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FORMULATION AND EVALUATION OF MOUTH DISSOLVING FILM OF HALOPERIDOL FOR THE MANAGEMENT OF PSYCHOSIS: A QbD APPROACH

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ABSTRACT

The study was aimed to formulate and evaluate the quick dissolving film of Haloperidol (HP) using pullulan as a polymer and Secondary objective was to optimize the formulation by Box-Benkhen design**.** Pullulan has been utilized as a polymer in the solvent casting method for making the oral dispersible films. Poly ethylene glycol 400 was used as a plasticizer, saccharine was used as a sweetening agent. Physical characteristics, thickness, folding endurance*, in vitro* disintegration, surface pH, as well as drug content uniformity were among the parameters that were assessed for the prepared films. *In vitro* dissolution test and stability study. The optimized formulation of quick dissolving film of β-Cyclodexrtin (β-CD) and HP showed the improved solubility the folding endurance was found to be 129 folds, the disintegration was found to be 24 seconds, the surface pH was found to be 6.5, the film burst was found to be 0.045 Kg/cm^2. The optimized formulation of quick dissolving film of β-CD and HP showed the improved solubility of HP which in term improves the bioavailability.

Key words: Haloperidol, Pullulan, Oral dispersible film, Box-Benkhen design, PEG 400

INTRODUCTION

Haloperidol is a butyrophenone neuroleptic used as a central-nervous-system antidepressant notably in the treatment of schizophrenia, mania and similar psychotic states. A mental health condition known as psychosis makes a person see or understand the world in a different way than those around them. The word "psychosis" refers to a range of conditions that affect the mind, in which there has been some loss of contact with reality. Schizophrenia is a serious mental illness that influences a person's thoughts, feelings, and behaviour. Schizophrenia patients might seem to have lost their awareness of reality, which can be upsetting to both them and their loved ones **[1]**.

Haloperidol is a BCS class-II drug which is having low solubility and high permeable, which is used for the treatment of various psychosis disorders where there is need of quick action of drug with short span of time, hence an attempt was made to develop the mouth dissolving film of haloperidol by forming complex with β-CD which may increase the solubility of drug, increase the absorption and improve the bioavailability of for the psychotic patients which are suffering from Dysphasia and other medical conditions where the patient have the problem with swallowing the solid dosage form.

To develop a optimized mouth dissolving film of haloperidol design of experiment (DoE) was applied, where DoE is a statistical technique that allows for the minimal number of experiments necessary for assessing various independent variables on a given response **[8-10]**.

An oral fast-dispersing dosage form is, by definition, a solid dosage that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need to administer water **[6]**. Dysphasia, or difficulty swallowing, affects people of all ages, but it is most prevalent in the elderly. Several diseases such as stroke, Parkinson's condition, AIDS, a thyroidectomy, head and neck thyroid therapy, and other neurological disorders such as cerebral palsy, are linked to dysphasia. Tablet size is the most frequently expressed concern, followed by surface form and taste **[7]**.

MATERIAL AND METHODS

Haloperidol procured from the Dham tech pharma, pullulan was purchased from the SDFCL, β-cyclodextrin, PEG400, ascorbic acid were purchased from SDFCL Mumbai and distilled water was used throughout the studies.

Preparation of HP-Beta CD inclusion complex.

A solubility study was carried out by dissolving the haloperidol and beta CD in 50% ethanol water solution the ratios are 1:0.5, 1:1, 1:1.5, 1:2 and 1:2.5 ratios it is stirred for 24 hours and lyophilized through freeze dryer. Among the above ratios 1:1 was best one so it is selected for the further formulation. The prepared complex is stored at air tight container. Until its use **[12]**.

Drug content of prepared complex: The complex is taken and dissolved in 6.8 pH phosphate buffer solution the solution was shaken and sonicated for 5mins then filtered through whatman filter paper. This stock solution was diluted. The drug content was measured using the UV –visible spectroscopy at 247nm using 6.8 phosphate buffer as a blank **[12]**.

selection of polymer: In this different concentration of pullulan was used in the preparation of film 20% and 30% of polymer shows very low elasticity and also high concentration 50% of polymer was used more elasticity, so 35%,45% and 55% of different concentration of pullulan was taken.

Selection of plasticizer: A vital component of the oral films is plasticizer. The choice of plasticizer is based on how well it works with the polymer and what kind of solvent is used to cast the film. It minimizes the oral film's stiffness and helps in increasing its flexibility. Plasticizer lowers the polymer's glass transition temperature, which greatly enhances the films characteristics. PEG400 was used at concentrations of 1 to 20% w/w; however, that lead to less flexible and increased stiffness films, so plasticizer concentrations of 25%, 35%, and 45% were used instead.

