F2	5.40 ± 0.100	6.366 ± 0.115	97.81 ± 2.574	41.55 ± 0.352	83.11 ± 0.359
F3	4.43 ± 0.057	6.966 ± 0.152	96.33 ± 0.577	47.83 ± 0.948	91.18 ± 0.740
F4	6.33 ± 0.251	5.166 ± 0.200	95.66 ± 1.466	41.90 ± 0.280	81.93 ± 1.004
F5	3.16 ± 0.057	5.733 ± 0.230	96.92 ± 1.408	49.41 ± 1.264	96.85 ± 0.117
F6	5.15 ± 0.608	6.833 ± 0.267	97.33 ± 1.527	43.77 ± 0.595	85.33 ± 0.179
F7	4.21 ± 0.028	7.664 ± 0.267	98.63 ± 0.224	48.98 ± 1.264	93.20 ± 0.626
F8	6.08 ± 0.076	5.526 ± 0.208	94.33 ±1.524	42.03 ± 0.338	84.06 ± 2.571

FC= Formulation Code.

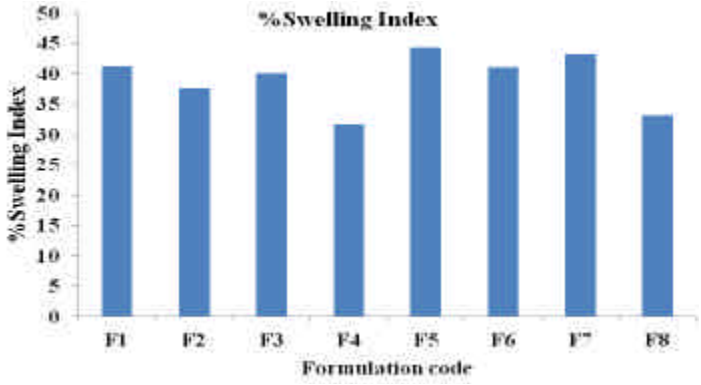

Fig 2: Comparative Swelling index of formulation F1 to F8.

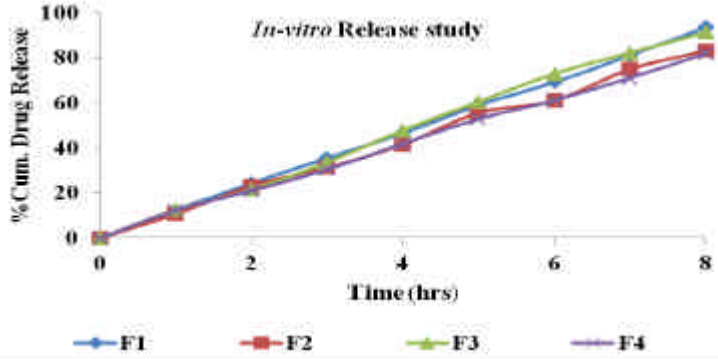

Fig 3: Comparative *in-vitro* drug release profiles of formulation F1 to F4.

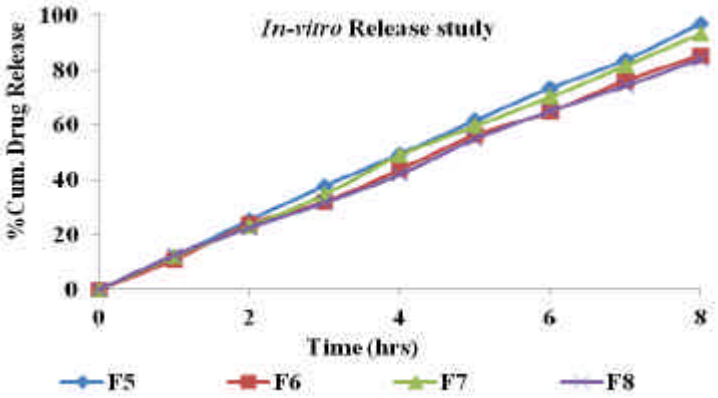

Fig 4: Comparative *in-vitro* drug release profiles of formulation F5 to F8.

The results of *in-vitro* studies are shown in the **Table 4.** The best formulations were wrapped in aluminum foil and stored at 45 ± 0.5ºC for period of three months were stored. Stability studies were suggesting that there was no significant change in drug content and *in-vitro* drug release. Kinetics drug release results shown in **Table 5** reveals that all formulations follows zero-order kinetics as correlation coefficient (r^2) values are higher than that of first-order release kinetics. Mechanism of drug release pattern i.e. diffusion and swelling was confirmed by Higuchi plots. The Higuchi plots represent of cumulative percentage drug release versus square root of time. The Higuchi plots were found to be linear with correlation coefficient values shown in **Table 5.** It was concluded that the release of drug from the films followed the diffusion controlled mechanism in all the formulations. The plots of log cumulative percentage drug release versus log time were found to be linear to the all formulations. On the basis of plots it is concluded that the release of zolmitriptan from films have obeyed Non-Fickian diffusion release mechanism. The correlation coefficient values were shown in **Table 5.**

