Research Article

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Formation development and evolution of oral fast disintegrating film of zolmitriptan.

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Abstract

The main aim of the present study was to develop oral fast disintegrating film of Zolmitriptan for the treatment of migraine. Oral fast disintegrating films were prepared by HPMC E5 as a polymer, ipropylene iglycol ias an iplasticizer, isodium istarch iglycolate is a super disintegrant, and aspartame it is a sweetener. Optimization was done by using the i23 factorial design. iThe optimized batch was prepared by using i4% of HPMC iE5, i1.5 i% of ipropylene iglycol, and i4% of isodium istarch iglycolate. It gave disintegration time I of I 9 sec, drug release of i98.15%, and folding endurance of i200 times. From the above research work it is concluded that oral fast disintegrating film of Zolmitriptan was successfully designed and developed by solvent casting method and it gives quick onset of action, patient compliance.

Keywords: Zolmitriptan, HPMC, solvent casting method.

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Introduction

Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest most convenient and economical method of the drug delivery having the patient compliance [1]. These drug delivery options allow the medication to bypass the first pass metabolism thereby making the medication more bioavailable [3].

Zolmitriptan is used to treat migraines. It helps to relieve headache, pain, and other migraine symptoms (including nausea, vomiting, and sensitivity to light/sound).Three distinct pharmacological actions have been implicated in the antimigrane effects of the Triptans (1) stimulation of presynaptic 5-HT1D receptors, which serves to inhibit both dural vasodilation and inflammation; (2) direct inhibition of trigeminal nuclei cell excitability via 5-HT1B/1D receptor agonism in the brainstem and (3) casoconstriction of meningeal, dural,cerebral or pial vessels as a result of vascular 5-HT1B receptor agonism.

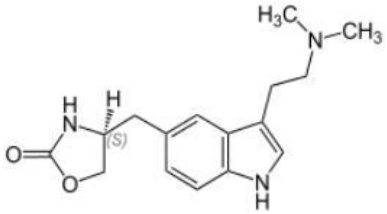

Figure01: chemical srucutre of zolmitriptan

Experimental work

Materials and methods

Zolmitriptan , HPMC E5 , Polyethylene glycol , Aspartame ,Sodium starch glycolate purchased from the commercial one with analytical grade quality all instruments were used calibrirated

Methodology 4-9

Preformulation studies:

Preformulation involves the application of biopharmaceutical principle to the physic-chemical properties of drug substance and are characterized with the goal of designing optimum drug delivery system.

FTIR studies

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As a part of the Preformulation studies, drug-polymer interaction study was performed by using Fourier Transform Infrared Spectroscopy [FTIR].

Calibration curve of Zolmitriptan

Analytical method development

The analytical method development employed in the present research work was carried out by UV spectroscopy. Zolmitriptan shown absorption maxima at 223nm.

Preparation of standard solution

10 mg of zolmitriptan was accurately weighed into 10 ml volumetric flask and dissolved in small quantity of phosphate buffer pH 6.8 finally the volume was made up to 10 ml with pH 6.8 buffer 1 ml of the above solution was pipette into another 10 ml volumetric flask and the volume was made up to 10 ml pH 6.8 phosphate buffers (100 µg/ml).

From the above stock-2 solution 0.2, 0.4, 0.6, 0.8 and 1ml solution was pipette out into 5 different 10ml volumetric flask respectively and the volume was made up to 10 ml with phosphate buffer pH 6.8 (2 µg/ml,4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml).

Preparation of fast disintegrating films

Fast disintegrating films of Zolmitriptan was prepared by solvent casting evaporation method. The composition of the formulation is presented in table 2.2. Dried film was carefully removed from film former and trimmed into 10×10 cm^2 size. Trimmed films were stored in air tight container and subjected for evaluation studies.

2^3 factorial design for formulation of films

Statistical analysis of the experimental work was carried out using Design Expert 10 portable software. A 3-factor, 2-level full factorial design was used to derive the second order polynomial equation. Concentration of HPMC E 5 (X_1), PG (X_2), SSG (X_3) were selected as independent variables while disintegration time (Y_1), *Invitro* drug release (Y_2), folding endurance (Y_3) were selected as dependent variables.