Selection of sweeteners: When it comes to the paediatric population, the formulation's sweet taste is more crucial. Hence sweeteners are used to increase the mouth-dissolving formulations' palatability and reduce the characteristic taste of dosage form hence saccharin was used in the concentration 10-20mg per casting of films.

Preparation of Oral Dispersible Film

The Box-Benkhen design was developed for the quick dissolving film

The Box-Benkhen design was employed to carry out the design of prepared film at 3 levels, 3 independent factors were studied. The selected independent variables were Pullulan (A), PEG400 (B), saccharine (C) above three are selected as a low, medium & high concentration 17 runs were carried out. The experiments were evaluated for responses folding endurance (Y1) and disintegration time (Y2). The experiment design matrix generated by the software is shown in **Table 1**. All other parameters (concentration of drug, ascorbic acid, strawberry flavour, method of preparation etc.) were kept constant to minimize fluctuations. The design is generated using Box–Behnken experimental design on

Design-Expert® Software Version 13. 05. A, B, and C are the factors studied. The design space for films was established targeting minimum disintegration time and maximum folding endurance. Predicted values were compared with experimental values to confirm the reliability and adequacy of the derived polynomial equations in predicting the responses. Contour plots and 3D plots for both responses along with overlay plot.

Formulation of Mouth dissolving films

Mouth dissolving films were formulated by dissolving the required amount of pullulan & PEG 400 in water and was stirred for 30 minutes on a magnetic stirrer after complete dissolving required amount of HP- β CD, ascorbic acid, saccharin and flavour was added and stirring was continued for another 30 minutes to form a uniform dispersion. Then the dispersion was put aside to get rid of any trapped air bubbles. In order to develop mouth dissolving film, the solution was finally casted in Petri plate and the plates were kept in a hot air oven at 60°C. After drying, the film was carefully removed from the glass plate and cutted into 2cm X 1.5cm containing 2mg haloperidol.

Dose calculation for films:

Size of the Petri plate: 9.1cm^2

Area of Petri plate $A = \pi r^2$

Area of Petri plate =65cm^2.

Each film contains 2 mg of drug (2cm X 1.5 cm).

Total area contains 43.4mg of drug

The 14.2mg of complex was containing 2mg of haloperidol, so each plate required 300mg of complex per Petri plate.

Table 1: Formulation of oral dissolving films

Batch code in mg	Complex	Pullulan	Ascorbic acid	PEG400	Saccharine	Strawberry
F1	300	350	20	225	20	QS
F2	300	350	20	325	10	QS
F3	300	550	20	325	15	QS
F4	300	350	20	125	10	QS
F5	300	450	20	225	20	QS
F6	300	350	20	125	15	QS
F7	300	350	20	125	20	QS
F8	300	550	20	125	10	QS
F9	300	450	20	125	15	QS
F10	300	350	20	225	15	QS
F11	300	550	20	325	10	QS
F12	300	550	20	225	10	QS
F13	300	350	20	325	20	QS
F14	300	450	20	225	20	QS
F15	300	450	20	325	10	QS
F16	300	550	20	125	20	QS
F17	300	450	20	125	15	QS

Evaluation of Fast Dissolving Film Formulation

Physical appearance and surface texture of films

These parameters were checked by visual inspection of films and by feel or touch. The observation suggests that the films are having smooth surface and they were elegant enough to see **[13]**.

Thickness

All the batches were evaluated for thickness by using calibrated Thickness gauge Baker, type K17 jewelled (0.001- 0.1 mm). Three samples from all the batches was withdrawn and evaluated for thickness **[14]**.

Weight Variation

Each film was weighed individually on electronic balance and average weight of three films was found **[15]**.

Folding endurance

Film flexibility can be quantitatively assessed using a concept called folding endurance. A small strip of the film was folded repeatedly at the same location until it broke. The value of folding endurance was determined by how many times a film could be folded in the same place without breaking **[16]**.

Surface pH

By allowing the films to come into contact with 1ml of distilled water, the surface pH was measured. By bringing previously calibrated pH meter up close to the films surface, the surface pH of film was measured **[17]**.

Drug content

This test was performed by dissolving a 3 cm^2 area of film in 6.8 pH Phosphate buffer 100ml with stirring. Whatman filter paper was used to filter the film dispersed solution, and the filtrate was then diluted to 100 ml in a volumetric flask using the same buffer, UV spectrometer was used to analyze the drug content.

