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FORMULATION AND EVALUATION OF RAPID DISSOLVING ORAL FILM CONTAING BREXPIPRAZOLE

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ABSTRACT

The objective of this research work was to formulate and evaluate rapid dissolving film containing brexpiprazole by enhancement of solubility by preparing solid dispersion of brexpiprazole and to increase patient compliance which is useful in the treatment. In this research, the method used to prepare rapid dissolving oral films was solvent casting to decrease time and cost. First prepare solid dispersion by solvent evaporation method then preliminary study was done for the selection of excipients such as, film-forming agent and plasticizers. Preliminary batches were evaluated for Physico-chemical parameters. 32 Full Factorial design was used for optimization by selecting two independent factors concentration of film forming agent (HPMC E5)-X I and concentration of plasticizer (PEG 400)-X II and their effect on Disintegration time-(R1), and % drug release-(R II). Optimization of factorial batches was done using Design Expert 13 software. Result: Best results were obtained in Batch F8 in which HPMC E5 (SD 1:2) was 40 mg and PEG 400 was 20mg with 34 seconds of disintegration time and 91.6 % cumulative drug release at 9 minutes. Check point batch shows 37 seconds of disintegration time 89.87 % cumulative drug release. A 1 month accelerated stability study was done on prepared films and it is stable for 1 month.

KEYWORD:- Rapid dissolving oral films, Brexpiprazole, Solid dispersion, PEG 6000, solvent evaporation, design expert.

INTRODUCTION

Schizophrenia is a chronic and severe neurological disorder characterized by symptoms such as hallucinations, delusional thinking, disorganized thoughts, and abnormal motor behaviour. This disconnection can cause substantial emotional distress, not only to the affected individuals but also to their families and social circles. If left untreated, the condition can become persistent and lead to significant disability.[1] Schizophrenia is linked to dysregulation in several neurotransmitter systems, with the following receptors playing a significant role Dopamine receptors, Serotonin receptors and Adrenergic receptors.[2] Brexpiprazole is a relatively new second- generation antipsychotic approved for the treatment of schizophrenia and as an adjunct in major depressive disorder therapy. Structurally, it is a phenylpiperazine derivative and closely resembles aripiprazole among available antipsychotics.[3] Brexpiprazole is BCS class 2 drug with low solubility and high permeability. Brexpiprazole is a serotonin-dopamine activity modulator used in the treatment of schizophrenia. It acts as a partial agonist at D2 and 5-HT1A receptors and as an antagonist at 5 HT2A, 5-HT2B, and several adrenergic receptors.[5,6] The research aims to develop Brexpiprazole rapid dissolving oral film that enhances patient compliance as compared to tablets, which gives faster effect in schizophrenia and depression which will provide fast dissolution or disintegration without the need for water. Fast onset of effect is possible because of the rapid absorption of the drug. The ideal drug delivery formulation for the unconscious as well as those with swallowing difficulties. The drug is absorbed 3 to 10 times faster through the rapid dissolving film than through the conventional tablet.[7]

MATERIALS AND METHODS

Brexpiprazole free gift sample was procured from Alembic pharmaceuticals, Gujarat. HPMC E5, HPMC E15 and HPMC was procured from SEVA fine chemicals. PG (Polyethylene glycol), PEG400 and Glycerol were procured from oxford fine chemicals. Aspartame,

Crosscarmellose sodium, Citric acid and Peppermint oil was procured from Research-lab fine chem industries. All the components were used were analytical grade for the formulation.

Solid dispersion of brexpiprazole

Solid dispersions of Brexpiprazole were prepared by solvent evaporation method. An appropriate amount of carrier (PEG 6000) was added to solution of Brexpiprazole in 15mL blend of acetone and dichloromethane (1:1). The solution was stirred at 60 rpm and the solvent was evaporated for 2 h. The obtained solid dispersions were subsequently stored in a room temperature for 48 h to remove the residual solvent. The dried solid residue was pulverized and sieved through 250 µm sieve. The samples obtained were stored in desiccator until use. Solid dispersions of Brexpiprazole were prepared using solvent evaporation. Drug: carrier ratios were used to prepare solid dispersions (1:1, 1:2 and 1:3).[8]

Evaluation parameters of solid dispersion[9]

Percent yield

The following formula was used to calculate the percent yield of the prepared solid dispersion. Percentage yield = Practical yield /Theoretical yield × 100

Drug content

A solid dispersion containing 10 mg of Brexpiprazole was accurately weighed and transferred to a 100 ml volumetric flask, the volume was made up with Phosphate buffer pH 6.8. Finally, 10 ml of the solution was taken out and diluted to 100 ml with buffer pH 6.8. Using a UV-Visible spectrophotometer, the absorbance of the resultant solution was measured at λmax of 216 nm.

