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DEVELOPMENT OF ORALLY DISSOLVING FILMS FOR THE SCHIZOPHRENIA-CENTRIC SYMPTOMS TREATMENT OF PALIPERIDONE

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ABSTRACT

This study aims to develop an orally dissolving film (ODF) formulation for treating schizophrenia using the Design of Experiments (DOE) approach. Schizophrenia, a complex mental disorder, often presents challenges in medication adherence due to cognitive impairments and negative symptoms. Orally dissolving films (ODFs) are an advanced dosage form that offers greater adaptability and convenience. ODFs are designed to dissolve rapidly in the mouth, allowing the drug to be quickly absorbed into the bloodstream, potentially resulting in a faster onset of action compared to conventional oral dosage forms. This characteristic is particularly beneficial for pediatric patients. paliperidone, an active metabolite of the antipsychotic drug risperidone, is a second-generation antipsychotic used in the treatment of schizophrenia. However, paliperidone is poorly soluble in water, which limits its bioavailability. Given its low aqueous solubility and bioavailability, paliperidone's effectiveness can be compromised. ODFs present a promising alternative dosage form that could enhance patient compliance and convenience by improving the solubility and absorption of the medication.

KEYWORDS: paliperidone, schizophrenia, mouth dissolving film, Design of experiments.

INTRODUCTION

Oral films: Oral film technology was first invented in the late 1970s just to overcome swallowing difficulties related to tablets and a capsule faced by geriatric and pediatric patients but now is trending in the pharmacy industry due to less fragility than other oral dosage forms, dosage accuracy, rapid release, ease of administration.[1,2] The oral route is one of the most preferred routes of drug administration as it is more convenient, cost-effective, and easy to administer leading to a high level of patient compliance.[3,4] The most favoured route of drug administration is the oral route due to cost efficiency and ease of administration which leads to high patient compliance for the pediatric and geriatric group, but it is still a challenging route due to swallowing difficulty for pediatric and geriatric patients.[5] Recently, fast-dissolving films are gaining interest as an alternative to fast-dissolving tablets. The films are designed to dissolve upon contact with a wet surface, such as the tongue, within a few seconds, meaning the consumer can take the product without the need for additional liquid. This convenience provides both a marketing advantage and increased patient compliance.[6,7] As the drug is directly absorbed into the systemic circulation, degradation in the gastrointestinal tract and the first-pass effect can be avoided. These points make this formulation most popular and acceptable among pediatric and geriatric patients and patients who fear choking. Today, Oral Thin Films are a proven and accepted technology for the systemic delivery of active pharmaceutical ingredients (APIs) for over-the-counter (OTC) medications and some prescription drugs. This delivery system consists of a thin film, which is simply placed on the patient's tongue or mucosal tissue, and instantly wet by saliva; then it rapidly disintegrates and dissolves to release the medication for oral mucosal absorption.[8] The fast-dissolving oral film is prepared using hydrophilic polymers that rapidly dissolve on the tongue or buccal cavity, delivering the drug to the systemic circulation via dissolution when contact with liquid is made. The fast-dissolving oral film has emerged as an advanced alternative to the traditional tablets, capsules, and liquids often associated with prescription and OTC medications.[9] These drug delivery options allow the medication to bypass the first-pass metabolism thereby making the medication more bioavailable.[10] As the thin oral film dissolves, the drug can enter the bloodstream through the enteric, buccal, or sublingual channels.

***Factorial Design*[10-14]:** Factorial experiments can be designed with one, two, three or more factors. Experiments with only one factor are often called simple comparative experiments. In these cases, t-tests or ANOVA were used for analysis. Factorial experiments with two factors (A and B) usually include two-level factorial designs for the identification of factor effects on the response variable by investigating all possible combinations of the factor levels. the factor effect is defined as the change in the response variable by changing the level of the factor. In factorial experiments with multiple factors (A, B… K), with two levels ("low" and "high") the complexity of experimentation might be a problem. The number of possible combinations goes up with the number of factors, for instance, a 2-level design with 8 factors has 256 combinations which very sets such type of experiments and analyzes data.