Film burst

Film burst is a measure of a resistance to rupture. It refers to the behaviour of the film after stretching beyond its rupture or deformation point. Texture analyzer was used in the investigation to study the burst strength of mouth dissolving film. The instrument was calibrated with 5kg load cell and fitted stainless steel probe the methodology consists of attaching the film to platform which was tightened with screws. The probe was initially calibrated with a pre-speed of 1 mm/sec and a trigger force of 1g. Each experiment was carried out in triplicate, and the test measured the penetration distance as the film is compressed **[18]**.

***In-vitro* Disintegration time**

In-vitro dispersion time was measured by dropping a in Petridish with 6 ml of water three films from each formulation were randomly selected and in-vitro dispersion time was performed **[19]**.

In-vitro Dissolution studies

Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API. Many times the dissolution test can be difficult due to tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed.

Stability study

The stability study of the formulated films were carried out under in house testing conditions The samples were stored at different temperatures. Refrigerator and in room temperature for 30 days. Stored in aluminium foil followed by self-sealing cover. It is observed after 30 days **[20]**.

RESULTS AND DISCUSSION

Table 2: Results of various characterization studies including the responses

Batch code	Thickness (mm)	Weight Variation (mg)	Folding endurance	Film burst (kg/cm))	Drug Content%
F1	0.06±0.01	0.032±0.0009	132	0.0192	100.2±0.0154
F2	0.07±0.01	0.035±0.0031	130	0.0222	98.13±0.133
F3	0.11±0.01	0.039±0.0048	102	0.0359	100±0.01251
F4	0.07±0.01	0.034±0.0026	128	0.0197	101.08±0.1
F5	0.08±0.01	0.032±0.0009	108	0.0195	96.54±0.107
F6	0.06±0.01	0.031±0.0004	127	0.0246	100.5±0.0154
F7	0.07±0.01	0.033±0.0011	119	0.0321	100.7±0.154
F8	0.10±0.01	0.038±0.0045	91	0.0384	96.6±0.107
F9	0.08±0.01	0.035±0.0031	114	0.0259	97.1±0.118
F10	0.07±0.01	0.034±0.00026	125	0.0496	99.8±0.023
F11	0.11±0.01	0.037±0.0033	97	0.0538	98±0.133
F12	0.10±0101	0.032±0.0009	95	0.0208	96.6±0.107
F13	0.06±0.01	0.032±0.0016	128	0.0304	97±0.118
F14	0.08±0.01	0.030±0.00094	116	0.0185	95±0.103
F15	0.09±0.01	0.038±0.00045	113	0.0315	99.8±0.023
F16	0.09±0.01	0.039±0.0046	101	0.0449	98±0.133
F17	0.08±0.01	0.032±0.0016	110	0.0615	97±0.118