In vitro drug release of solid dispersion

Utilizing Dissolution Testing Equipment with the United States Pharmacopeia (USP) 2 (paddle method), the rate at which solid dispersions release brexpiprazole was determined. 500 milliliters of the dissolution test were used to pH 6.8 phosphate buffer, 37±0.5 °C, 50 rpm, 45 minutes. Solution was taken for dissolution studies in amounts equal to 2 mg of brexpiprazole. Through collecting samples at predetermined intervals and passing them through a membrane filter with a 0.45 m pore size, drug was released. quantified. The medium used for replacement was maintained at the same temperature as utilized as an alternative to the extracted samples.

Drug excipient compatibility study by using FTIR study

Brexpiprazole was subjected to an FT-IR analysis using a Shimadzu 8400S. Prior to background scanning, the potassium bromide (KBr) was first triturated using a Selection of batch for formulation and optimization mortar and pestle. Next, a little amount of potassium bromide and Brexpiprazole is combined, and the mixture is put in a sample holder before being scanned for different functional groups. Outcome of the FT-IR is state in the result and discussion section.[10]

Method of preparation of fast dissolving oral film

The film-forming polymer is dissolved in a water, and thoroughly mixed to ensure complete dissolution. The brexpiprazole, plasticizers, and other excipients (such as flavourings and stabilizers) are added to the polymer solution, with continuous stirring to ensure a uniform mixture. The resulting homogeneous solution is poured onto a flat surface or casting plate, where it is evenly spread using an applicator to achieve the desired film thickness. The cast solution is dried at a controlled temperature to evaporate the solvent, solidifying the film.[11]

Selection of Factors, Levels and Responses of 32 Full-Factorial Designs

It is best to create pharmaceutical products with minimal amounts of labour and ingredients, but this requires effective product development. When several factors influencing a pharmaceutical formulation at different stages are known, an appropriate formulation is always achieved. The conventional trial-and-error approach of optimization is today seen as time-consuming, arduous, and ingredient-wasting. An experimental design ought to be used in the development of pharmaceutical goods. As a result, it assists in avoiding the waste of labor and ingredients. The One Factor at a Time (of AT) design was utilized in the past, but it takes a long time to complete and is only capable of checking the effects of interactions. Using statistical analysis, the generated formulation's complexity and interactive responses were assessed. Full factorial design is used to optimize the fast-dissolving oral film of Brexpiprazole. The table below illustrates the factors and levels. The two factors that were chosen as independent variables were: X I (concentration of HPMC E5, a film-forming agent) and X II (concentration of PEG 400, a plasticizer). For each criteria, three levels have been chosen: -1, 0. +1. The responses, or dependent variables, were: Y1: Disintegration Time Y2: in vitro drug release at 9 min shown in table 1.

The impact of factors (independent variables) on dependent factors (responses) was examined using the Design Expert 13 programme.

Table 1: Layout of 3^2 full factorial designs.

Independent variable					
XI			XII		
HPMC E5(concentration)(mg) (film foaming polymer)			PEG400(concentration) (mg)(plasticizer)		
-1	0	+1	-1	0	+1
40	45	50	15	20	25
Dependent variable					
Y1			Y2		
Disintegration-Time (sec)			In vitro drug release at 9 min		

Table 2: Factorial batches coded values for formulation of rapid dissolving oral film.