Schizophrenia*[15-18]*: Schizophrenia is a devastating mental illness that impairs mental and social functioning and often leads to the development of comorbid diseases. These changes disrupt the lives of patients as well as their families and friends. Family physicians can play an important role in the effective treatment of schizophrenia; they are in a position to recognize the early signs of illness, make referrals to appropriate mental health professionals, help patients and their families cope with the devastating effects of schizophrenia, and encourage a multidisciplinary approach to address all dimensions of the illness. Schizophrenia has a prevalence of 1 per cent in all cultures and is equally common in men and women. Men typically present with the disease in their late teenage years or early 20s, whereas women generally present in their late 20s or early 30s. It is unknown if the range of severity and clinical manifestations reflect problems in different brain regions, in different causalities, or in different diseases that share some phenotypic features. The Finnish Adoptive Family Study of Schizophrenia has confirmed that genetics plays a major role in the development of schizophrenia. It also found that persons with a genetic risk of schizophrenia are especially sensitive to the emotional climate of their family environment. Then euro transmitter dopamine also plays an important role. For example, drugs that cause psychoses similar to the positive symptoms of schizophrenia increase dopaminergic neuropterans mission, and almost all antipsychotics decrease dopaminergic neurotransmission. Still, dopaminergic pathways cannot entirely explain the pathophysiology of schizophrenia, and the roles of other neurotransmitters are being investigated.

MATERIALS

Drug Paliperidone was obtained as gift sample from Kivi Pvt. Ltd. HPMCK15, HPMC10, Sodium Alginate, PEG600, PEG400, Crospovidone, KyronT-314 were obtained from Chemdyes Corporation, Delhi.

METHODOLOGY

Calibration Curve for Paliperidone in Phosphate buffer* pH *6.8: The calibration curve of the drug was made by transferring 2, 4, 6,8 and 10 from a standard stock solution of 100µg/ml in each 10ml volumetric flask. Volume was adjusted with methanol up to 10ml in a volumetric flask. The solution obtained has concentrations of 2, 4, 6, 8 and 10 µg/ml respectively. The absorbance of the solution was measured at 200 to 400 nm wavelength. The calibration curve was prepared by plotting the absorbance versus concentration of the drug and a regression question was obtained.

Identification of Paliperidone by FT-IR Spectroscopy: The potassium bromide IR spectra will be made utilizing a water-powered pellet press with 1mg of paliperidone, checked at 4000-400 cm-1 in FTIR, and the IR spectra contrasted with the paliperidone reference range.

***Thickness of Films*:** A micrometres screw check was utilized to gauge the thickness of the film at five unique places, and a normal of three estimations was determined. This is expected to give consistency in the film thickness, which is connected to portion precision in the film.[19-20]

Folding endurance: Collapsing perseverance is estimated by collapsing a similar piece of film again and over until it breaks. The collapsing perseverance esteem is the times a film can be collapsed in a similar spot without breaking.[19-20]

Weight Uniformity: A foreordained fixed region should be fragmented and show an advanced equilibrium. The normal weight and standard deviation will be determined utilizing individual loads.[19-20]

Surface pH: keep it away for 30 seconds in a Petri dish. In wake of bringing anode of pH meter in contact with the outer layer of the plan and permitting 1 moment for equilibration, the pH was recorded. For every plan, a normal of three judgments was made.[19-20]

In vitro disintegration test: At the point when an oral film comes into contact with water or salivation, it starts to crumble quickly. A quick dissolving film's breaking down time ought to be between 5 to 30 seconds. One more technique was to plunge film in 25 mL water in a measuring utensil to outwardly decide the deterioration time. The second the film started to break or crumble was caught when the container was delicately shaken. After precisely gauged amount of film (over 100 mg) is broken down in 100 mL of Phosphate.[19-20]

Drug content Determination: Phosphate buffer pH 6.8 in which medicine is solvent, the arrangement is shaken constantly for 24 hours in a shaker hatchery. The arrangement is then sonicated completely. After sonication and sifting, how much medication in the arrangement is resolved spectrophotometrically.[19-20]

Tensile Strength
Tensile strength=F/a x b (1+L/l)

Stability Studies as per ICH: The picked combination was put in golden-shaded containers that were painstakingly fixed and cotton-stopped up. They were then kept at 40°C/75% RH for a month and assessed at predefined spans for actual appearance, in vitro breaking down time, drug content homogeneity, and medication discharge tests.[19-20]

RESULT AND DISCUSSION
Pre-formulation study of Drug: Pre formulation study was performed by Physical Examination of the Drug Paliperidone.