The results are expressed in average ±standard deviation for n=3

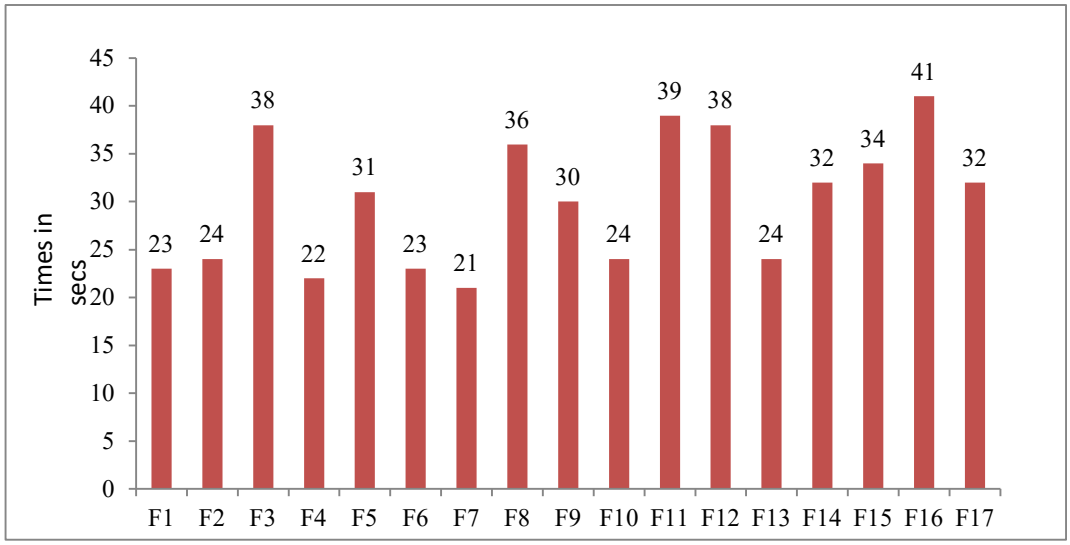

Figure 1: Comparison of disintegration time of all the formulation

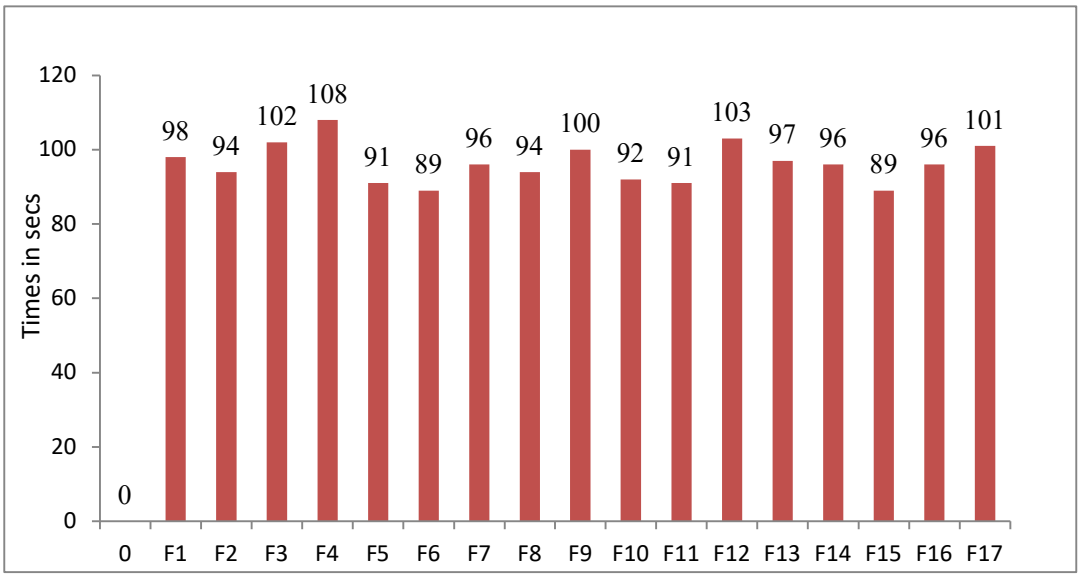

Figure 2: Comparsion of cumulative drug release of all the formulation

Table 3: ANOVA data Fit statistics for quadratic model for folding endurance

Significant	**2625.09**	**3**	**875.03**	**53.99**	**<0.0001**
A- Pullulan	**2389.98**	**1**	**2389.98**	**147.48**	**<0.0001**
B-PEG400	**12.44**	**1**	**12.44**	**0.7679**	**0.3968**
C-Saccharine	**3.63**	**1**	**3.63**	**0.2243**	**0.6436**