Formulation	Coded value	
	HPMC E5 (film foaming polymer)(mg)	PEG400 (plasticizer) (mg)
F1	0	0
F2	-1	-1
F3	0	-1
F4	1	-1
F5	-1	1
F6	1	1
F7	0	1
F8	-1	0
F9	1	0

Table 3: Final formulation table for factorial batches.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Brexpiprazole	2	2	2	2	2	2	2	2	2
HPMC E5	45	40	45	50	40	50	45	40	50
PEG 400	20	15	15	15	25	25	25	20	20
Aspartame	1	1	1	1	1	1	1	1	1
Crosscarmellose sodium	4	4	4	4	4	4	4	4	4
Citric acid	2	2	2	2	2	2	2	2	2
Peppermint oil	2	2	2	2	2	2	2	2	2
water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Evaluation parameters film thickness

To assess the thickness of the oral film, a micrometer screw gauge is used at multiple critical points across the strip. Consistency in thickness directly relates to uniformity in drug dosage, as there is a proportional relationship between strip thickness and drug content. [12]

Strip weight

The individual weights of the films are measured using an analytical balance. The average weight is then calculated to ensure uniformity. Consistent strip weight indicates proper formulation and dosage precision.[13]

Percentage elongation

When subjected to stress, the film stretches, and this extension is termed elongation. The extent of this elongation is influenced by the concentration of plasticizers in the formulation. Strain is calculated using the following equation:

% Elongation = (Final length − Original length) × 100 / Original length[14]

Moisture content

To determine residual moisture, the film is weighed and stored in a desiccator for 24 hours. The process continues until the weight stabilizes, indicating that the moisture has been effectively removed. The difference in weight is used to calculate the moisture percentage.[15]

pH Measurement

To evaluate pH, the strip is immersed in distilled water for approximately one hour. After soaking, the pH of the resulting solution is measured using a calibrated pH meter. This test ensures the formulation's compatibility with oral tissues.[15]

Disintegration time

Disintegration time is an essential parameter for oral fast-dissolving films (OFDFs). Though no specific pharmacopoeia standard exists for these films, a benchmark of 30 seconds used for orodispersible tablets is commonly applied. A standard disintegration test apparatus may be employed, with typical disintegration times ranging from 5 to 60 seconds.[16]

Folding endurance

This parameter evaluates the film's flexibility and resistance to mechanical stress. The film is repeatedly folded at a 180° angle until it tears. The number of successful folds before rupture is recorded as the folding endurance value.[17]

In vitro dissolution study

The dissolution profile is assessed using a beaker containing 125 ml of phosphate buffer (pH 6.8) as the dissolution medium. The film is affixed to the beaker wall using adhesive tape. A magnetic stirrer operates at 200 rpm, and samples of 5 ml are withdrawn at intervals of 3,5,7,9.12 and 15 minutes. Each sample is replaced with fresh buffer. Drug release is analysed spectrophotometrically by measuring absorbance at a specific wavelength.[18]

Generating of Quadratic Model for 32 FFD (Full Factorial Design)

A quadratic polynomial model was used for assess the influence of independent factors on dependent variables. From the acquired data of disintegration time and percent (%) drug release, a quadratic model equation was generated using polynomial regression analysis. The process of finding the polynomial equation that best fits a set of data is known as quadratic regression.

Selection of optimized batch

The final formulation was selected based on the lowest disintegration time and highest drug release at 9 min. According to desirability value, the optimized levels of HPMC E5 concentration and PEG 400 concentration. According to the selected levels using the same methodology Brexpiprazole containing rapid oral dissolving film were prepared.

Stability study

Stability study aims to ascertain how different environmental factors, including temperature, humidity, and light, affect the quality of therapeutic substances or medication formulations over time. To ascertain the product's shelf life and recommended storage conditions, a stability study is carried out. An "accelerated stability study" was carried out on prepared films at 40 °C 2 °C/75 percent RH 5% (percent) RH, in accordance with the ICH Q1A guideline. The "ICH Q1A guideline" governs the stability assessment of innovative pharmaceutical compounds and products. An expedited stability study should last at least six months, according to the ICH Q1A standard, but due to scheduling constraints, the study only lasted one month. A month later, the films were examined for a number of characteristics, including fold-through durability, disintegration time, drug percentage content, and percentage CDR.

RESULT AND DISCUSSION

Evaluation parameter of Solid dispersion Percent yield

The percent yield of all the prepared solid dispersions are mentioned in table 4.

Drug content

The % drug content values of prepared solid dispersions are given in table 4. The drug content values of solid dispersions prepared by solvent evaporation method ranged from 72.24-79.90%.

Table 4: Evaluation parameter of Solid dispersion.

Formulation code	Ratio	Percent yield (%)	ug content (%)
F1	1:1	78.38± 1.12	72.24± 0.95
F2	1:2	83.12± 0.92	75.95± 0.54
F3	1:3	86.9± 0.87	79.90± 0.80

Table 5: Solubility after solid dispersion.

