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FORMULATION, OPTIMIZATION AND EVALUATION OF FAST DISSOLVING SUBLINGUAL FILM OF ZIPRASIDONE USING STATISTICAL DESIGN

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ABSTRACT The purpose of this investigation was to formulate, optimize and evaluate sublingual film for the treatment of schizophrenia and bi polar disorder. Sublingual films were prepared by solvent casting method. Present investigation were formulated by using HPMC E15 (X_1) as polymer and Polyethylene glycol (X_2) as plasticizer were chosen as independent variables in 3^2 full factorial design while Tensile strength (TS), Disintegration time (DT) and % Cumulative drug release at 10 min. (% CDR) were taken as dependent variables. The various physical parameters were evaluated for sublingual films such as thickness, tensile strength, folding endurance, disintegration time, surface pH and % CDR. From the experimental study, it was concluded that the optimized batch ZSF_4 showed 98.4 %, the highest release of the drug. Stability study was performed by taking an optimized formulation and it was observed stable. The sublingual films showed acceptable results in all studies. 3^2 full factorial design was successfully applied during preparation, optimization and evaluation of sublingual films of Ziprasidone. The present investigation showed quick disintegration and fast release of the drug for the treatment of schizophrenia and bi polar disorder.

KEYWORDS : Sublingual film, Schizophrenia, Ziprasidone, HPMC E15, Polyethylene glycol, 32 full factorial design

INTRODUCTION

Development of a formulation involves a great deal of study and experimental work to get optimum results. Sublingual route of administration will provide quick drug delivery into the systemic circulation by overcoming first pass metabolism. The advantage of the sublingual drug delivery is that the drug can be directly absorbed into systemic circulation bypassing enzyme degradation in the gut and liver. These formulations are particularly beneficial to pediatric and geriatric patients. In addition sublingual mucosa and abundance of blood supply at the sublingual region allow excellent drug penetration to achieve high plasma drug concentration with rapid onset of an action [1]. Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods. Because the oral mucosa is highly vascularised, drugs that are absorbed through the oral mucosa directly enter the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism in the liver [2]. Sublingual means literally 'under the tongue' refers to a method of administering substances via the mouth in such a way that the substances are rapidly absorbed via the blood vessels under the tongue rather than via the digestive tract [3]. Medically, sublingual drug administration is applied in the field of cardiovascular drugs, steroids, some barbiturates and enzymes. It has been a developing field in the administration of many vitamins and minerals which are found to be readily and thoroughly absorbed by this method [4]. The delivery of drugs in oral mucosal cavity is classified into two categories such as local delivery and systemic delivery [5]. Consequently, permeability decreases in the order: sublingual > buccal > palatal. TranscellularandParacellular routes are the two possible routes for drug absorption [6]. The sublingual route can produce rapid onset of action due to high permeability and rich blood supply [7]. Factors affecting the sublingual absorption are Lipophilicity of drug, Solubility in salivary secretion, pH and pKa of the saliva, binding to oral mucosa, Thickness of oral epithelium and Oil-to-water partition coefficient [8-11].

Solvent Casting Method is the most preferred method to manufacture fast dissolving film [12].

Ziprasidone is a newer “atypical” or “second-generation” antipsychotic. Ziprasidone (Ziprasidone hydrochloride) administered orally was approved by the U.S. Food and Drug Administration (FDA) for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorder (with or without psychotic features). Regarding tolerability, ziprasidone, has important advantages in that it is not associated with clinically significant weight gain or adverse changes in cholesterol, triglycerides, or glycemic control, and patients may experience moderate improvement in these measures when switching to ziprasidone from a different antipsychotic agent. It also lacks significant persistent effects on prolactin levels, is not anticholinergic, and only infrequently causes extrapyramidal side effects or postural hypotension, although it can be associated with somnolence. Therefore, ziprasidone may be considered a first-line drug option in the treatment of schizophrenia [13]. An estimated 50% of patients with schizophrenia relapse within 1 year of their most recent episode and 15% to 20% of those patients require hospitalization. Ziprasidone may be associated with beneficial effects on depressive symptoms associated with schizophrenia in patients undergoing long-term treatment, based on a post hoc analysis [14].

MATERIALS AND METHODS

Materials and Reagents: Ziprasidone was obtained from Cadila Heathcare Pvt. Ltd., India. HPMC E5 and HPMC E15 were obtained from Colorcon, Goa. Polyethylene glycol, Propylene glycol were purchased from SAVA Fine Chemical, Mumbai, Maharashtra. All other materials and chemicals used were of either pharmaceutical or analytical grade.

Drug Excipients Compatibility Study

Drug-Excipients interaction plays a vital role in achieving stability of drug in dosage form. Fourier transform infrared spectroscopy (FT-IR) was used to study the physical and chemical interactions between drug and excipients. FT-IR spectra of Ziprasidone, HPMC E15 and Polyethylene glycol and their mixture were recorded using potassium bromide mixing method on FT-IR spectrophotometer. (FTIR-1700, Shimadzu, Kyoto, Japan) [15].

