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DEVELOPMENT AND CHARACTERIZATION OF ZOLMITRIPTAN MUCOADHESIVE BUCCAL PATCHES

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ABSTRACT

The objective of present study was to develop matrix type buccal patch therapeutic systems of Zolmitriptan using natural polymers as matrix formers. Zolmitriptan buccal patches were developed by using solvent casting technique. Various physicochemical parameters like weight variation, thickness, folding endurance, drug content, moisture content, moisture absorption parameters like mucoadhesive strength, force of adhesion, and bond strength were evaluated. An *in vitro* drug release study was designed, and it was carried out using commercial semipermeable membrane. Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction was observed. The in vitro release study revealed that F5 formulation showed maximum release in 8 hrs. The release of Zolmitriptan appears to be dependent on lipophilicity of the matrix. Moderately lipophilic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the in vitro dissolution data the F5 formulation was concluded as optimized formulation.

KEYWORDS: Buccal Patch, Buccal Delivery System, Zolmitriptan, Synthetic Polymers, Solvent Casting Technique, Diffusion Mechanism.

INTRODUCTION

Buccal 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.[1] The administration of drugs via buccal route facilitates a direct entry of drug molecules into the systemic circulation, avoiding the first-pass metabolism and drug degradation in the harsh gastrointestinal environment, which are often associated with oral administration.[2,3] The buccal cavity is easily accessible for self-medication, and hence it is safe and well accepted by patients, since buccal patches can be very easily administered and even removed from the application site, terminating the input of drug whenever desired. Moreover, buccal patches provide more flexibility than other drug deliveries.[4] Buccal patches also ensure more accurate dosing of the drugs as compared to gels and ointments.[5] Zolmitriptan is a second-generation triptan prescribed for patients with migraine attacks, with and without an aura, and cluster headaches. It has a selective action on serotonin receptors and is very effective in reducing migraine symptoms, including pain, nausea and photo or phonophobia.[6]

MATERIALS

Zolmitriptan was obtained from Alkem Pvt Mumbai, HPMC and Eudragit procured from SD fine chemicals Mumbai. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY

Compatibility Studies of Drug and Polymers[7]

In the formulation of Zolmitriptan patch formation, API and Excipient may interact as they are in close communication with each other, which could lead to the instability of drug. FT-IR spectroscopy was employed to ascertain the compatibility between Zolmitriptan and the selected polymers. The pure drug and drug with excipients were scanned separately.

Formulation Design

Table 1: Formulation Design of Zolmitriptan Buccal Patches.

S. No.	F. Code	Ingredients (mg)				
		Drug (mg)	HPMC k5M	Eudragit RL100	PEG	DMSO
1	F1	5	100	-	1ml	0.1ml
2	F2	5	200	-	1ml	0.1ml
3	F3	5	300	-	1ml	0.1ml
4	F4	5	400	-	1ml	0.1ml
5	F5	5	-	100	1ml	0.1ml
6	F6	5	-	200	1ml	0.1ml
7	F7	5	-	300	1ml	0.1ml
8	F8	5	-	400	1ml	0.1ml

Preparation Method[8]

Solvent Casting Method

Zolmitriptan buccal patches were formulated by the solvent casting evaporation technique. The drug Zolmitriptan was diffuse in methanol. Polymers HPMC K100M, Eudragit were taken in a boiling tube, to this add Zolmitriptan drug which was previously dissolved in suitable solvent. Sufficient care was taken to prevent the creation of lumps. PEG was taken as a plasticizer and Dimethylsulfoxide as permeation enhancer and added to the mixture and mixed well. It was set aside for 2 hours to exclude any entrapped air and was then transferred into a previously cleaned petri plate (40cm^2), drying of patches was carried out in vacuum oven at room temperature. Dried patches were packed in aluminium foil and stored in a desiccator for further evaluation.