Sr. no.	Drug: carrier	Ratio	water	PBS 6.8
1	Brexpirazole:PEG6000	1:1	0.0081±0.003	0.0634±0.002
		1:2	0.0134±0.004	0.0951±0.014
		1:3	0.0105±0.002	0.0897±0.023

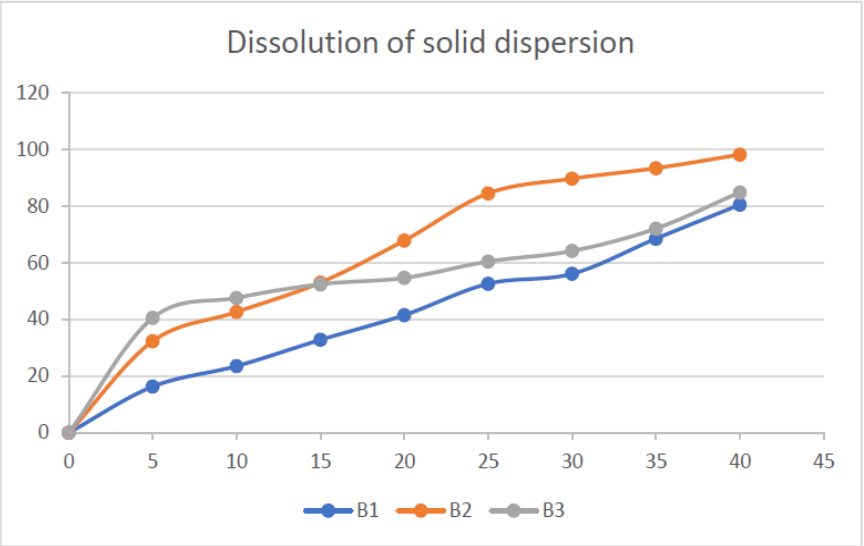

Fig. 1: Dissolution of solid dispersion.

FTIR study of Brexpiprazole and other excipients

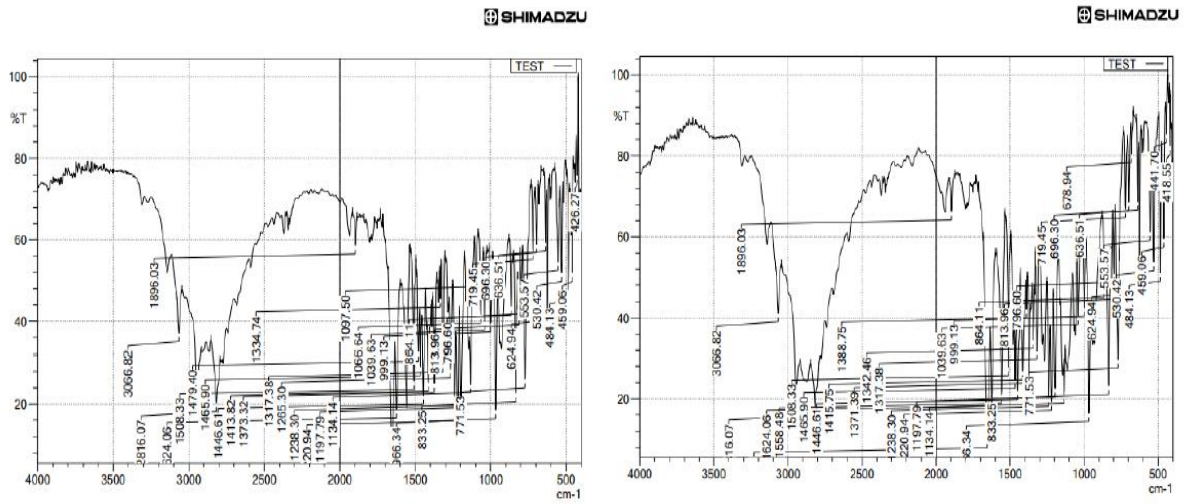

Fig. 2: Observed FTIR of Brexpiprazole and FTIR of PEG6000 + Brexpiprazole.