Table 01: Formulation table of Zolmitriptan oral fast disintegrating films using 2^3 Factorial Design

S. no	Ingredients	Formulation codes							
		F1	F2	F3	F4	F5	F6	F7	F8
1	Zolmitriptan (mg)	125	125	125	125	125	125	125	125
2	HPMC E 5 (%)	4	4	6	6	6	4	6	4
3	Propylene glycol (ml)	1	1	3	1	1	3	3	3
4	Sodium starch glycolate (%)	2	4	2	2	4	4	4	2
5	Aspartame (mg)	15	15	15	15	15	15	15	15
6	Water (ml)	10	10	10	10	10	10	10	10

Characterization of Zolmitriptan oral fast disintegrating films (ZOFDF's) [10-19]

a) Morphological Properties

Morphological properties such as the homogenous nature of film, colour, transparency and surface of ZOFDF'S are tested visually. All the formulations were stored at room temperature (25± 3°C) in air tight containers.

b) Uniformity of film Thickness

OFDF's thickness was measured by using micrometer screwgauge at 5 different strategic locations. This helps in determining the uniformity of thickness of oral fast disintegrating films which directly relates to the accuracy of the dose.

c) Folding endurance

Folding endurance proved the information regarding the flexibility as well as the physical ability of the OFDF'S. It was measured by firmly folding OFDF'S repeatedly at the middle. The number of folds on the same crease, required to produce crack in the film was noted as the value of folding endurance.

d) *In vitro* disintegration time

There was no official disintegration test for fast disintegrating films. From the previous literature search of the most used method was selected and performed.

Petri dish method

This method was performed by using Petri dish. In this method Petri dish was filled with 10ml of pH 6.8 phosphate buffer and the OFDF'S was carefully placed at the centre of the Petri dish. Time taken by the film to disintegrate is measured and the test is performed in triplicate manner.

e) Surface pH

OFDF'S to be tested was cut into 2×2 cm^2 square shaped and is placed in a Petri dish and moistened by 1 ml of water and kept for 1 min. surface pH of the OFDF's was measured by using a pH meter (ELICO-L1120). An average of 3 trials was taken as surface pH. For all the formulations, surface pH was calculated and values were compared by using bar chart.

f) Drug content uniformity:

Three OFDF's were trimmed from 3 different places of the total casted film. Each film was separately dissolved in a volumetric flask containing 100 ml of pH 6.8 phosphate buffer. Three volumetric flasks were shaken until OFDF's gets dissolved. All the

solutions were filtered and samples were analysed by using Double beam UV spectrophotometer used plain placebo solution as blank. An average of the 3 trails was taken as drug content in each OFDF's. The same procedure was repeated for the remaining formulations.

g) *In vitro* dissolution studies:

In vitro dissolution studies were carried out in USP type I apparatus (basket), 900 ml of phosphate buffer pH 6.8 was used as dissolution media at 37±0.5°C. 2×2cm² OFDF's was placed in dissolution basket. Dissolution was carried out by withdrawing aliquot of 5ml samples at regular time intervals 1, 2, 3, 4, 5min time intervals and the fresh medium was replaced. Samples were filtered using borosil quantitative grade 1 what man filter paper and diluted suitably and analysed by using a UV spectrophotometer at 223nm by blank correction method. Dissolution of each formulation was performed in triplicate manner and average value of 3 trials were taken and used to calculate the drug release profile.

h) Tensile strength

Three films from each formulation were took and cut in to 5 cm width and 10 cm length. Breaking force of each film was determined using Tensile strength apparatus (H1KS Tensile strength apparatus HTE-500N) and the mean and standard deviation were calculated using the formula;

Tensile strength = Breaking force / Area of cross section

I) Percentage Elongation:

Percentage elongation provides the information regarding mechanical property of the OFDF's. When the physical force is applied on the OFDF's it stretches and it is referred as strain. Strain refers the deformation of OFDF's divided by the original dimension of the OFDF's. Percentage elongation increases with an increase in the plasticizer concentration. It was calculated by using following formula.

Percentage elongation = (L-L$_o$) / L$_o$ × 100

Where, L = final length, L$_o$ = initial length

h) Percentage moisture loss:

The percentage moisture loss studies were carried to check film physical stability. Initially weighed OFDF's of predetermined size (3×3cm²) was placed in a desiccators containing anhydrous calcium chloride (inside the desiccators) for three days. The films were removed and weighed again to calculate the percentage moisture loss by using following formula.

% Moisture loss = (Initial weight – Final weight / Initial weight) × 100

I) Percentage moisture uptake:

Weighed films are kept in desiccators at room temperature for 24 hours. These are then taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in desiccators, until a constant weight is achieved. % moisture uptake is calculated as given below. % moisture uptake % moisture loss of all the five formulations was compared by using bar chart

%Moisture uptake = (Final weight – Initial weight / Final weight) × 100

Results and Discussion

Zolmitriptan standard calibration curve:

Serial dilutions are made from standard working solution with phosphate buffer pH 6.8 to get a concentration from 2 to10 µg/ml and the absorbance was measured at 223nm.