Preparation of Calibration Curve of Paliperidone Table
Table 1: Calibration Curve of Paliperidone.

Sr. No	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	2	0.123 ± 0.15
3	4	0.348 ± 0.24
4	6	0.579 ± 0.08
5	8	0.746 ± 0.37
6	10	0.934 ± 0.45

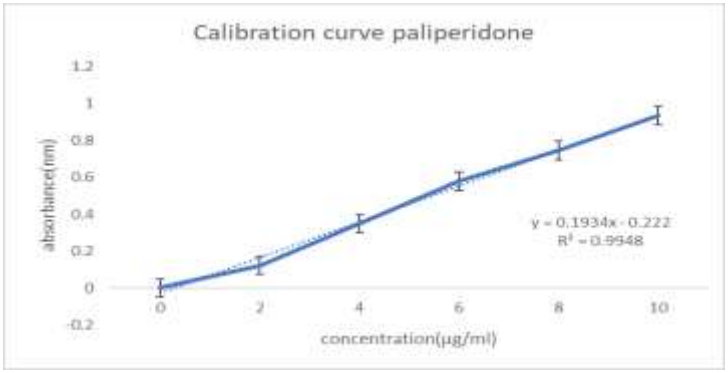
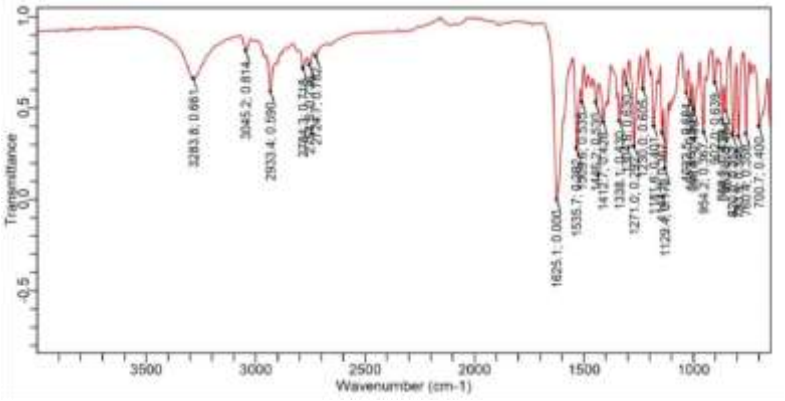


Figure 1: Calibration Curve of Paliperidone.

Identification of Drug- Paliperidone by FT-IR Spectroscopy
Table 2: FTIR Interpretation.

Type of Vibration	Standard Wave number (cm^{-1})	Observed Wave number (cm^{-1})
NH2 Stretching	3600-3200	3283
OH Stretching	3200-2800	3045.2
C=O Stretching	1760-1690	1625
C-N Stretching	1360-1180	1271
C-O Stretching	1300-1050	1129
C-C Stretching	800-600	700.7
C-F Stretching	1400-1000	1535



: FT-IR Spectrum of Paliperidone

Formulation and development of Paliperidone using 3^2 factorial design approach:
3^2 factorial design approach

Table 3: 3^2 factorial design batches.

Independent variables	Low (-1)	Medium (0)	High (+1)
Concentration of HPMC K15 (mg) (X1)	250	275	300
Concentration of Kyron T-314 (mg) (X2)	2.5	5	7.5
Dependent variables			
Y1=disintegration time (second)			
Y2=%CDR (%)			

Formulation design by 3^2 factorial designs

Table 4: Formulation design by 3^2 factorial designs.