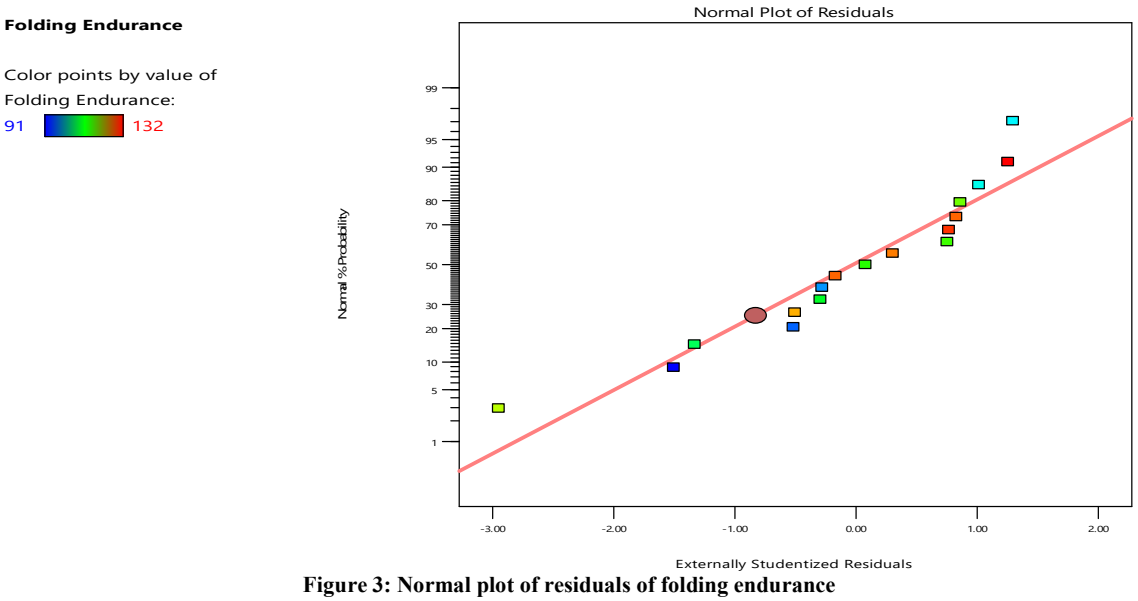

Figure 3: Normal plot of residuals of folding endurance

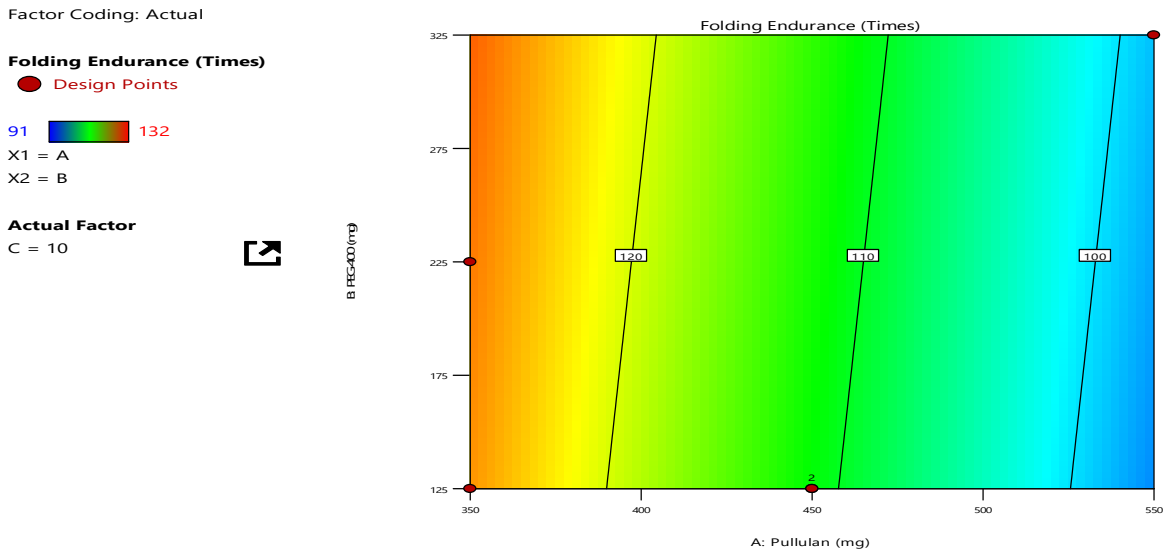

Figure 4:2D contour plot showing the relationship between A. Pullulan and B. PEG400 as the Folding endurance response variable

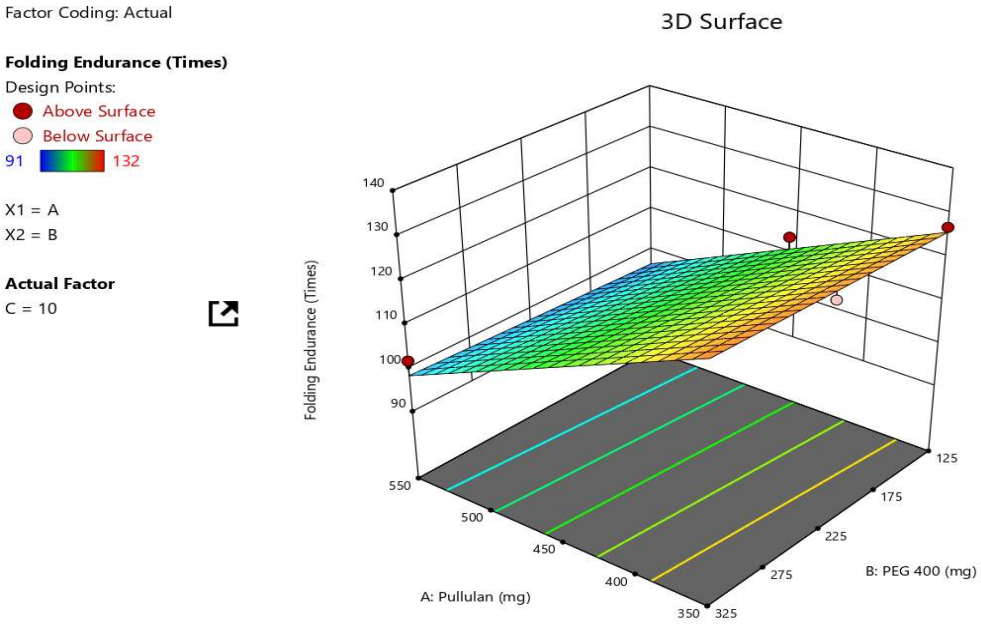

Figure 5: 3D-Repsonse surface plots showing the relationship between A. Pullulan and B.PEG400 as the folding endurance response variables