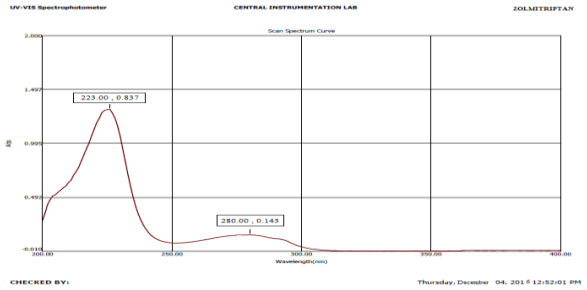
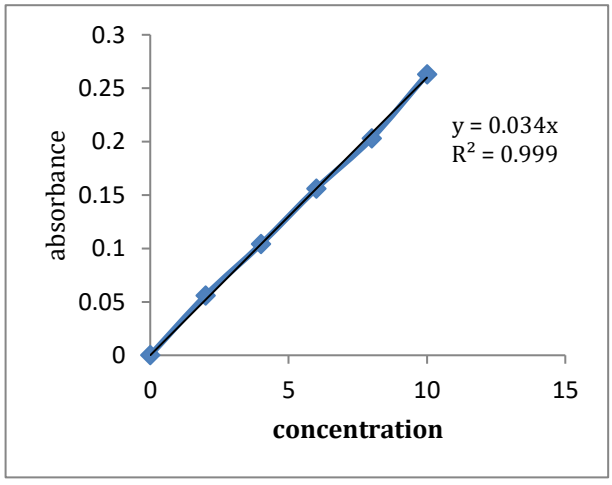


Fig 02: Scan spectrum of Zolmitriptan pure drug

Table 02: Calibration table of Zolmitriptan

S.NO	Concentration (µg/ml)	Absorbance at 223 nm
1	2	0.056±0.018
2	4	0.104±0.027
3	6	0.156±0.010
4	8	0.203±0.005
5	10	0.263±0.005



Physical appearance and surface texture of films

The appearance of all the films was uniform having transparent in appearance. The observation suggests that the films were having smooth surface and they were elegant enough to see. The results are shown in table.no.6.

***In vitro* dissolution study**

The dissolution of Zolmitriptan oral fast disintegrating films were carried out in USP I basket type apparatus. Dissolution study for all eight formulations was performed for 5 min. The results were tabulated in table no.14 and shown graphically in figures 8-9. From the results it can be said that as the concentration of polymer and plasticizer increases drug release decreased.

Surface pH

All the formulations were tested for the surface phi Surface pH of the eight formulations ranges from 6.53± 0.03 to 6.80± 0.02 which is similar to the pH of saliva. As the OFDF's are having a similar pH there will not be any irritation in the oral cavity. PH of all the eight formulations is shown in table.no.6.

Table 04: various physicochemical properties of fast dissolving oral films of Zolmitriptan

Formulation code	Physical appearance	Surface texture	Surface pH	Thickness
F1	Transparent	Smooth	6.67 ± 0.062	0.020 ± 0.002
F2	Transparent	Smooth	6.70 ± [illegible]	0.158 ± [illegible]
F3	Transparent	Smooth	6.60 ± 0.026	0.189 ± 0.004
F4	Transparent	Smooth	6.86 ± 0.023	0.273 ± 0.003
F5	Transparent	Smooth	6.75 ± 0.030	0.012 ± 0.003
F6	Transparent	Smooth	6.60 ± 0.020	0.145 ± 0.005
F7	Transparent	Smooth	6.83 ± 0.030	0.215 ± 0.005
F8	Transparent	Smooth	6.66 ± 0.030	0.231 ± 0.001

Drug content uniformity

Zolmitriptan in all the eight formulations is in the range of 98.32 to 99.81%. Thus all the formulations were within the specification limits (85 % 115%). The result of drug content studies is presented in table 07.

Percentage moisture uptake

Percentage moisture uptake gives the information about the stability of the oral films. As the percentage moisture uptake is more, less will be the stability of the film. Percentage moisture uptake values are shown in table 07. It is clear that as the polymer concentration increases moisture absorbing capacity also increases, which finally influence the stability of the film.