Characterization of Buccal formulation[9,10,11]

Physico- Chemical Evaluation

Physical Appearance

All the formulated Zolmitriptan films were observed for color, clarity, flexibility, and smoothness.

Folding Endurance

Buccal patches folding endurance was estimated by frequently double over at the same place till it broke. The number of times the film could be folded at the same place without breaking is the folding endurance. This was restate on all the films for three times and the mean values plus standard deviation was calculated.

Thickness of the Film

The thickness of each film was measured by using screw gauze. Buccal patches thickness was estimated at various sites on each patch and the average thickness of the Buccal patch was capture as the thickness of the patch.

Weight Uniformity

The formulated Buccal patches are to be dried at 60^{0}C for 6 hours before trial. A identify the area of 4.52 cm^2 of film is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Drug Content

The formulated Buccal patch was assayed for drug content in each case. Three patches from each formulation were assayed for content of drug. Each formulation was casted in triplicate and one patch from each was taken and assayed for content of drug.

The Buccal films (4.52 cm^2) were added to conical flask containing 100 ml of phosphate buffer pH 7.4 contain 0.5% SLS. This was then stirred with magnetic bead at 400 rpm for 2 hrs. The contents were filtered and the filtrate was analyzed spectrophotometrically. Similarly a blank was prepared from Buccal films without drug.

Moisture Absorption Studies

The buccal patches were weighed exactly and placed in a desiccators containing aluminium chloride to maintain 79.50% RH. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated using the following formula.

$$\text{Perentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture Loss Studies

Three patches were weighed separately and kept in a desiccator contains calcium chloride at 37^{0}C for 24 hours. Then the last weight was noted when there was no further change in the weight of the patch. The percentage of moisture loss was calculated using the following formula.

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

***In Vitro* Release Study**[12]

The release rate of the drug was determined by using Franz diffusion cell apparatus temperature maintained at 37 ± 0.5 ^{0}C and stirred at a rate of 200 rpm. Sink conditions was maintained all over the study. The vessel containing 10ml of phosphate buffer pH 6.8 phosphate buffer solution. Aliquots of 1ml of samples were withdrawn at various time meanwhile and then analyzed using a UV Spectrophotometer.

% release rate of drug was determined using the following formula.

$$\text{Perentage drug release} = \frac{Da}{Dt} \times 100$$

Where, Dt = Total amount of the drug in the film
Da = The amount of drug released

Conditions
Medium: Phosphate buffer pH 7.4 phosphate buffer
RPM: 200
Temperature: 37 ± 0.5^0C
Time intervals: 1, 2, 3, 4, 5, 6, 7, 8 hours.

Drug Release Kinetics[13]
In order to describe the Drug release kinetics from individual formulations, the corresponding dissolution data were fitted in various kinetic dissolution models Zero order, first order, and Higuchi respectively.

Qt = Q0 + K0 t……..

Where, Qt is the amount of drug released at time t; Q0 the amount of drug in the solution at t = 0, (usually, Q0 = 0) and K0 the zero order release constant.

logQt = logQα+ (K1 /2.303) t……..

Qα being the total amount of drug in the matrix and K1 the first order kinetic constant.

Qt = KH. t ½…….

Where,
KH is the Higuchi rate constant.
Further, to better characterise the mechanism of drug release from matrices, dissolution data were analyzed using the equation proposed by Korsmeyer and Peppas.

Q (t-*l*) /Qα = KK (t-*l*)n…….

Where, Qt corresponds to the amount of drug released in time t, *l* is the lag time (*l* = 2 hours), Qα is the total amount of drug that must be released at infinite time, KK a constant comprising the structural and geometric characteristics of the tablet, and n is the release exponent indicating the type of drug release mechanism. To the determination of the exponent n, the points in the release curves where Q (t-*l*)/Qα>0.6, were only used. If n approaches to 0.5, the release mechanism can be Fickian. If n approaches to 1, the release mechanism can be zero order and on the other hand if 0.5<n<1, non-Fickian (anomalous) transport could be obtained. Anomalous (non-Fickian) transport generally refers to the drug release by the summation of both diffusion and erosion of the polymeric matrix. The criteria employed to select the ‘‘best model’’ was the one with the highest coefficient of determination (r^2).