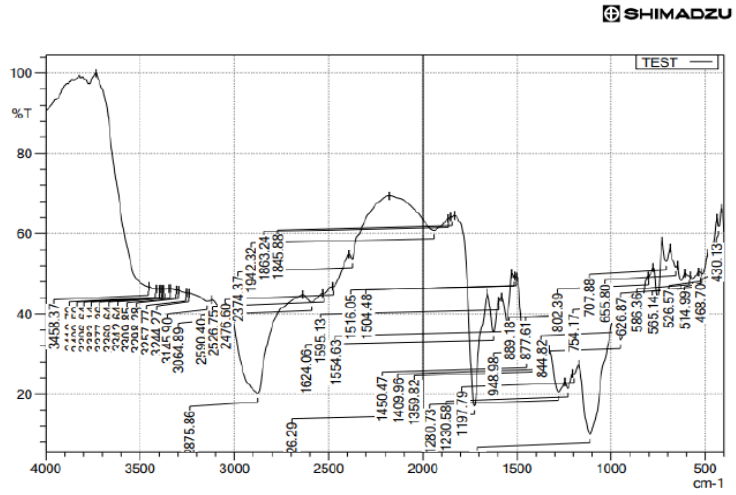

Fig. 3: Observed FTIR of all excipients + Brexpiprazole.

Evaluation of factorial batch

Table 6: Evaluation of factorial batch.

Batches	Appearance	Smoothness	peel ability	Thickness (mm)	Folding endurance	pH	Weight variation
F1	Translucent	Smooth	Average	0.31±0.03	142±2.12	6.7±0.14	74±2.23
F2	Translucent	Smooth	Good	0.36±0.05	150±3.41	7.2±0.21	75±1.13
F3	Translucent	Smooth	Average	0.36±0.2	146±3.25	6.6±0.16	73±2.321
F4	Translucent	Smooth	Good	0.41±0.05	156±2.36	7.4±0.9	76±2.36
F5	Translucent	Smooth	Good	0.42 ±0.2	145±4.13	6.9±0.19	74±3.15
F6	Translucent	Smooth	Poor	0.36± 0.02	125±2.14	7.1±0.24	75±1.23
F7	Translucent	Smooth	Average	0.38±0.12	146±3.15	6.7±0.52	73±1.13
F8	Translucent	Smooth	Good	0.32±0.11	179±5.25	7.1±0.21	74±2.24
F9	Translucent	Smooth	Average	0.42±0.02	138±4.36	6.4±0.12	76±3.36

n = 3±SD

Table 7: Evaluation of factorial batch.

Factorial batch	% Elongation	Drug content	Disintegration time (sec)	Moisture content
F1	17.84±0.31	99.21±0.36	56±2.24	1.681±0.059
F2	18.16±0.21	98.26±0.21	44±2.32	1.864±0.029
F3	18.26±0.14	99.32±0.45	50±1.23	1.691±0.021
F4	13.76±0.23	99.78±0.98	66±3.12	1.549±0.064
F5	15.52±0.54	99.14±0.36	45±2.52	1.613±0.042
F6	12.45±0.65	99.65±1.54	65±1.14	1.794±0.039
F7	14.65±0.12	98.75±0.38	57±1.63	1.439±0.052
F8	11.74±0.34	99.21±0.45	34±1.12	1.547±0.010
F9	12.15±0.95	99.71±0.31	69±2.32	1.846±0.073

n = 3±SD

In-vitro Dissolution of factorial batches

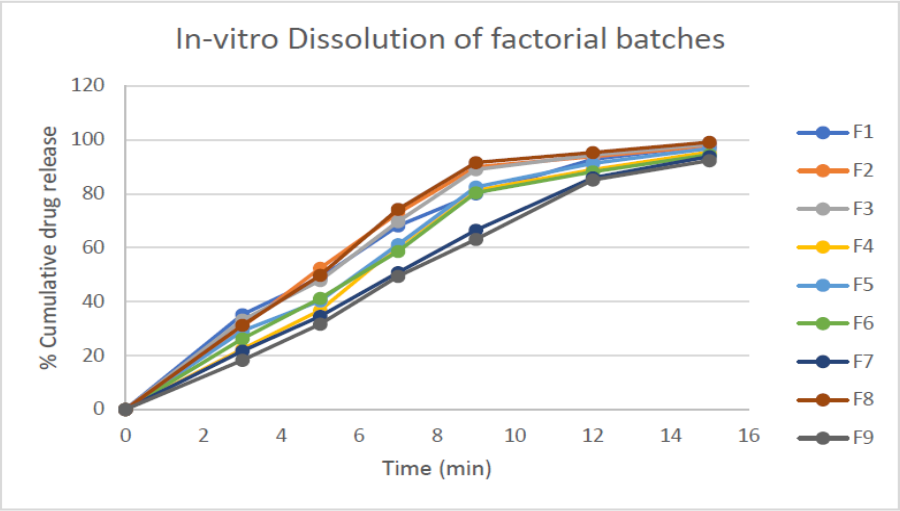

Fig. 4: In vitro dissolution of factorial batch.