Formulation of Sublingual Film containing Ziprasidone:

Sublingual film of Ziprasidone was prepared using hydrophilic polymers by solvent casting method. In this method, polymer was dissolved in 10 ml water and kept for 30 min in a sonicator. Drug, polyethylene glycol and aspartame were dissolved in 5ml ethanol to form a clear solution. Both the mixtures were mixed to form homogenous viscous solution and placed in a sonicator for 30 min to remove entrapped bubbles if any. Then, the resultant viscous solution was casted in petridish and it was dried in the oven at 40°C at 5 hrs. The film was carefully removed from the petridish by forcepsand cut into 2 cm×2 cm in size. Each film contained 10 mg of Ziprasidone. The sample was stored in a desiccator maintained at a temperature of 30°±1°C and relative humidity 60±5% [16].

Preliminary Screening of Sublingual Film with different Polymers: Preliminary study of different polymers were carried out to check its effect on release profile of sublingual film formulation. The preliminary trial batches T_1 to T_6 were formulated and evaluated for Disintegration Time, Tensile Strength and Cumulative % drug release at 10 min and their composition and results were shown in Table 1.

Table 1:Preparation of trial batches

Ingredients	T1	T2	T3	T4	T5	T6
Ziprasidone	79.5	79.5	79.5	79.5	79.5	79.5
HPMC E5	200	400	-	-	-	-
HPMC E15	-	-	200	400	-	-
Guar Gum	-	-	-	-	400	800
Polyethylene Glycol (%)	0.5	2.0	0.5	2.0	0.5	2.0
Aspartame	20	20	20	20	20	20
Citric acid	25	25	25	25	25	25
Preservative	0.5	0.5	0.5	0.5	0.5	0.5
Ethanol	5	5	5	5	5	5
Water	10	10	10	10	10	10

Based on results obtained in trial batches the Factors and level of factors were decided. It was observed that HPMC E15 alone was not able to produce fast disintegration. So, it was combined with Polyethylene Glycol to increase the fast disintegration of the prepared film. The main characteristic of sublingual film is to dissolve quickly. In order to achieve rapid disintegration of film, combination of these two polymers play a crucial role in formulation of sublingual film. Hence, the two factors for Factorial design were:

i) Concentration of HPMC E15(X_1)
ii) Concentration of Polyethylene Glycol (X_2)
Two levels for each factor were selected to study the effect of X_1 and X_2.

Experimental Design of sublingual film of Ziprasidone containing HPMC E15 and Polyethylene Glycol

A 3^2 full factorial design was used in the present study. On the basis of preliminary results, the amount of HPMC E15 (X_1) and the amount of Polyethylene Glycol (X_2) were chosen as independent variables in 3^2 full factorial design, while Tensile strength (TS), Disintegration time (DT) and % Cumulative drug release after 10 min (% CDR) were taken as dependent variables. Thus to achieve the formulation with desired Tensile strength (TS), Disintegration time (DT) and % Cumulative drug release after 10 min. (% CDR), the formulation prepared by using different combination of HPMC E 15 and Polyethylene Glycol were optimized and evaluated using 3^2- full factorial design.

Full factorial design

This design is useful when a detailed analysis of higher order interactions among the factors is needed. Runs are made at all possible combinations of factor levels. As the number of runs required increases rapidly as the number of factors increases, full factorials are usually used when a relatively small set of factors that are known to be important are available or when collecting a large number of observations is feasible. More information is obtained with less work and effects are measured with maximum precision.

The number of experiments required for these studies is dependent on the number of independent variables selected. The response (Y) is measured for each trial.

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2$$

In The 3^2- full factorial design 2 independent factors were evaluated, each at 3 levels, and experimental trials were performed for all 9 possible combinations. The design layout of 3^2- full factorial design as shown in table 2 and table 3.

Two independent variables were selected as below:
X_1 = % w/v concentration of HPMC E15
X_2 = % w/v concentration of Polyethylene Glycol

Table 2: Variables With Coded And Exact Values For 3^2 Full Factorial Design

Independent Variables	Low	Medium	High
Coded values	**(-1)**	**(0)**	**(+1)**
X_1= concentration of HPMC E 15 (mg)	250	350	450
X_2= concentration of Polyethylene Glycol (%)	0.50	1.00	1.50
Dependent Variables			
Y_1 = Tensile strength (g/cm^2)			
Y_2 = Disintegration time (sec)			
Y_3 = Cumulative drug release at 10 min.(%)			

Table 3: Formulations showing factors optimized by 3^2 full factorial design, (Formulation = ZSF) (n = 9)

Formulation Code	Factor 1	Factor 2
	concentration of HPMC E15 (mg/ml)	concentration of Polyethylene Glycol (mg/ml)
ZSF 1	250	0.50
ZSF 2	350	0.50
ZSF 3	450	0.50
ZSF 4	250	1.00
ZSF 5	350	1.00
ZSF 6	450	1.00
ZSF 7	250	1.50
ZSF 8	350	1.50
ZSF 9	450	1.50

Weight Uniformity of the film:

One square inch film was cut at five different places in the caste film. The weight of each filmstrip was taken and the weight variation was calculated [17].