Table-5: Kinetic parameters of zolmitriptan buccal films:

FC	Zero-order (r^2)	First-order (r^2)	Higuchi plot (r^2)	Peppas plot (r^2)
F1	0.9997	0.8629	0.9188	0.9998
F2	0.9970	0.9434	0.9193	0.9966
F3	0.9971	0.9215	0.9145	0.9950
F4	0.9990	0.9457	0.9213	0.9964
F5	0.9994	0.8104	0.9229	0.9992
F6	0.9985	0.9422	0.9227	0.9975
F7	0.9992	0.8810	0.9186	0.9989
F8	0.9987	0.9457	0.9219	0.9972

FC= Formulation Code.

In **Fig 5** shows IR spectrum of the pure drug and physical mixture of formulations: The IR spectrum of the pure drug zolmitriptan has indicating presence of absorption peak due to presence of N-H of the lactam, as well as secondary amine absorption, suggesting that these functionalities are present in the drug molecule. The aromatic and aliphatic C-H absorption are noticed from 2850 cm^{-1} to 3100 cm^{-1}.The characteristics O-C= O of the drug exhibited a absorption peak at 1750 cm^{-1} which is in cyclic form. These are the characteristics of the zolmitriptan.

The IR spectrum of drug with NaCMC and PVP shown characteristics absorption peak have been remained in the formulated product, hence formulation is a mixture but not a reaction product. The IR spectrum of drug along with HEC and PVP gives the strong absorption peak at 3500 cm^{-1} suggesting that presence of C-O-O is present. The amide absorption by strong absorption peak is ob-

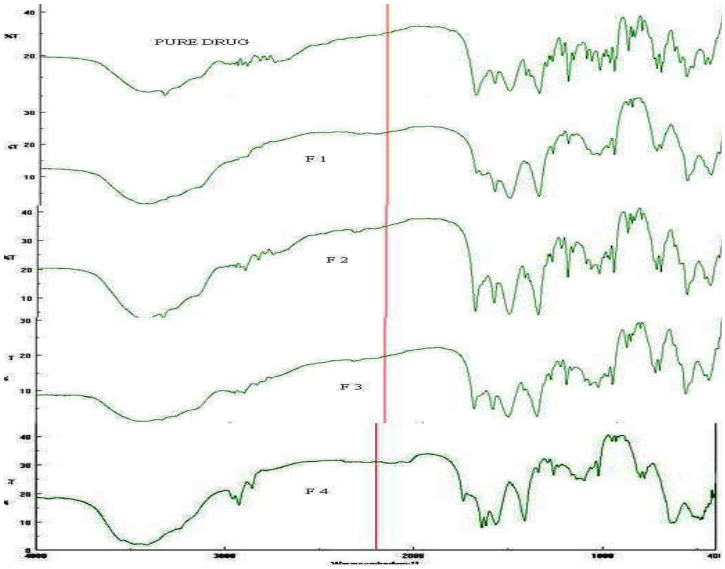

Fig 5: IR Spectra pure drug and Formulations F1, F2, F3 and F4.

tained at 1650 cm^{-1} indicating the presence of amide bond in molecule. IR spectrums of the product has remained all the characteristics of peak drug and excipients suggesting that the functionalities of the drug and excipients have remained unaffected, and have no chemical reaction take place.

The IR spectrum of drug along with HPMC and PVP also carried out and it shows all the characteristics absorption peak of the drug and excipients are in unaffected form. Hence there was no chemical reaction takes place. The IR spectrum of drug along with chitosan and PVP was also carried out. In this case also formulated product has remained all the characteristics peak of three constituents used during formulation. Suggesting that is a chemical mixture, but not reaction product.

PVP is a water soluble polymer, not known as sustain release matrix former. This polymer might act as release retardant due to possibility of complex formation with cationic drugs and/or cationic polymers. In the present situation Chitosan, a cationic polymer might have formed complex with PVP, and non-ionic polymer leading to a favorable extension of the drug release. Thus, in this work combination of Chitosan and PVP could act as rate controlling polymer when incorporated in the PVA patches. In addition, presence of chitosan may also improve mucosal permeation of the drug.

CONCLUSION:

From this study it was concluded that the buccal films containing 2.5 mg of Zolmitriptan can be successfully prepared by using NaCMC, HEC, HPMC (5cps), chitosan and PVP (F2 and F4 formulations) were best formulations. Hence these formulations of Zolmitriptan mucoadhesive buccal films promising one as the controlled drug delivery, shows moderate swelling, convenient residence time and *in-vitro* drug release, greater therapeutic efficacy may improve the bioavailability. The prepared buccal films were found to stable after performing stability testing for one month.

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