Generation of Quadratic Model - 32 [FFD] Full Factorial Design

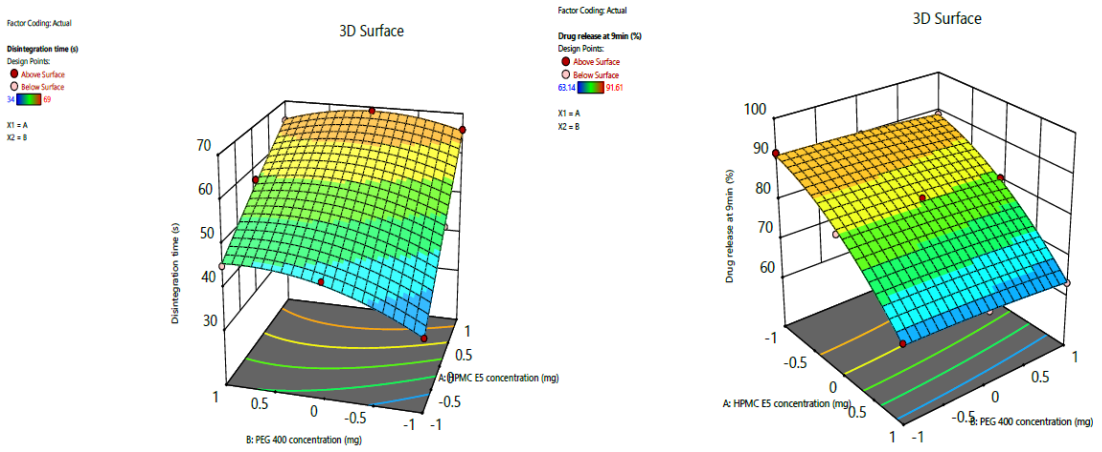

Fig. 5: 3D surface plot of RI and RII.

Selection of optimized batch of rapid dissolving oral film

The final formulation was selected based on the lowest disintegration time and highest amount of drug release at 9min. The desirability amount was found to be 0.989, the optimized levels of HPMC E5 concentration and PEG 400 concentration is 40mg and 20mg respectively.

According to the selected levels using the same methodology brexpiprazole loaded rapid dissolving oral film were prepared.

Table 8: Selection of optimized batch.

Independent variables		Dependent variables	
HPMC E5 (mg) (film forming agent)	**PEG 400 (mg) (plasticizer)**	**Disintegration Time (s)**	**% Drug Release at 9 min**
Predicted values			
40	20	34	90.96
Actual values			
		34	91.61
% Error		0	0.714

Evaluation of optimized batch

Table 9: Evaluation of optimized batch.

Parameter	**observation**
Transparency	Translucent
Smoothness	Smooth
Peel ability	Good
Disintegration time (sec)	34
Weight variation	74±2.24
Surface pH	7.1±0.21
Folding endurance	179±4.25
Thickness (mm)	0.32±0.12
% Elongation	11.74±0.34
Moisture content	1.547±0.014
Drug content	99.21±0.45
% CDR at 9 min	91.6±0.32