Stability Studies[14]
Optimized medicated buccal films were subjected to short term stability testing. The Buccal films were sealed in aluminium foils and kept in a humidity chamber maintained at 40 ± 2^0C and 75 ± 5% RH for 3 months as per ICH guidelines.

RESULTS AND DISCUSSION

Compatibility Studies of Drug and Polymers
All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Zolmitriptan and polymer. It also confirmed that the stability of drug during microencapsulation process.

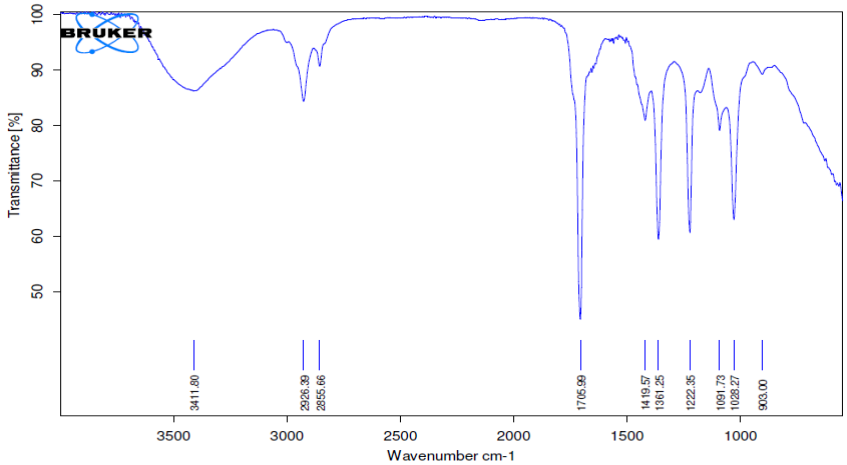

Fig. 1: FTIR Studies of Zolmitriptan.

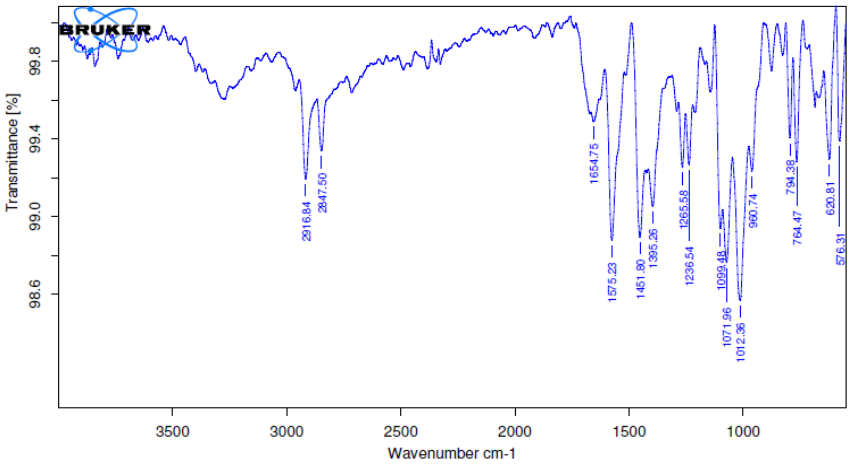

Fig. 2: FTIR Studies of Physical Mixture of Drug and Excipients.

Physical Appearance and Surface Texture of Buccal Patches

These parameters were checked simply with visual inspection of patches and by feel or touch. The observation reveals that the patches are having smooth surface and they are elegant in appearance.

Weight Uniformity of Buccal Patches

The weight of the patches was determined using digital balance and the average weight of all patches.