Batch no	Concentration of HPMC K15 (mg) (X1)	Concentration of KyronT- 314 (mg) (X2)	Disintegration time (sec)	% CDR
PF1	250	7.5	10±1.26	89.33±1.23
PF2	275	5	15±1.24	83.42±1.26
PF3	250	5	15±1.26	85.51±1.25
PF4	300	5	20±1.23	82.78±1.24
PF5	275	2.5	24±1.24	79.33±1.27
PF6	250	2.5	22±1.25	83.16±1.26
PF7	275	7.5	11±1.26	87.5±1.22
PF8	300	7.5	17±1.23	86.23±1.23
PF9	300	2.5	27±1.24	79.01±1.24

Characterization batch of PF1 to PF9

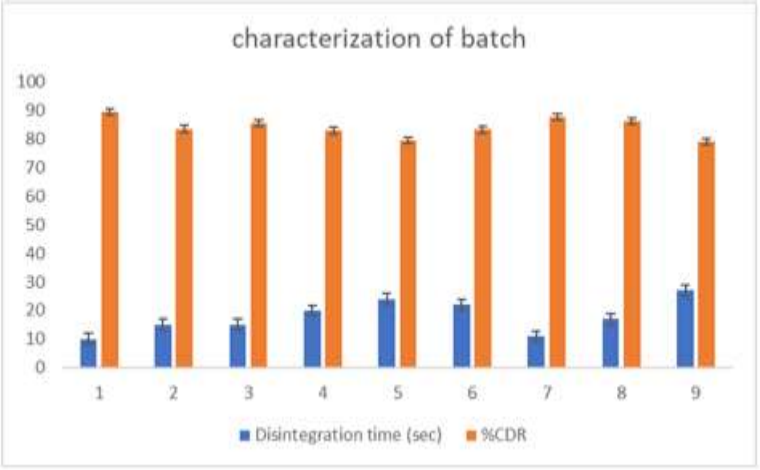


Figure 2: Characterization of batch PF1 to PF9

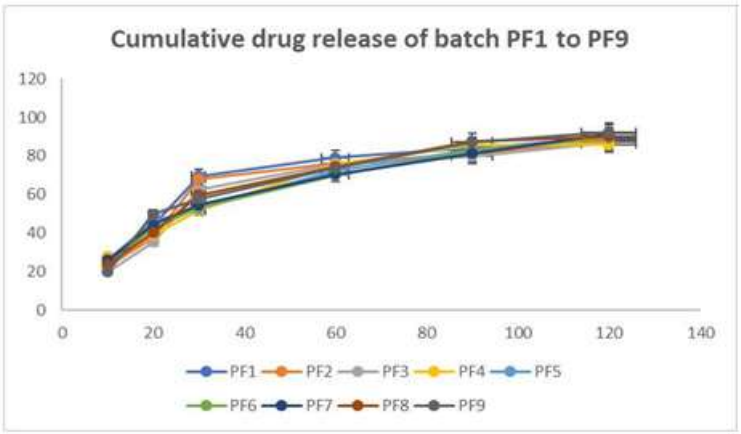


Figure 3: Cumulative drug release of batch PF1 to PF9.

Statistical analysis

Effect on disintegration time (Y1) surface response study

Positive value of coefficient A indicates decrease in Disintegration time. Positive value of coefficient B indicates increase in disintegration time. It indicates linearity of surface response and contour plot as show in figure Full modes was found significant for two independent variables and detailed ANOVA, Response surface counter plot and 3D plots are as follows:

Disintegration time = 15.44 + 2.83* A - 5.83* B +0.50* AB +1.83 * A^2 +1.83 * B^2

Table 5: ANOVA TABLE for Response surface Y1.

Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		**Mean**	**F**	**p-value**	
Source	Squares	df	Square	Value	Prob > F	
Model	266.78	5	53.36	75.82	0.0023	significant
A-HPMC Concentration	48.17	1	48.17	68.45	0.0037	
B-Kyron concentration	204.17	1	204.17	290.13	0.0004	
AB	1.00	1	1.00	1.42	0.3189	
A2	6.72	1	6.72	9.55	0.0537	
B2	6.72	1	6.72	9.55	0.0537	
Residual	2.11	3	0.70			
Cor Total	268.89	8				

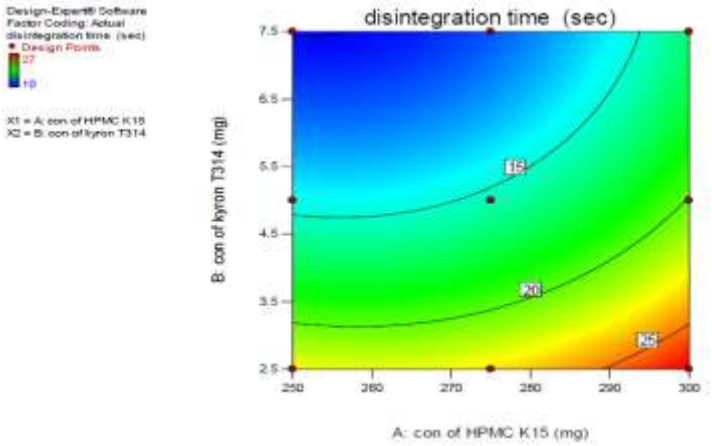


Figure 4: Response surface plot Conc. of HPMC K15 and Kyron on Disintegration time (Y1).

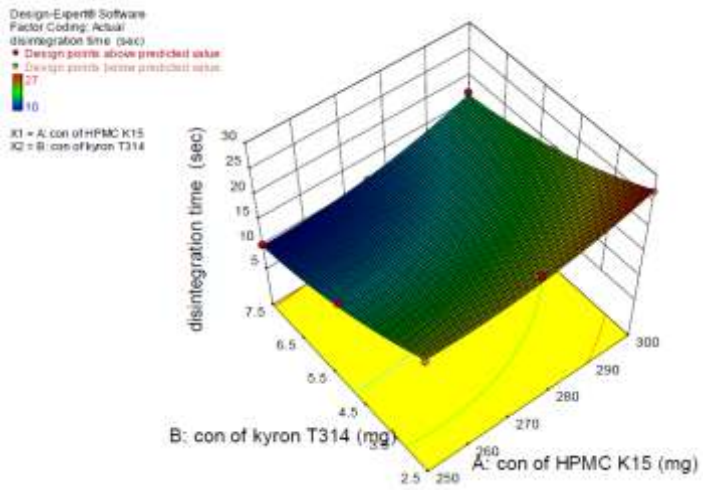


Figure 5: 3D surface plot A conc. of HPMC K15 and Kyron on Disintegration Time.

Effect on %CDR (Y2) Surface response study

Positive value for coefficient of B concentration of Kyron in equation indicates increase in %CDR. Positive value of coefficient of A indicates linearity of surface response and counter plot in %CDR.

%cdr = +83.29 - 1.66 * A + 3.59 * B + 0.262 * AB + 0.92 * A^2 + 0.19 * B^2

Table 6: ANOVA Table for Response (Y2).

ANOVA for Response Surface Quadratic model						
Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		Mean	F	p-value	
Source	Squares	df	Square	Value	Prob > F	
Model	96.11	5	19.22	55.97	0.0037	significant
A-HPMC Concentration	16.60	1	16.60	48.34	0.0061	
B-Kyron concentration	77.47	1	77.47	225.59	0.0006	
AB	0.28	1	0.28	0.80	0.4363	
A2	1.69	1	1.69	4.93	0.1130	
B2	0.072	1	0.072	0.21	0.6778	
Residual	1.03	3	0.34			
Cor Total	97.14	8				