Thickness of the film:

The thickness of the film was measured with the help of micro meter screw gauge and the average thickness of all films were calculated [18].

Tensile strength:

Tensile strength of the film was determined with digital tensile tester, which consists of two load cell grips. The lower one is fixed and upper one is movable. The test film of specific size 2×2 cm can be fixed between these two cell grips and force will be gradually applied till the film breaks. Results of tensile strength in kg will be taken [19].

$$\text{Tensile strength (Ncm}^2\text{)} = \frac{\text{(force at break (Kg)} \times 9.8)}{\text{(Initial cross sectional area of sample(cm}^2\text{)}}$$

Folding endurance:

The folding endurance of the film was determined by repeatedly folding a small strip of the film at the same place till it broke and the average folding endurance of all films was measure [20].

Disintegration time:

The disintegration time limit of 30s or less for orally disintegrating described in CDER guidance can be applied to sublingual film .although no official guidance is available for sublingual film, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeia disintegrating test apparatus may be used for study. Typical disintegration time for film 5-50s.Test was performed using disintegration test apparatus. 2×2 cm film was placed in the basket; it was raised and lowered it in such a manner that the complete up and down movement at a rate equivalent to thirty times a minute [21].

Drug Content uniformity:

Sublingual film prepare with various polymer were subjected to the uniform dispersion of drug throughout the film, in each case three films were used and the average drug content was calculated. Suggesting that drug was uniformly dispersed throughout all film. Films were cut in 2 × 2 cm size, dissolved in Phosphate buffer pH 6.8 and volume was made up to 100 ml. Solution was diluted if necessary. Absorbance was measure at 270 nm [22].

$$\text{\% Drug content} = \frac{\text{(Actual amount of drug in film)}}{\text{Thoritical amount of drug presant in film}} \times 100$$

In-vitro Drug Release:

The in-vitro dissolution studies were conducted using simulated saliva fluid (300 ml). The dissolution studies were carried out using USP dissolution apparatus at 37 ± 0.5°C and at 50 rpm. Each film with dimension (2×2 cm2) was placed on a stainless-steel wire mesh with

sieve opening 700 µm. The film sample placed on the sieve was submerged into dissolution media. 5ml samples were withdrawn at time intervals of 1, 2,5,8,and 10, min, filtered through 0.45 µm Whatman filter paper and were analyzed spectrophotometrically at 223 nm .To maintain the volume, an equal volume of fresh dissolution medium was added after withdrawing samples [23].

Accelerated Stability Study:

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. The optimized formulation was wrapped in aluminum foil and stored at 45 ± 0.5ºC and 50% RH for period of one month. After the period of one month, film was tested for weight Uniformity of film, Thickness of film, Tensile strength, Folding endurance, Disintegration time, Content uniformity and in-vitro drug release study. Both the data were compared and no change was observed [24].

RESULTS AND DISCUSSION

Drug Excipients Compatibility Study

Fourier transform infrared spectroscopy (FT-IR) was used to study the physical and chemical interactions between drug and excipients. FT-IR spectra of Ziprasidone, HPMC E15, Polyethylene glycol and their mixture of Ziprasidone, HPMC E15, Polyethylene glycol were recorded by using KBr mixing method on FT-IR instrument. The drug exhibited peaks due to Carboxylic group, C-N, Aromatic ring, -C-O and C=O stretching. It was observed that there were no or very minor changes in drug main peaks in the IR spectra of the mixture and pure drug. The FTIR study revealed no physical or chemical interaction of Ziprasidone, HPMC E15, Polyethylene glycol [25].

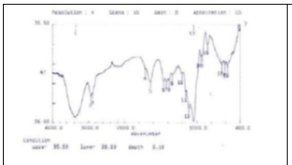

Figure 1.1 FT-IR spectra of Ziprasidone

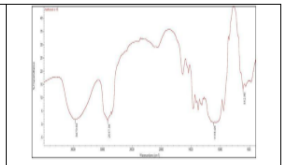

Figure 1.2 FT-IR spectra of HPMC E 15

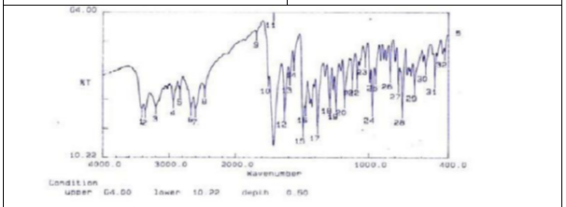

Figure 1.3 FT-IR spectra of Ziprasidone and HPMC E15

EVALUATION PARAMETER:

Thickness of Film

The average thickness of all the formulations was between 0.07±0.01 to 0.11±0.01 mm.