Table 05: Percentage moisture loss, percentage moisture absorption, disintegration time and drug content uniformity, folding endurance of all formulations

Formulation code	% moisture loss	% moisture absorption	Disintegration time (sec ± SD)	% Drug content (% ± SD)	Folding Endurance (folds)
F1	1.17 ± 0.48	2.61 ± 0.08	10± 0.04	96.36 ± 2.46	260
F2	2.47 ± 0.37	3.20 ± 0.09	09 ±0.24	99.10 ± 1.64	270
F3	1.98 ± 0.50	3.53 ± 0.10	15 ± 0.03	98.60 ± 1.28	290
F4	2.21 ± 0.08	4.82 ± 0.97	14 ± 0.28	94.22 ± 1.44	270
F5	2.88 ± 0.55	5.63 ± 0.89	13 ± 0.24	95.65 ± 0.42	275
F6	2.66 ± 0.43	4.91 ± 0.54	08 ± 0.01	99.81 ± 1.09	270
F7	2.98 ± 0.51	2.65 ± 0.08	16 ± 0.03	95.75 ± 0.78	290
F8	3.23 ± 0.53	2.53 ± 0.06	12 ± 0.10	97.45 ± 0.91	280

The disintegration time was calculated by Petri dish method. The disintegration time for all eight formulations ranged from 8 to 16 sec as shown in table 07. From the results it can be said that at higher concentration of superdisintegrant the film takes less time to disintegrate. Thus addition of superdisintegrant helps the faster breakdown of the film and hence fast release is obtained.

Folding endurance

Table 06: In vitro release studies of fast disintegrating oral films of Zolmitriptan

Time (ofmin)	% of Cumulative drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	54.67±0.030	49.56±0.035	38.25±0.030	45.61±0.021	46.12±0.012	58.65±0.036	36.95±0.006	45.21±0.010
2	68.89±0.010	52.35±0.025	45.32±0.024	65.68±0.051	43.23±0.015	72.24±0.041	42.58±0.001	56.29±0.013
3	73.09±0.002	63.26±0.012	57.56±0.026	75.24±0.005	54.23±0.005	85.00±0.005	54.63±0.003	72.52±0.005
4	86.67±0.001	75.25±0.024	63.23±0.034	84.62±0.012	68.25±0.012	89.47±0.035	65.23±0.021	80.24±0.003
5	87.76±0.016	89.16±0.030	82.32±0.041	93.63±0.013	82.19±0.003	94.84±0.030	83.18±0.003	93.170.001

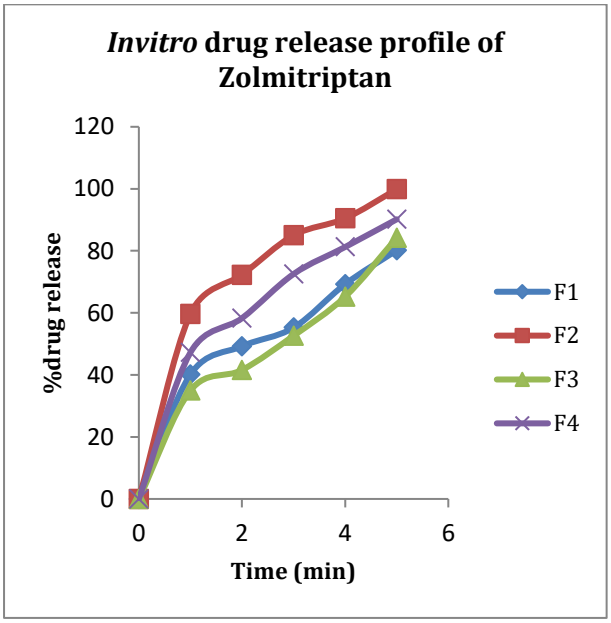


Fig 03: *In-vitro* drug release profile of Zolmitriptan (F1-F4)

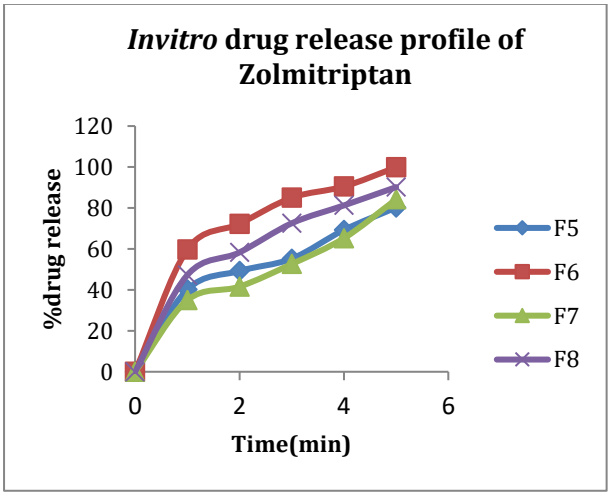


Fig 04: In-vitro drug release profile of zolmitriptan (F5-F8)