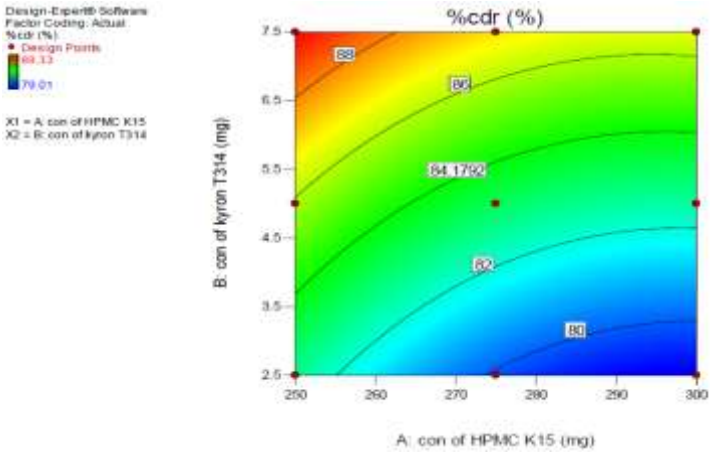


Figure 6: Response surface plot conc. of HPMC K15 and Kyron on %CDR

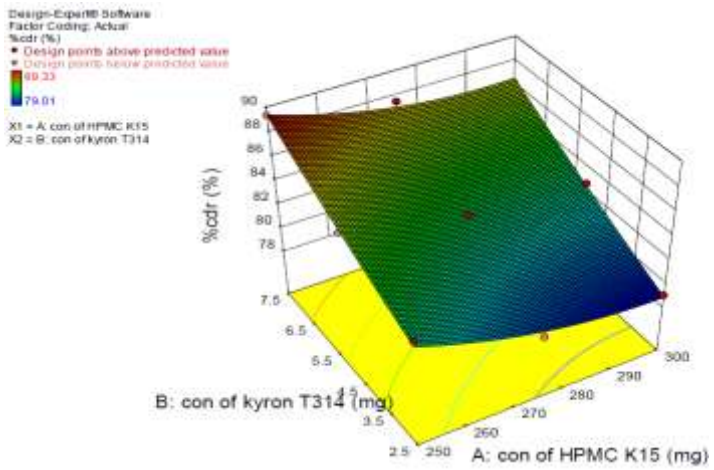


Figure 7: 3D surface plot A conc. of HPMC K15 and Kyron on %CDR.

Validation

From polynomial equation generated for response, intensive grid and integrated examine was performed over experiment field using design Expert software 10. During independent variable characterization study, impact of parameter concentration of Kyron (mg) and concentration of HPMC K15 (mg) were assessed. Criteria consideration of response disintegration time (Y1) and %CDR (Y2) is between 12-30 second and 85-95% respectively. Design space shown in also called as overly plot which is shaded region with yellow color indicates that region of successful operating ranges.

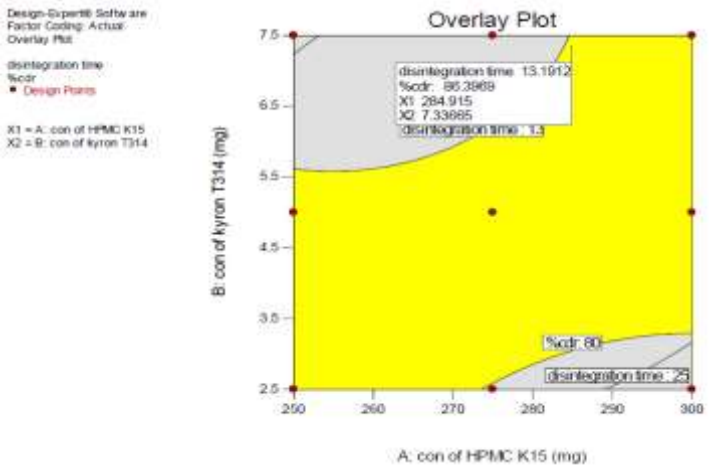


Figure 8: Overlay Graph 1.