Table 4: ANOVA data Fit statistics for quadratic model for disintegration time

Model	Sum of squares	D f	Mean square	F-value	p-value
Significant	711.57	10	237.1	53.99	<0.0001
A-PULLULAN	673.78	1	673.78	147.48	<0.0001
B-PEG400	3.59	1	3.59	0.7679	0.2359
C-SACHARINE	7.204	1	0.7204	0.2243	0.5870

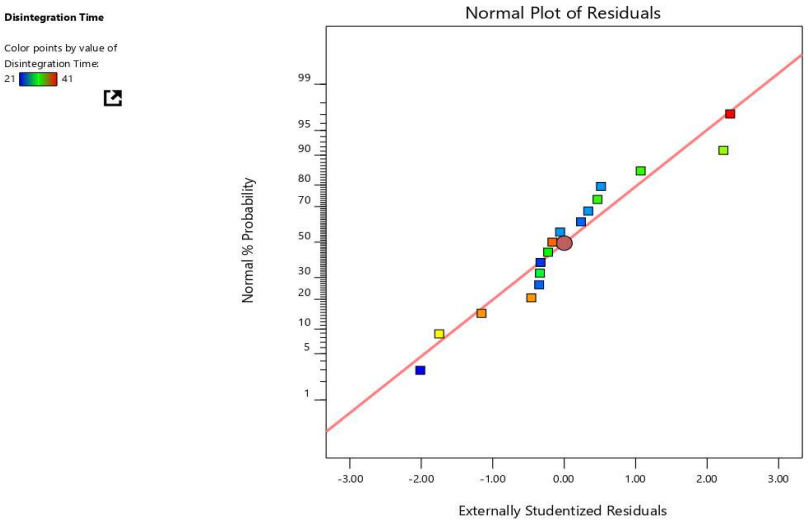

Figure 6: Normal plot for the residuals of disintegration time

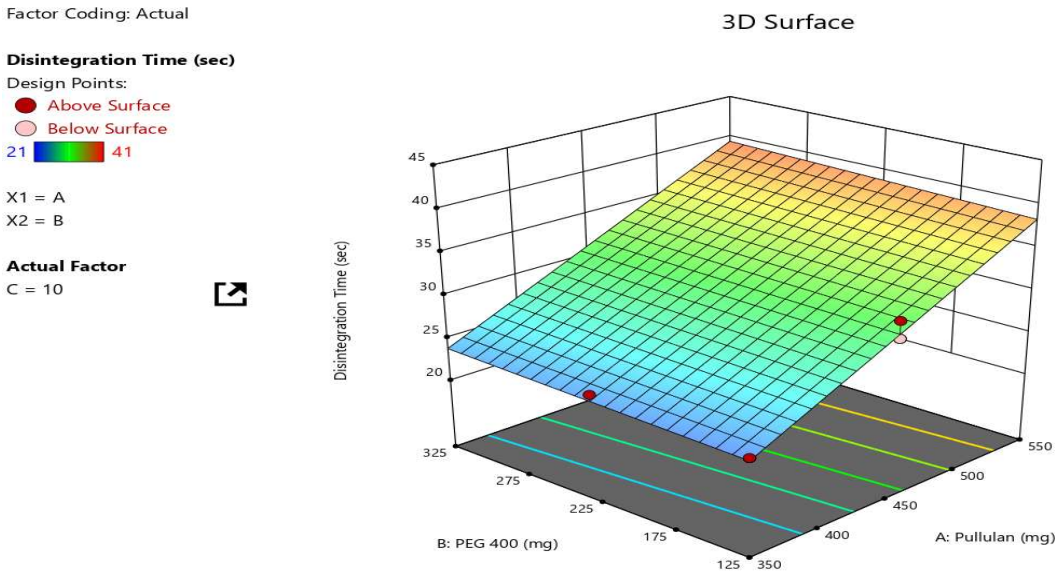

Figure 7: 2D contour plot showing the relationship between A. Pullulan and B.PEG400 as the disintegration rate response variable

Table 5: Evaluation parameters of optimized formulations

S. No.	Parameters	Values
1	Thickness (mm)	0.06±0.01
2	Weight variation(mg)	0.034±0.00215
3	Surface pH	6.5
4	Folding Endurance	126
5	Film burst	0.045
6	DT (secs)	25
7	DC%	98
8	*In vitro* drug release	99.5%