Thickness of Buccal Patches

The thickness of the patches was measured using screw gauge and the average thickness of all patches.

Folding Endurance of Buccal Patches

The folding endurance gives the idea of flexible nature of patches. The folding endurance was measured manually, patches were folded repeatedly till it broke, and it was considered as the end point. The folding endurance was found optimum and the patches exhibited good physical and mechanical properties and the average folding endurance of all patches.

Drug Content Uniformity of Buccal Patches

Zolmitriptan buccal patches prepared with various polymers were subjected to the valuation for uniform dispersion of drug throughout the patch. In each case three patches were used and the average drug content was calculated.

% Moisture Loss

The moisture content in the buccal patches ranged from 8.45 to 8.95%. The moisture content in the formulations was found to be increased by increase in the concentration of polymers.

% Moisture Absorption

The moisture absorption in the buccal patches ranged from 9.90 to 10.55%.

Swelling Index

The swelling index in the buccal patches ranged from 14.48 to 15.90 %.

Table 2: Physicochemical Evaluation Data of Zolmitriptan Buccal Patches.

F. Code	F1	F2	F3	F4	F5	F6	F7	F8
Thickness (mm)	0.32	0.36	0.35	0.34	0.39	0.31	0.29	0.34
Weight Variation (mg)	35.69	38.89	42.15	42.19	39.68	46.93	42.91	36.95
Drug Content Uniformity	92.15	92.19	90.85	90.15	93.65	91.2	91.65	92.38
Folding Endurance	78	71	78	71	75	77	78	80
% Moisture Loss	8.95	8.45	8.47	8.6	8.91	8.88	8.93	8.7
%Moisture Absorption	10.22	10.15	9.9	10.25	10.16	10.55	10.25	10.12
Swelling Index	15.9	15.72	14.48	15.2	15.54	15.7	14.6	15.15

Drug Release Studies

Table 3: *In Vitro* Release Data of Buccal Patch F_1 to F_8.

Time (hrs.)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
0	0	0	0	0	0	0	0	0
1	12.30	14.08	13.80	14.60	15.85	14.20	13.80	14.56
2	27.45	25.89	26.50	25.55	26.70	25.89	26.50	25.55
3	35.12	36.87	37.70	38.25	37.89	36.87	37.70	38.25
4	47.16	45.23	44.50	47.59	48.18	45.23	44.50	47.59
5	59.82	68.35	67.65	66.55	69.75	68.35	67.65	66.55
6	74.23	70.34	71.98	75.32	76.89	70.34	71.98	75.32
7	87.90	86.77	85.32	80.28	88.86	86.77	85.32	80.28
8	91.40	92.50	90.12	88.22	95.96	93.50	90.52	89.20

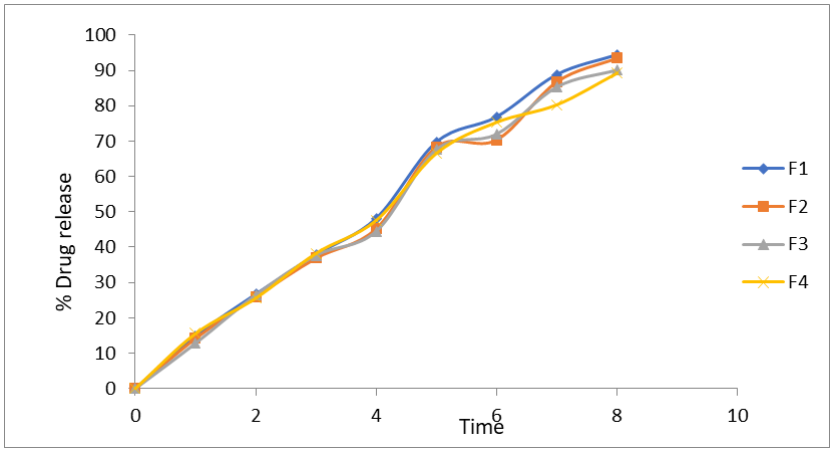

Fig. 3: In Vitro Drug Release of (F1- F4) Formulation.