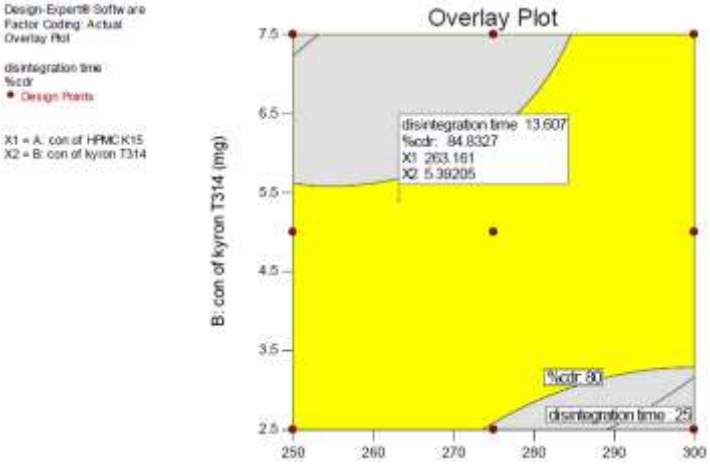


Figure 9: Overlay Graph 2.

Check point analysis of validation batches

PF10 and PF11 formulation was made for check point analysis and predict and compare experimental values.

Table 7: Validation batch of PF10 and PF11: Predicted & Actual Response.

Batch no	Concentration of HPMC K15 (X1)	Concentration of Kyron (X2)	Disintegration time (Y1)	%CDR (Y2)
PF10 (Predicted)	284.914	7.33	13.19	86.39
PF10 (Actual)	285	7.35	12.29	85.39
PF11 (Predicted)	263.16	5.39	13.60	84.83
PF11 (Actual)	264	5.40	12.40	83.83

OPTIMIZED BATCH FORMULATION FROM 3^2 FACTORIALDESIGN

Table 8: optimized formulation batch.

INGREDIANTS	Quantity(mg)
Paliperidone	6
HPMC K15	285
PEG 400	2
Kyron T-314	7.33
Citric acid	15
Sodium saccharine	10
Water	q.s

CHARACTERIZATION OF OPTIMIZED BATCH OF PALIPERIDONE FAST DISSOLVING FILM:

Table 9: Characterization of Paliperidone fast dissolving film.

Characterization of PF	Optimized Batch (Mean± S.D.) (n=3)
Weight of film (4cm2)(mg)	51 ± 1.4
Thickness (mm)	0.04 ± 0.02
Surface pH of film	6.3 ± 0.04
Folding endurance of film	44 ± 3
Drug content	87.65 ± 1.2
Tensile strength	1.4 ± 0.08
% Elongation (%)	9 ± 1.5
Disintegration time (sec)	10 ± 1

Stability study

The final optimized film was subjected for stability study, in which the film was stored at room temperature for 30 days. The stability of the film was analyzed by following parameter such as pH, %CDR, and Disintegration time.

Table 10: Stability Study of final batch PF.

Sr.no	Time (Days)	Climatic Condition	Evaluation Parameter		
			pH (Mean±S.D.) (n=3)	%CDR (Mean± S.D.) (n=3)	Disintegration time (sec) (Mean± S.D.) (n=3)
1	1	Room Temperature	6.3 ± 0.06	86.39 ± 0.7	10 ± 1
2	15	Room Temperature	6.3 ± 0.1	86.17 ± 0.9	10 ± 1
3	30	Room Temperature	6.5 ± 0.08	86.16 ± 1.1	10 ± 1

CONCLUSION

Fast-dissolving films of Paliperidone provide a convenient dosage form for patients, particularly those who may have difficulty swallowing traditional oral tablets or capsules. The ease of administration without the need for water makes these films suitable for various patient populations, including the elderly, pediatric, and psychiatric patients.

The fast-dissolving nature of the film allows for rapid dissolution and absorption of Paliperidone through the oral mucosa, potentially leading to a quicker onset of therapeutic action compared to conventional oral formulations. This can be particularly beneficial in the management of acute psychiatric conditions where rapid symptom relief is desired. Fast-dissolving films may offer enhanced bioavailability of Paliperidone by bypassing first-pass metabolism in the liver and facilitating direct absorption into the systemic circulation through the oral mucosa. This could result in more consistent drug levels and improved therapeutic outcomes. Patient preference and acceptability studies can provide valuable insights into the usability and palatability of Paliperidone fast dissolving films. Factors such as taste, texture, and ease of administration should be evaluated to optimize patient satisfaction and adherence.

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