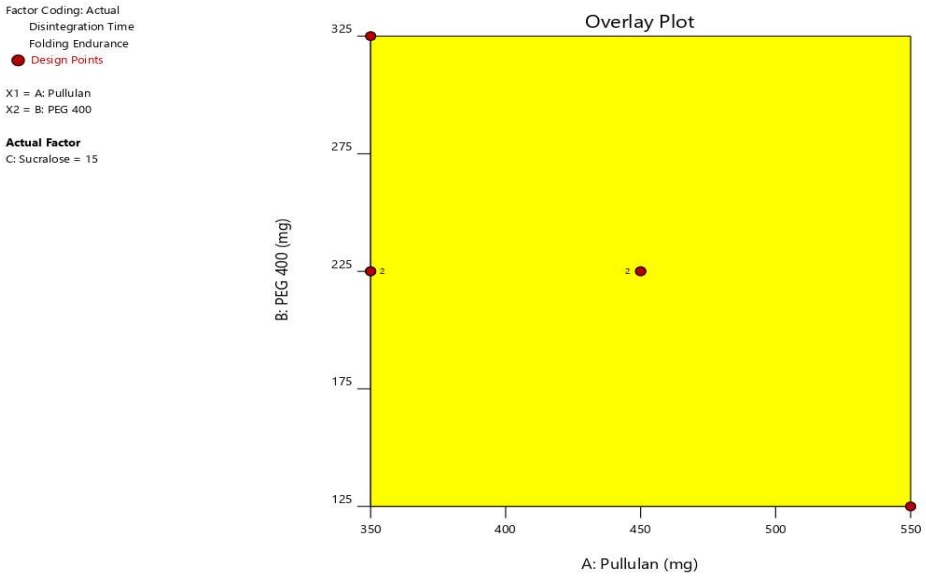

Figure 8: The overlay plot displaying the optimized film formulation in the design space and their predicted response

Table 6: comparison between experimental values and predicted values for optimized formulation

Responsible variables	Experimental values	Predicted values	%error
Folding Endurance	129	126.450	2.02
Disintegration Time (secs)	24	22.926	4.7

DISCUSSION

To carry out the quick dissolving film by solvent casting method by using the different concentration of pullulan as a polymer, PEG 400 as a plasticizer, sweetener as a saccharine. The prepared film was evaluated and optimized by Box-Benkhen design.

ANOVA (Analysis of variance) for folding endurance (Y1)

After Responses Y1were obtained experimentally, analysis of variance (ANOVA) is done, Actual values (experimental values) and predicted values were compared to evaluate the model and after complete analysis, software generates optimal formula (predicted solutions) of factors with desired responses to give optimized formulation. Depicted in, **Table 6**.

Statistical Analysis of Response for folding endurance(Y1). Analysis of the chosen model

The ANOVA for response of folding endurance given in **Table 3**. ANOVA was applied for analyzing the coefficients of polynomial equation for each of the studied response variables. ANOVA parameters, which indicated statistically significant, model terms ($p < 0.05$), the model F-value of 22.64 implies the model is significant, and there is only a 1.32% chance that F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms were significant. Adequate precision measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of indicates an adequate signal. This model can be used to navigate the design space.

Response Surface Plots in 3Dimensional (3D), Y1 folding endurance.

Using a surface plot one can visualize the response surface. Plots are useful for establishing desirable response values and operating Surface conditions. The responsesurface plots for Y1 is showing **Figure 3-5** depicts the 3D-response surface plot and 2D-contour plot for the strength as the response variable relationship between pullulan and PEG400. The figure suggests a sharp line values of folding endurance between low to high levels of the factors. The 3D-response surface plot and 2D-contour plot indicates that the amount of polymer & plasticizer has been a significant effect on folding endurance. A direct correlation was observed between concentration of pullulan and PEG400 of the film.

ANOVA (Analysis of variance) for disintegration time(Y2)

After Responses Y2 were obtained experimentally, analysis of variance (ANOVA) is done, Actual values (experimental values) and predicted values were compared to evaluate the model and after complete analysis, software generates optimal formula (predicted solutions) of factors with desired responses to give optimized formulation.Depicted in, **Table 4**.

Statistical Analysis of Response for disintegration time. (Y2).

Analysis of the chosen model The ANOVA for response, DT in **Table 4**. ANOVA was applied for analyzing the coefficients of polynomial equation for each of the studied response variables. ANOVA parameters, which indicated statistically significant, model terms ($p < 0.05$), the model F-value of 5.15 implies the model is significant, and there is only a 2.41% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case B is significant model terms, insignificant lack of fit and low values of predicted sum of squares.

Adequate precision measures the signal to noise ratio. A ratio greater than 2 is desirable. The ratio of 5.3277 indicates an adequate signal. This model can be used to navigate the design space. A significance level of 0.05 indicates a 5% risk of concluding that a difference exists when there is no actual difference).