Fitting of the model

Response 1 (Y1): effect on disintegration time

The model purpose the following polynomial equation for disintegration time.

$$Y1 = +8.88+1.12A-0.88B-0.12AB-0.62AC$$

Where, Y1 is disintegration time, A is the concentration of polymer, B is the concentration of plasticizer and C is the concentration of superdisintegrant. The model F-value 0.0406 indicates the model is significant ($p < 0.05$). A positive value in above equation represents the synergic effect of the independent variable and a negative value represents the antagonistic effect.

Table 07: Analysis of variance for response Y1

Source	Sum of squares	Df	Mean squares	F value	p-value Prob >F	Significance
Model	19.50	4	4.88	10.64	0.0406	S
A	10.12	1	10.12	22.09	0.0182	S
B	6.13	1	6.13	13.36	0.0354	S
C	0.13	1	0.13	0.27	0.6376	S
AC	3.12	1	3.12	6.82	0.0796	S

Response 2 (Y2): effect on drug release

Table 08: Analysis variance for response Y2

Source	Sum of squares	Df	Mean squares	F value	p-value Prob >F	Significance
Model	385.00	4	96.25	11.55	0.0363	S
A	312.5	1	312.5	37.5	0.008	S

	0		0	0	8	
B	50.00	1	50.0	6.00	0.0917	S
C	4.50	1	4.50	0.54	0.5157	S
BC	18.00	1	18.00	2.16	0.2380	S

Response 3 (Y3): effect on folding endurance

Table 09: Analysis variance for response Y3

Source	Sum of squares	Df	Mean squares	F value	p-value Prob >F	Significance
Model	1962.50	4	490.63	24.79	0.0124	S
A	378.13	1	378.13	19.11	0.0222	S
B	903.12	1	903.12	45.63	0.0066	S
C	152.12	1	153.12	7.74	0.0689	S
AB	528.12	1	528.12	26.68	0.0141	S

Optimization [20-21]

The formulation of 8 batches of oral films according to 2^3 factorial design was carried out. The formulated batches were evaluated for various physicochemical parameters. All the formulations shows good characteristics but there is a need to optimize the formulation because from the contour plots (10, 12 &13) there is an decrease in disintegration time and drug release due to increase in polymer and plasticizer concentrations because there is an interaction between the factors. The interaction was shown in plots.no. 21, 22&23.so from the interaction plots it clears that the concentration of polymer is 4% and plasticizer concentration is 1.5%. The optimized formulation contains 4% of polymer, 1.5% of plasticizer and 4% superdisintegrant. The prepared formulation was evaluated for drug release, disintegration time and folding endurance.

Table.no.10 results of optimized formulation

Confirmation Report						
Two-sided	**Confidence =**	**95%**	**n =**	**1**		
Factor	**Name**	**Level**	**Low Level**	**High Level**	**Std. Dev.**	**Coding**
A	HPMC E5	6.00	4.00	8.00	0.000	Actual
B	PROPYLENE GLYCOL	7.00	4.00	10.00	0.000	Actual
C	SSG	4.00	2.00	6.00	0.000	Actual

Response	**Predicted Mean**	**Predicted Median[1]**	**Observed**	**Std Dev**	**n**	**SE Pred**	**95% PI low**	**Data Mean**	**95% PI high**
DISINTEGRATION TIME	8.875	8.875	-	0.677003	1	0.72	6.59		11.16
DISSOLUTION RATE	86.5	86.5	-	2.88675	1	3.06	76.76		96.24
FOLDING ENDURANCE	279.375	279.375	-	4.44878	1	4.72	264.36		294.39

Summary and Conclusion

The main aim of the present study was to develop oral fast disintegrating film of Zolmitriptan for the treatment of migraine. Oral fast disintegrating films were prepared by HPMC E5 as a polymer, propylene glycol as a plasticizer, sodium starch glycolate as a super disintegrant and aspartame as sweetener. optimized batch was prepared by using 4% of HPMC E5, 1.5 % of propylene glycol and 4% of sodium starch glycolate. It gave disintegration time of **9** sec, drug release of 98.15% and folding endurance of 200 times.

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