Weight variation

The average weight of film formulations was within the range of 0.018±0.44 to 0.028±0.60 mg. So, all films passed weight variation test as the % weight variation was within the pharmacopoeial limits.

Tensile Strength

The measured tensile strength of each batch were between 16.3±0.10 to 21.1±0.18 kg/cm2.This ensure good handling characteristics of all batches.

Folding Endurance

Folding endurance of batch ZSF1 to ZSF9 was found to be in the range of 120±2.10 to198±3.18. It was found that polymer and plasticizer concentration markedly affect the folding endurance of film.

Disintegration time

The disintegration time of all the batches lies between 30±0.20 to 47±1.80 sec. It was observed that as the concentration of HPMC E15 increases, then disintegration time decreases. On the other hand, as the concentration of Polyethylene glycol increases, then disintegration time increases.

Surface pH

Surface pH of factorial batches ZSF1 to ZSF9 was found to be in the range of 7.3±0.02 to 7.4±0.1. It was observed within limits.

Drug content

The percentage drug content of the all batches was between 95.13 ±5.15 to 99.89 ±0.48, which is within acceptable limits indicate dose uniformity in each batch.

***In-vitro* dissolution study**

From dissolution study it was concluded that as concentration of HPMC E 15 increases amount of drug released decreases and as the concentration of Polyethylene glycol increases amount of drug released increases.

Table 4: *In-vitro* Dissolution of Batch ZSF1 to ZSF9

Time (in sec)	% Drug Release								
	ZSF1	ZSF2	ZSF3	ZSF4	ZSF5	ZSF6	ZSF7	ZSF8	ZSF9
0	0	0	0	0	0	0	0	0	0
60	8.2	10.6	11.5	14.5	16.5	18.2	12.8	11.6	10.2
120	13.5	16.5	17.2	26.8	28.8	28.5	21.4	20.4	18.2
180	18.2	24.2	21.6	38.2	39.2	37.2	28.4	27.5	25.6
240	29.5	29.5	32.8	49.5	51.5	50.5	40.2	38.9	34.8
300	37.8	35.6	44.3	61.8	63.8	63.6	45.7	44.8	42.5
360	49.3	44.6	57.7	72.6	71.6	72.6	58.7	56.5	54.2
420	64.1	61.2	67.4	83.5	82.5	83.5	68.1	64.1	62.6
480	72.2	72.4	78.5	89.2	88.2	89.2	79.6	75.6	73.5
540	86.4	83.6	89.6	94.5	92.5	93.2	89.4	83.4	82.4
600	98.9	97.8	96.4	99.4	97.6	96.8	95.6	91.4	90.2

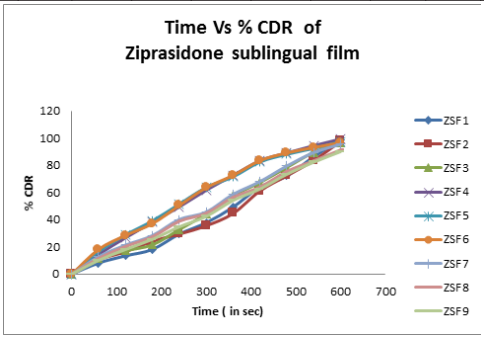

Figure 2: Drug release profile of batch ZSF1-ZSF9

Statistical Analysis

The results of 3^2 full factorial design were analyzed. A considerable information was gathered by using statistical design to optimize the formulation. All the responses were fitted to a quadratic model and compatibility of the model was verified by ANOVA, lack of fit and co-efficient of determination (R^2). To optimize the responses, every response should be interconnected with each other and the most supportive zone must be required for every response to exclude bias. Desirability function was supported by much literature to optimize the multiple responses [26, 27].

The statistical analysis of the factorial design batches was performed by multiple linear regression analysis. The Tensile Strength (Y_1), Disintegration time (Y_2) and % cumulative drug release at10 min. of Ziprasidone (Y_3) were selected as dependent variables.