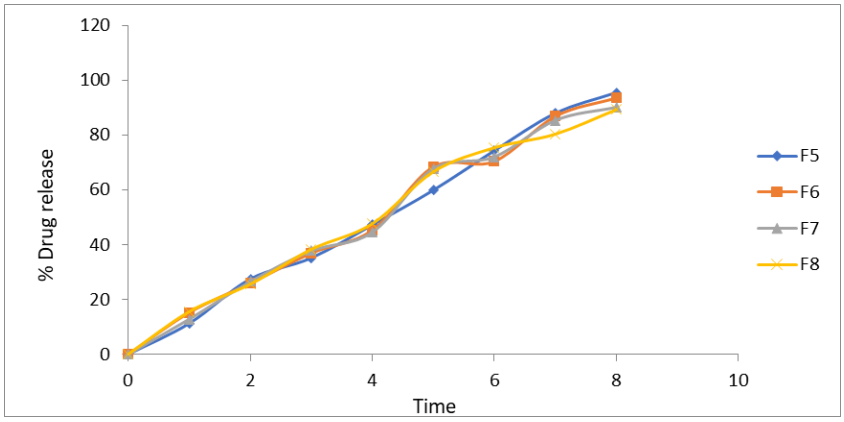

Fig. 4: In Vitro Drug Release of (F5- F8) Formulation.

Drug Release Kinetics

All the formulation of prepared Zolmitriptan buccal patches were subjected to in vitro release studies these studies were carried out using Franz diffusion cell apparatus.

The dissolution medium consisted of 10 ml of Standard buffer pH 6.8 period of time.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows

- Cumulative percent drug released vs. time (zero order rate kinetics)
- Log cumulative percent drug retained vs. time (First Order rate Kinetics)
- Cumulative percent drug released vs. square root of time (Higuchi's
- Classical Diffusion Equation)
- Log of cumulative % release Vs log time (Peppas Exponential Equate).

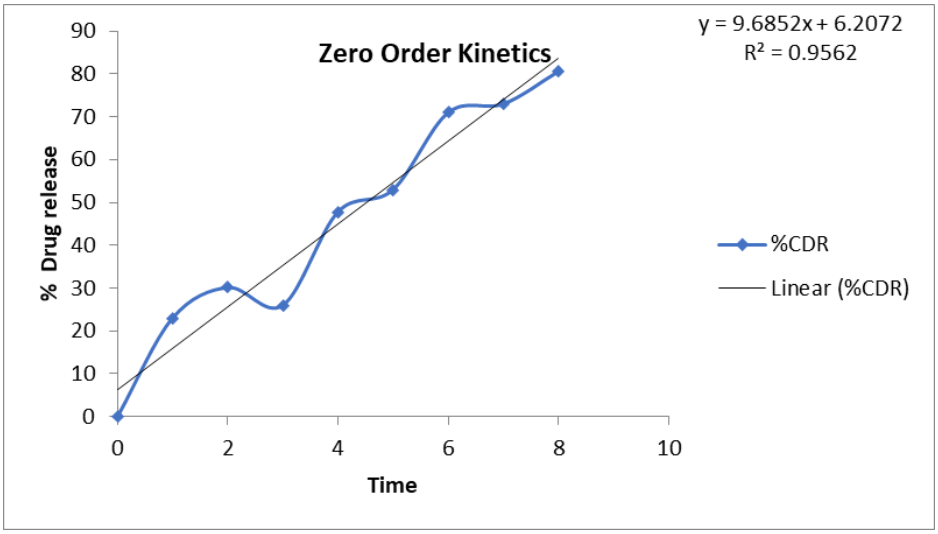

Fig. 5: Zero Order Kinetics of Optimized Formulation.