In vitro drug release of optimized batch

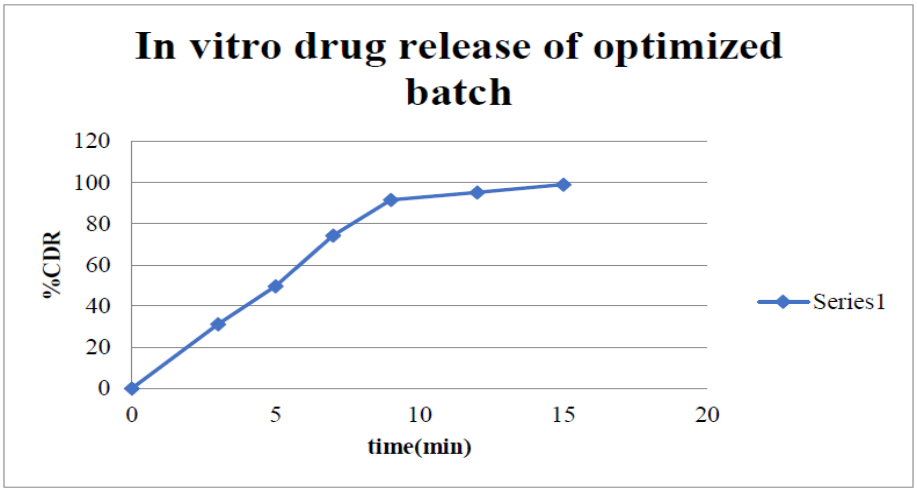

Fig 6: In vitro drug release of optimized batch.

Validation of model

The flag point batch is formulated from the coded values provided by design expert software putting into the equation below, where values of X1 intermediate is 45, coded value is -1.68, X1 high and X1 low is 50 and 40. For the X2 the same equation is followed, where the intermediate, high, low and coded values are 20,25,15 and 0.067 accordingly. Which is shown in fig 7.

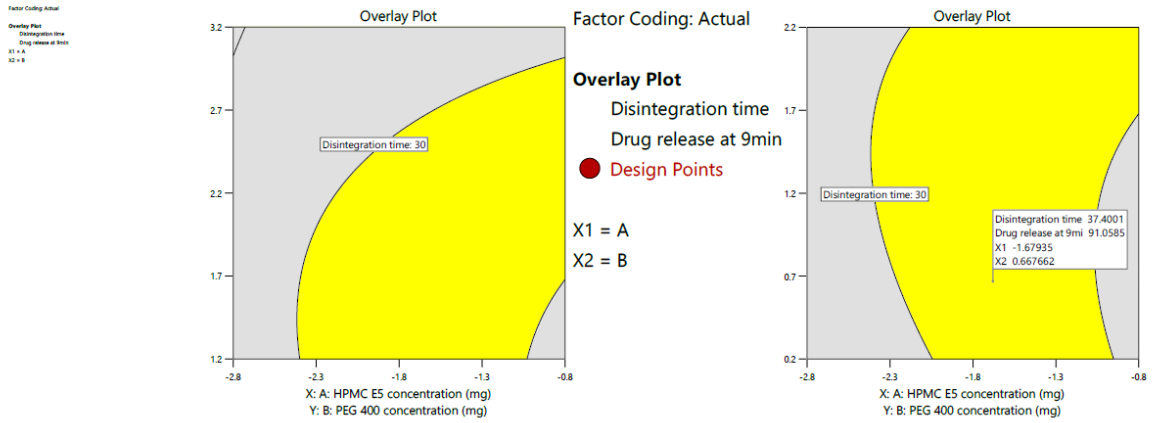

Fig. 7: Overlay plot and check point batch.

Table 10: Evaluation of check point batch.

Independent variables		Dependent variables	
HPMC E5 (mg) (film forming agent)	PEG 400 (mg) (plasticizer)	Disintegration Time (s)	% Drug Release at 9 min
Predicted values			
36.6	23.35	37.40	91.05
Experimental values			
		37.26	89.87
% Error		0.37	1.29

6.11 Stability study of optimized batch

The films that were formed underwent a one-month accelerated stability investigation at 40°C ± 2 °C and 75% RH ± 5% RH. After one month, films were evaluated according to several criteria.

Table 11: Stability study of optimized batch.

Condition	40°C ± 2 °C and 75% RH ± 5% RH	
Evaluation	**Initial observation**	**After a month**
Appearance	Translucent	Translucent

% Drug content	99.21±0.45	98.94±0.12
Disintegration time(sec)	34±0.32	35±0.45
Folding endurance	179±0.25	176±0.54
%CDR at 9 min	91.6±0.41	90.9±0.65
±SD n =3		

The results of the parameter assessment indicate that there are very few variations in the parameter results, indicating that the formulated films were stable for one month. There are also very few variations in the percentage CDR and drug content, as well as in the disintegration time, but these were all found to be within the normal range.

CONCLUSION

Rapid dissolving oral film containing brexpiprazole were formulated using HPMC E5 as a film forming agent and PEG 400 as a plasticizer by solvent casting method. Hence, from the results it was concluded that faster disintegration and faster drug release can be achieved by the rapid dissolving oral film of brexpiprazole by oral route.

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