Table 5: Optimization of Ziprasidone sublingual films using 32 full factorial design (Formulation - ZSF) (n = 9)

Formulation Code	Response 1 (Y_1) Tensile Strength (kg/cm^2)	Response 2 (Y_2) Disintegration time (sec)	Response 3 (Y_3) % Cumulative Drug release at 10 min.
ZSF1	16.3±0.10	30±0.20	98.9
ZSF 2	17.1±0.50	34±1.06	97.8
ZSF 3	19.4±0.24	41±0.40	96.4
ZSF 4	18.1±0.36	32±1.28	99.4
ZSF 5	18.4±0.40	37±0.20	97.6
ZSF 6	19.3±0.25	43±1.30	96.8
ZSF 7	19.1±0.64	36±0.10	95.6
ZSF 8	20.2±0.80	42±0.50	91.4
ZSF 9	21.1±0.18	47±1.80	90.2

*Data from each response is presented in mean±SD (n=3)

The fitted equations (full model) relating the responses that is, Tensile Strength (Y_1), Disintegration time (Y_2) and % cumulative drug release at 10 min of Ziprasidone (Y_3) to the transformed factor are shown in Table 5. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e. positive or negative). Data were analyzed using Design of Expert version 9.

R^2 values for Tensile Strength (Y_1), Disintegration time (Y_2) and % cumulative drug release at 10 min. of Ziprasidone (Y_3) were 0.9522, 0.9947 and 0.9813 respectively indicating good correlation between dependent and independent variables. There was no need to develop reduced models because response variable were significant i.e. $P < 0.05$. The terms with $P < 0.05$ were considered statistically significance and retained in the full model.

The results of ANOVA suggested that *F* values calculated for Tensile Strength (Y_1), Disintegration time (Y_2) and % cumulative drug release at 10 min of Ziprasidone (Y_3) were 11.94, 112.80 and 31.40 respectively .Calculated *F* values were greater than tabulated for all dependent variables therefore factors selected have shown significant effects. From the results of multiple regression analysis, it was found that both factors had statistically significant influence on all dependent variables as $p < 0.05$ (Table 6).

Table 6: Summary of regression analysis of the responses (ZSF)

Quadratic Model	R^2	Adjusted R^2	SD	Adequate Precision	p-value
Tensile Strength (kg/cm^2)	0.9522	0.8724	0.53	10.670	0.0340
Disintegration time (sec)	0.9947	0.9859	0.67	32.456	0.0013
% Cumulative Drug release at 10 min.	0.9813	0.9500	0.71	16.743	0.0086

Polynomial equation with intercept and coded factors

$Y_1 = +18.39 + 1.05A\ (*P < 0.05) + 1.27B\ (*P < 0.05) - 0.28AB\ (*P > 0.05) + 0.32A^2\ (*P > 0.05) + 0.27B^2\ (*P > 0.05)$

$Y_2 = +37.00 + 5.50A\ (*P < 0.05) + 3.33B\ (*P < 0.05) + 0.001AB\ (*P > 0.05) + 0.50A^2\ (*P > 0.05) + 1.000B^2\ (*P > 0.05)$

$Y_3 = 97.52 - 1.75A\ (*P < 0.05) - 2.65B\ (*P < 0.05) - 0.72AB\ (*P > 0.05) + 0.62A^2\ (*P > 0.05) - 2.88B^2\ (*P < 0.05)$

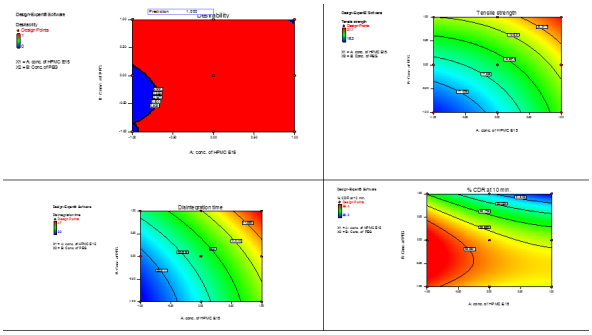

Fig. 3: 2D Response surface contour showing desirability between factors and responses

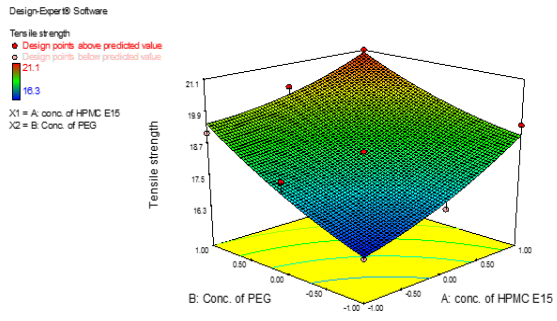

Fig 4: Response surface plot showing the effect of HPMC E 15 (X1) and Polyethylene Glycol (X^2) on Tensile Strength (Y^1)

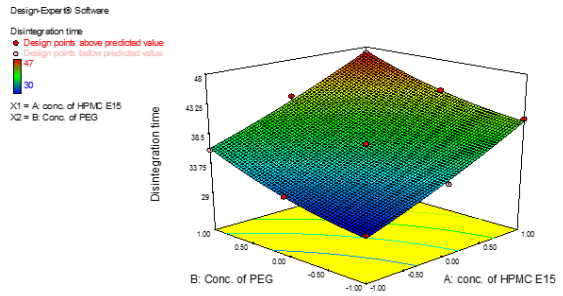

Fig 5: Response surface plot showing the effect of HPMC E 15 (X1) and Polyethylene Glycol (X^2) on Disintegration time (Y^2)