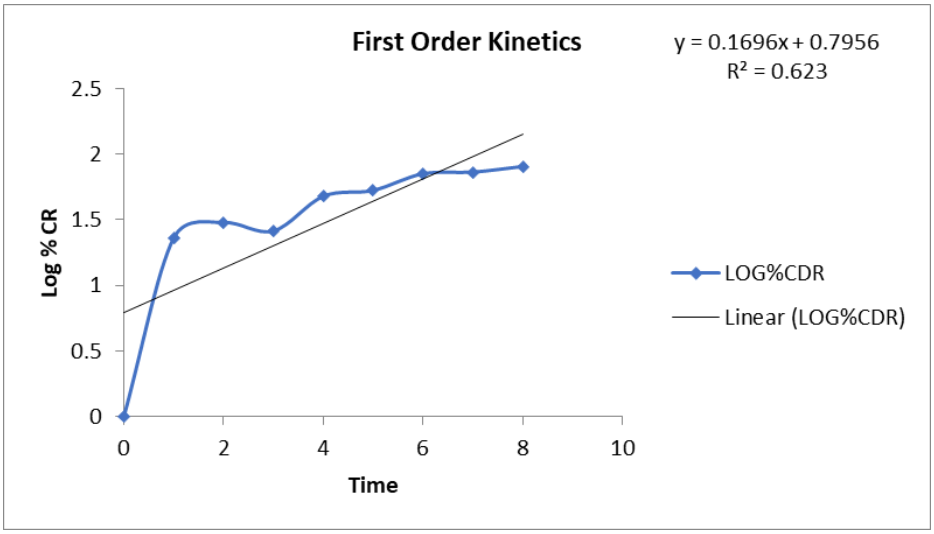

Fig. 6: First Order Kinetics of Optimized Formulation.

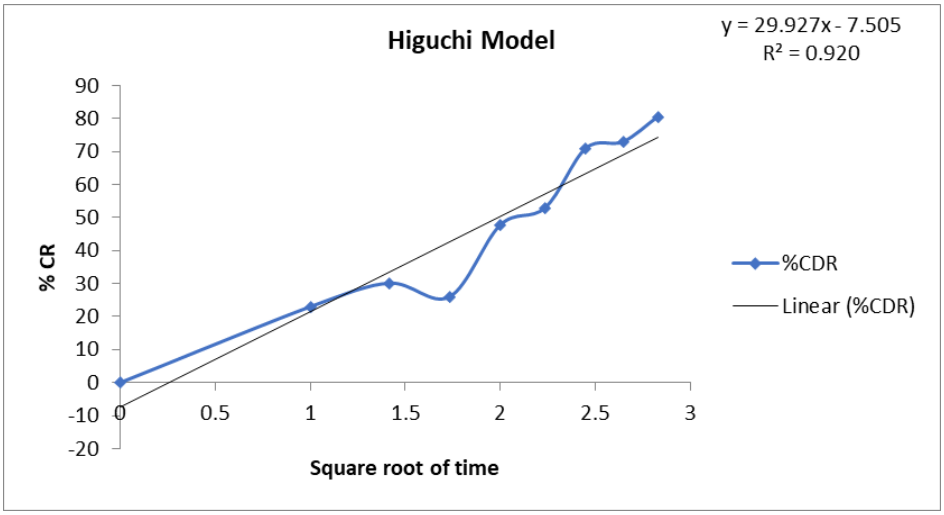

Fig. 7: Higuchi Model of Optimized Formulation.