Response Surface Plots in 3 Dimensional (3D), Y2

DT Using a surface plot one can visualize the response surface. Plots are useful for establishing desirable response values and operating Surface conditions. The response surface plots for Y2 is shown in **Figure 5-6** depicts the 3D-response surface plot and 2D-contour plot for DT as the response variable relationship between sodium pullulan and PEG400.The 3D-response surface plot and 2D-contour plots indicates that the amount of pullulan has significant effect on DT. A direct correlation was observed between concentration of pullulan and PEG400 of the film.

Preparation of HP-Beta CD Inclusion Complex.

Haloperidol is a BCS class-II drug with low solubility & high permeability, hence to increase the solubility of HP in saliva we developed the complex of HP-β-CD complex using different concentration of HP-β-CD 1:0.5,1:1,1:1.5,1:2,1:2.5 in water. On analysis ratio of HP-β-CD complex 1:1 was containing 87.04 % of HP, hence we used 1:1 complex of HP-β-CD for the formulation of mouth dissolving film.

Thickness

A micrometer screw gauge was used to measure the film thickness. In order to obtain uniformity of film, thickness is

measured at 5 different locations. The thickness of fast dissolving films was in the range of 0.06±0.01. It was observed as the concentration of pullalan increased thickness of film was increased.

Weight variation

Three films were randomly selected and their average weight was weighed. Individual films were weighed and compared with the average weight for the deviation. The weight variation of fast dissolving films was within the acceptable range.

Folding endurance

To determine mechanical characteristics of the formulated film is rapidly folded at the same place till the film is broked. The number of times the film could be folded at the same place without breaking gives the value of folding endurance. Folding endurance for film were between 100-150.Folding endurance of the films increased as the polymer concentration and plasticizer concentration was increased.

Surface pH

The surface pH of the mouth 6 to 6.5. The prepared quick dissolving film three are randomly selected 1 ml of 6.4 phosphate buffer was taken in Petri dish the film was dipped in that the film was observed and the surface pH of the quick dissolving film was 6 -0.5.

Drug content

This test was performed by dissolving the film in 100 ml of 6.5 pH phosphate buffer with stirring. This solution was filtered using a whatman filter paper, and the filtrate was analysed using UV spectrometer. The average three formulation drug content was carried out. The 3D- response surface plots, 2D-contour plots and perturbation graphs generated by the Design Expert® software were used to understand the relationship between the independent and dependent or response variables. Finally, the optimization of film was carried out based on achieving the desired formulation attributes such as disintegration time, and folding endurance by numerical and graphical optimization technique. The method was executed by employing the desirability function and overlay plot in the design space. The location of the optimized formulation was highlighted with a flag in the overlay plot. Further, the validation of the developed method was carried out by preparing the optimized formulation and evaluating the disintegration time, and folding endurance. Comparing the predicted and observed responses.

Film Burst

This test was performed by the test measures the penetration distance as the film is compressed each experiment was performed in triplicate. The film burst was found to 0.0192kg to 0.0615kg. This test ensure the tensile strength of the film.

***In vitro* Disintegration time**

The disintegration of prepared formulation was formed to be 21 to 41 sec. By DoE it was found that amount of pullalan was significant effect on Disintegration time as concentration of pullalan and PEG400 was decreased disintegration time was reduced**.**

***In-vitro* Dissolution studies**

In vitro drug release studies were performed for all the prepared formulation by using phosphate buffer pH 6.8 as dissolution medium and measuring drug concentration UV spectrophotometrically at 247nm. All the formulation show more than 90% release within 100 to 120 seconds, hence we concluded that the complex of HP-β-CD complex can increase the solubility of HP. This in turn increases the bioavailability of BCS-II Class drug like HP.

Optimized Formulation

The optimized quick dissolving film formulation was identified by numerical and optimization and desirability function by "trading off" folding endurance and disintegration time variable for attaining the maximum folding endurance and minimum disintegration time by the concentration 350mg of pullalan, 324.882mg of PEG400 and 20mg of saccharine using suggested optimized formulation developed by Box Benken design with desirability of 88.4%, where optimized formulation showed a disintrgration time of 24 seconds & folding endurance 129 & the film burst was found to be 0.045 Kg/cm^2.

Stability Study

The formulation was subjected to stability study at room temperature. Stability studies were performed on the basis of drug content, disintegration time and *In Vitro* drug release. The results observed were not much different indicating the integrity of the film. There were no significant changes in drug content, disintegration time, surface pH, dissolution rate.

CONCLUSION

In the present work an effort has been made to improve the solubility and enhance the bioavailability of haloperidol complexed with the β-CD. The quick dissolving film was developed by solvent casting method containing pullulan as polymer and PEG400 was used as plasticizer.The prepared mouth dissolving film will induce quick release of medication Haloperidol- β-CD and show antipsychotic effect within short time.

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Conflict of Interest

The author has no conflicts of interest, financial or otherwise, to declare

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