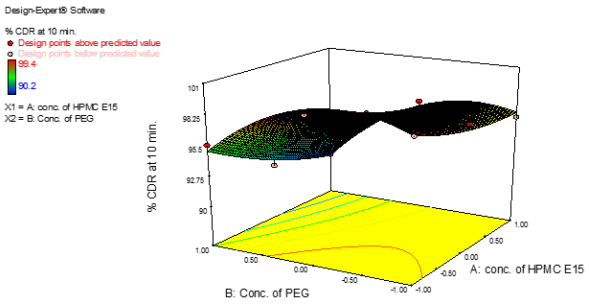

Fig. 6 : Contour plot showing the effect of HPMC E 15 (X1) and Polyethylene glycol (X^2) on %CDR (Y^3)

Table 7 : Comparison of predicted and observed values of ZSF

Confirmation Location	Conc. of HPMC E 15 (X_1)	Conc. of Polyethylene glycol (X_2)	*Bias %
	392	**0.78**	
Response	**Predicted value**	**Observed value (n=3)**	
Tensile Strength (kg/cm^2)	18.46	17.92±0.40	-0.0301
Disintegration time (sec)	38.3	41±0.10	-00658
% CDR at 10 min.	97.59	96.86±0.50	+0.0075

*Bias % = (Predicted value−Observed value) *100 / Observed value

*Data from each response for the observed values is presented in mean ± SD (n=3)

Full and reduced model for Tensile Strength of Ziprasidone

The contour plot and 3D response surface graph for tensile strength was observed in Fig. 3 and Fig. 4 respectively and revealed that a corresponding increase of tensile strength was observed with increase in concentration of Polyethylene glycol (X_2). Moreover, the results also indicated that the effect of Polyethylene glycol (X_2) was more significant. From regression, it was observed that X_1 and X_2 was significant model term which affect the flexibility and elasticity of film. Interaction and non-linearity was not observed.

For Tensile Strength, the significant levels of the coefficients b_{12}, b_{11} and b_{22} were found to have P value of 0.3771, 0.4616 and 0.5294. So, it was omitted from the full model to generate a reduced model. The coefficients b_0, b_1 and b_2 were found to be significant at $P < 0.05$. Hence, they were retained in the reduced model.

The reduced model for tensile strength was:

Tensile Strength = $+18.39 + 1.05*X_1 + 1.27*X_2$

Full and reduced model for Disintegration time of Ziprasidone

The contour plot and 3D response surface graph for Disintegration time was observed in Fig.3 and Fig. 5 respectively and revealed that a corresponding decrease in the disintegration time of tablet was observed with increase in concentrations of HPMC E 15. Moreover, the regression coefficient values of both factors can be concluded that the disintegration time appeared to decrease more with an increasing amount of the HPMC E 15 and decreasing the amount of Polyethylene glycol. Interaction and non-linearity was not observed.

For disintegration time, the significant levels of the co-efficients b_{12}, b_{11} and b_{22} were found to have P value of 1.0000, 0.3667 and 0.1240. So, it was omitted from the full model to generate a reduced model. The coefficients b_0, b_1 and b_2 were found to be significant at $P < 0.05$. Hence, they were retained in the reduced model.

The reduced model for Disintegration time was:

Disintegration time = +37.00 + 5.50*X_1 + 3.33*X_2^2

Full and reduced model for % CDR at 10 min. of Ziprasidone

The contour plot and 3D response surface graph for % CDR at 10 min. was observed in Fig. 3 and Fig. 6 respectively and revealed that a corresponding decrease in the % drug release of tablet was observed with increase in concentrations of Polyethylene glycol and decrease in concentration of HPMC E15. Interaction and non-linearity was not observed.

For disintegration time, the significant levels of the coefficients b_{12} and b_{11} were found to have P value of 0.1352 and 0.3091. So, it was omitted from the full model to generate a reduced model. The coefficients b_0, b_1, b_2 and b_{22} were found to be significant at $P < 0.05$. Hence, they were retained in the reduced model.

The reduced model for % CDR was:

% CDR = +97.52 – 1.75*X_1^2 – 2.65X_2 - 2.88*X_2^2

Validation by Check point batch

A check point batch was prepared to confirm the validity of response surface plot and equation generated by multiple regression analysis which was shown in table 10. An overlay plot was obtained by adding desired range of evaluation parameters from Design Expert 9. The overlay plot is shown in Fig. 7. Yellow colour area in overlay plot showed optimum concentration range for desired result. A batch was prepared by taking concentration of HPMC E15 (X_1) and concentration of Polyethylene glycol (X_2) observed in overlay plot and the actual responses were evaluated from the prepared check point batch. The overlay plot indicated that optimum concentration which showed the best result. The practically obtained values were closer to the predicted values as shown in table 11. Thus, it justified the validation of design.