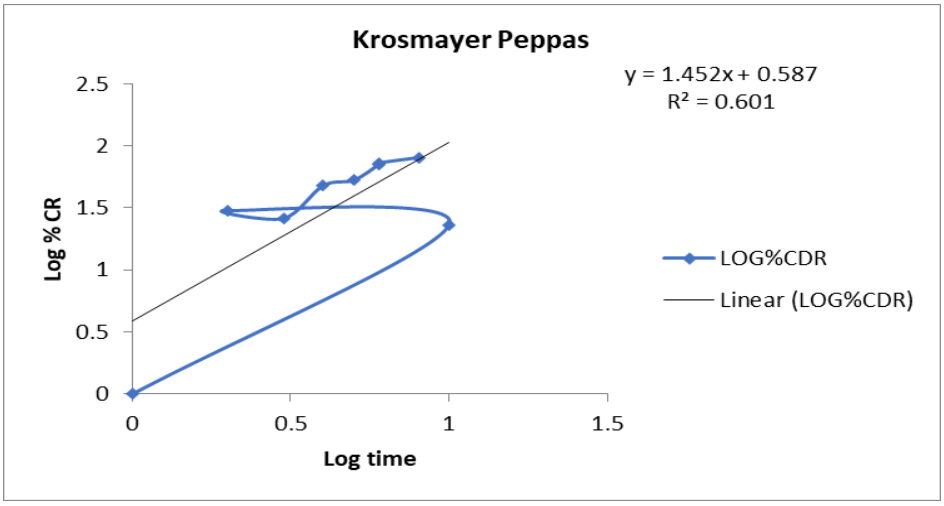

Fig. 8: Korsmayer Peppas of Optimized Formulation.

The values of in vitro release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi matrix, Peppas were respectively. Regression values are higher with Zero order release kinetics. Therefore all the Zolmitriptan nanoparticles Zero order release kinetics.

Table 4: Regression Equations of Zolmitriptan Buccal Patches.

F. No.	In Vitro Release In Phosphate Buffer P^h 6.8 Regression Values			
	Zero Order	First Order	Higuchi Plot	Kross Mayer peppas
F5	0.956	0.623	0.920	0.601

The table indicates that r^2 values are higher for Higuchi's model compared for all the formulation. Hence Zolmitriptan release from all the buccal films followed diffusion rate controlled mechanism.

Stability Studies

Optimized formulations F5 was selected for accelerated stability studies as per ICH guidelines. The patches were observed for color, appearance and flexibility for a period of three months. The folding endurance, weight, drug content, % cumulative drug release of the formulation was found to be decreasing. This decrease may be attributed to the harsh environment (40^0C) maintained during the studies.

Table 5: Stability Studies of Optimized Formulations.

S.No.	Time In Days	Physical Changes	Mean % Drug Release Zolmitriptan		
			25^0C/60%	30^0C/75%	40^0C/75%
1.	01	No Change	95.96	94.90	93.45
2.	30	No Change	95.96	94.86	93.34
3.	60	No Change	95.96	94.80	92.60
4.	90	No Change	95.96	94.75	91.56

CONCLUSION

FTIR studies revealed that there is no incompatibility or interaction between Zolmitriptan and excipients. Formulated buccal films gives satisfactory film characteristics like physical appearance, surface texture, weight uniformity, thickness uniformity, folding endurance, surface pH, percentage swelling index, percentage moisture uptake, drug content uniformity, in-vitro drug release. The low values for standard deviation for average weight, thickness, surface pH, percentage swelling index, percentage moisture uptake, in vitro drug release and drug content indicated uniformity within the batches. Based on in vitro drug release, formulation F5 exhibited a drug release of 95.96 % in 8 hours. The drug release could be retarded more than 8 hr with controlled release behaviour. The prepared buccal patches were found to stable after performing stability testing for three month. The optimized formulation followed zero order kinetics. Short term stability studies of optimized formulation as per ICH guidelines indicated that there is no significant change in physical appearance, drug content determination and in vitro drug release. So finally it can be concluded that buccal films of Zolmitriptan could provide sustained buccal delivery for prolonged period. A further clinical investigation has to be conducted to establish the safety and efficacy of the developed formulation.

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