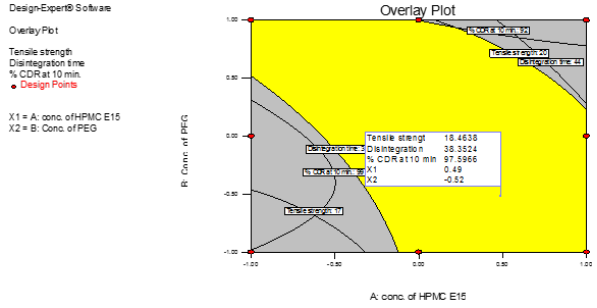

Fig 7: Overlay plot of Check point batch

Accelerated stability study

The stability study indicated that the optimized formula was physically and chemically stable with no significant changes in any of the evaluated parameters when stored at the 40oC and at 75% ± 5 RH conditions. From stability studies it was concluded that the sublingual films of Ziprasidone was stable.

Table 8: Result of short term stability study of optimized batch

Evaluation Parameters	Before Stability period	After Stability period
Tensile Strength (kg/cm^2)	18.1±0.36	18.6±0.60
Disintegration time(sec)	32±1.28	46±0.80
% CDR at 10 min.	99.4	98.20

The results of 3^2 full factorial design were analyzed. The utility of this statistical design resulted in providing considerable information to optimize the formulation. All the responses were fitted to a quadratic model and compatibility of the model was verified by ANOVA, lack of fit and co-efficient of determination (R^2). In the present study, the following constraints were arbitrarily used for the selection of an optimized batch: DT lies between 30±0.20 sec to 47±1.80 sec, Tensile Strength lies between 16.3±0.10 to 21.1±0.18 kg/cm^2 and % CDR at 10 min. lies between 90.2 to 99.4. Batch F_4 showed the highest % cumulative drug release (99.4) at 10 min. Thus, Batch F_4 was selected as an optimized batch. The optimized formulation was subjected to accelerated stability study.

On the basis of Desirability approach, formulation containing HPMC E15 and Polyethylene Glycol in the amount of 350 mg and 1 % batch was selected as an optimized batch. From the *in vitro* study, it was found that the developed formulation provided fast release of the drug at 10 min. by formulating in the form of sublingual Ziprasidone films.

CONCLUSION

The sublingual films of Ziprasidone were successfully prepared, optimized and evaluated using Design Expert software by 3^2 full factorial design. The present investigation showed quick disintegration and fast release of the drug for treatment of schizophrenia and bi polar disorder. HPMC E15 and Polyethylene Glycol were used as film forming polymer that showed rapidly disintegration time of film in saliva fluid. These formulations were evaluated for the parameters like drug excipient compatibility study, uniformity of weight, thickness, tensile strength, content uniformity, folding endurance, i*n- vitro* drug release and accelerated stability studies. On the basis of preliminary results, the amount of HPMC E15 (X_1) and the amount of Polyethylene Glycol (X_2) were selected as independent variables in 3^2 full factorial design, while Tensile strength (TS), Disintegration time (DT) and Cumulative % drug release at 10 min. (%CDR) were taken as dependent variables. Multiple linear regression analysis, ANOVA and graphical representation of the influence of factor by contour plots and 3D response surface graphs were performed using Demo version of Design Expert. Check point batch was prepared to validate the evolved model. Batch F_4 was selected as an optimized batch. The optimized formulation was subjected to accelerated stability study. The optimized batch F_4 was found to be stable in the stability evaluation.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

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REFERENCES

[1] Dixit R.P. (2009), " Puthli S.P. Oral Strip Technology: Overview and Future Potentia", J. of Controlled Release. 139,94-107.
[2] Panda B.P, Dey N.S. (2012), "Development of Innovation Orally Fast Disintegration Dosage Films", International Journal of Pharmaceutical Science. 5,1666-1678.
[3] Arya Arun, Chandra Amrish. (2010), "Fast Dissolving Oral Films. An Innovation Drug Delivery System and Dosage Form", International Journal Chem. Tech Research. 2,576-83.
[4] Francesco C., Irma E. (2008), "Fast Dissolving Films Made of Maltodextrins", European Journal of Pharmaceutics and Biopharmaceutics. 895–900.
[5] Patel V, Patel F, Liu F, Brown M. (2011), "Advance in oral transmucosal drug delivery. Journal of Controlled Release. 11(153),106-16.
[6] Madhav S, Shakya A, Shakya P, Singh K. (2009). Orotransmucosal drug delivery system: A Review", Journal of Controlled Release. 140, 2-11.
[7] N.L Prasanthi.and C. Sowmya.(2012), "Design and Development of Sublingual Fast Dissoiving Film For An Antiasthmatic Drug", Scholars Research Library. 382-95.
[8] Marina Koland and V.P Sandeep. (2009), "The Design and Characterization of Sublingual Films of Ondansetron Hydrochloride", International Journal Chem. Sci. 2927-2938.
[9] Narang Neha, Sharma Jyoti. (2011), "Sublingual Mucosa as A Route For Systemic Drug Delivery", International Journal of Pharmacy and Pharmaceutical Sciences. 3(2),18-22.
[10] Sahoo Satyajit,Makwana Ami, Sahu Asit Ranjan, Keshri Asha, Dash Vikash. (2020), "Formulation and Evaluation of Sublingual Film of Asenapine Maleate by using 3^2 Full Factorial Design", Aegaeum. 8(4),80-94.
[11] Katz Martin, Barr Martin.(1955), "A Study of Sublingual Absorption I. Several Factors Influencing the Rate of Absorption", Journal of the American Pharmaceutical Association (Scientific ed.). 44(7), 419-23.
[12] Sahoo Satyajit, Bhatt J J, Oza N A, Sahu A R, Patel L D. (2015), Formulation Development and Optimization of Mouth Dissolving Film Containing Escitalopram Oxalate using 3^2Full Factorial Design", Inventi Rapid: Pharm Tech. 4,1-7.
[13] Greenberg William M., Citrome Leslie. (2007), "Ziprasidone for Schizophrenia and Bipolar Disorder: A Review of the Clinical Trials", CNS Drug Reviews. 13(2),137–77.
[14] Addington Donald E, Labelle Alain, Jayashri, Kulkarni Gordon Johnson, Antony Loebel et al. (2009), "A Comparison of Ziprasidone and Risperidone in the Long-Term Treatment of Schizophrenia: A 44-Week, Double-Blind, Continuation Study", The

Canadian Journal of Psychiatry, 54(1), 46-54.
[15] Carlson E, Chandler W, Galdo I, Kudla T. (2005), "Automated integrated forced degradation and drug excipients compatibility studies", J Assoc Lab Autom. 10,374-80.
[16] Arya A, Chandra A, Sharma V, Pathak K. (2010), "Fast Dissolving Oral Film: An Innovation Drug Delivery System and Dosage Form", International Journal of Chem. Tech Research. 2(1), 576-83.
[17] Yellanki SK, Jagtap S, Masareddy R. (2013), "Dissofilm: A novel approach for delivery of Phenobarbital: Design and Characterization", Journal of Young Pharmacist. 1(3), 181-88.
[18] Kalyan S, Bansal M. (2012), "Recent Trends in the Development of Oral Dissolving Film" , International Journal of Pharma Tech Research. 4(2), 725-33.
[19] Juluru N. (2013), "Fast dissolving Oral Films: A Review. Internatinal Journal of Advances in Pharmacy, Biology and Chemistry. 2(1),108-12.
[20] Ciluzzo F, Cupone I, Minghetti P, Buratti S, Gennari C, Montanari L. (2011), "Diclofenac fast-dissolving film: suppression of bitterness by a taste-sensing system", Drug Development and Industrial Pharmacy. 37(3), 252-59.
[21] Chauhan S, Lin S, Madan P. (2012), "Preparation and evaluation of Nicotin hydrogen tartrate fast dissolving films for smoking cessation", Asian Journal of Pharmaceutical Sciences. 7(3), 181-92.
[22] M Koland, VP Sandeep, NR Charyulu. (2010), " Fast Dissolving Sublingual Films of Ondansetron Hydrochloride: Effect of Additives on In Vitro Drug Release and Mucosal Permeation", Journal of Young Pharmacist. 2(3), 216-22.
[23] N.L Prasanthi, C. Sowmya. (2012), "Design and Development of Sublingual Fast Dissolving Film for an Antiasthmatic Drug", Scholars Research Library. 382-95.
[24] Guideline ICH. Stability testing guidelines: stability testing of new drug substances and products. ICH Q1A (R2) (CPMP/ICH/2736/99); 1999.
[25] Pavia DL, Lampman GM, Kriz GS, Vyvyan JR. Introduction to Spectroscopy. 5th ed.Cengage Learning India Pvt. Ltd., India, 2015, 37-38.
[26] Sahoo Satyajit, Malviya Kirti, Makwana Ami, Mohapatra Prasanta Kumar, Sahu Asit Ranjan. (2021), "Formulation, Optimization and Evaluation of Sublingual Film of Enalapril Maleate Using 3^2 Full Factorial Design", International Journal of Applied Pharmaceutics. 13(1), 178-86.
[27] Bolton S. Optimization techniques in Pharmaceutical Statistics. Practical and Clinical Applications. 3rd ed. New York: Marcel Dekker;1997.