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SOLUBILITY ENHANCEMENT AND QUALITY BY DESIGN (QBD) ASSISTED FABRICATION OF FAST DISSOLVING BUCCAL FILM FOR RISPERIDONE

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Keywords:

Risperidone, Solid dispersion, Solvent Evaporation method, Fast dissolving Buccal film, Drug content, *In-vitro* dissolution

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ABSTRACT: Rapidly Dissolving Drug Delivery Systems have become interested in the pharmaceutical industry as frameworks that provide quick onset of action with enhanced dissolution characteristics. Risperidone, a poorly water-soluble drug, is a second-generation antipsychotic of the benzisoxazole derivatives used in treating schizophrenia and other mood disorders. The present research work aimed to fabricate fast dissolving buccal film of Risperidone solid dispersion, using a quality by design (QbD) approach. Formulation with the drug: polymer ratio of 1:1 prepared by a solvent evaporation method using polyethylene glycol 400 showed the highest drug release. QbD was applied to the films prepared by the solvent casting method. Preliminary screening studies, along with initial risk assessment and the use of Box- Behnken design, allowed the selection of HPMC E5, PEG 400, and Croscarmellose sodium as critical material attributes for film formulation and as independent variables. In contrast, folding endurance, disintegration time, and tensile strength were taken as response variables. The films were evaluated based on in-vitro percent drug dissolution, disintegration time, percent elongation, tensile strength, folding endurance, thickness, and uniformity of mass. The optimized transparent formulation showed faster in-vitro drug dissolution within 12 min and an average disintegration time of 31.66±0.5773. The *ex-vivo* studies showed a dissolution of 95.43%. DSC, XRD, and SEM studies revealed excellent film characteristics. The results concluded that fast dissolving buccal film (FDBF) containing solid dispersion of the drug may provide the advantage of faster onset of action, enhanced dissolution, avoidance of extensive first-pass metabolism, and improved patient compliance for the delivery of Risperidone.

INTRODUCTION: Around 60% of all formulations are solid dosage forms, and the most accepted and favoured route of administration for systemic effect is the oral route [1]. Rapidly Dissolving Drug Delivery Systems has become interested in the pharmaceutical industry [2]. These dosage forms provide accurate dosing compared to liquid dosage forms, with no water requirement and no fear of choking and serve as the newest method in drug delivery technology used for pharmaceutical and nutraceutical products [3].

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Insufficient bioavailability is generally a consequence of the poor solubility of drug substances in water and their low dissolution rate in aqueous, leading to failure in formulation development [4]. Therefore, preparing solid oral dosage forms and enhancing oral bioavailability of such poor water-soluble drugs currently serve as a

major objective and greatest challenge in new formulation development [5]. Quality by design (QbD) is a methodology used in pharmaceutical preparation to build quality into products. A very common tool or element used in the QbD is the quality target product profile (QTPP), along with Critical quality attributes (CQA's) and critical process parameters (CPP's). Hence a proper balance of the CQA's and CPP's explains the design space [6, 7].

An ideal Fast Dissolving Buccal Film (FDBF) should have good flexibility, easy administration, and handling, be physically stable, and rapid disintegration. These features can be translated into CQA's (high tensile strength, high folding endurance, low disintegration time) followed by identification of the CPP (concentration film forming agents, amount of plasticizer, and amount of super disintegrant that influence the CQA. Combining the CQA and CPP will obtain a product that meets the quality objectives [8]. The study's main aim was to formulate, evaluate and optimize the fast dissolving films of Risperidone. Solid dispersion of Risperidone was prepared using PEG 4000 and PVP K30 and was formulated into fast dissolving films using different grades of HPMC as film-forming polymers. The effect of different concentrations of polymer, plasticizer and super disintegrant on the folding endurance, disintegration time, and tensile strength using QbD was studied. The fast-dissolving films were evaluated for physicochemical properties and drug release.

MATERIALS AND METHODS:

Materials: Risperidone was obtained as a gift sample from Cadila Healthcare Ltd. (Goa, India), Polyethyleneglycol 4000, Potassium dihydro-genorthophosphate, Sodiumhydroxide flakes were obtained as a gift sample from Molychem (Mumbai, India), PVP K30, Polyethyleneglycol 400 was obtained as a gift sample from BASF India Ltd. (Mumbai, India), Hydroxy-propylmethylcellulose- LVE5 was obtained as a gift sample from Colorcon on Asia Pvt. Ltd. (Goa, India), Methanol (HPLC-Grade) was obtained as a gift sample from Fisher Scientific India Pvt. Ltd. (Mumbai, India), Citric acid was obtained as a gift sample from Lobachemie Ltd. (Mumbai, India). All other chemicals and solvents used were of pharmaceutical and analytical grade and the experimentation was carried out in 2020 at Goa College of Pharmacy, Panaji-Goa.

Methods:

Preformulation Studies: Preformulation is the research phase and a development method wherein physical, chemical and mechanical characteristics of a drug substance are identified alone and in combination with excipients to develop a stable, safe and effective dosage form. Preformulation studies aimed to establish the important physicochemical characteristics of the drug substance and to check the compatibility of the drug substance with different excipients.

A. Identification Tests:

Color, Odour and Surface Nature of Drug: The drug's physical parameters (color, odour, and surface nature) were characterized by visual observations.

Solubility Analysis: The solubility profile of Risperidone was determined using the modified shake flask method in selected suitable solvents. An excess amount of Risperidone was added to each 10 ml flask maintained at room temperature. The precaution was taken to see that an excess of the drug was always maintained. The flasks were shaken (vortex mixed); portions of the supernatants were filtered and suitably diluted for quantification of the drug.

Melting Point Determination: The melting point of the pure Risperidone was measured by the open capillary method. For that, a small amount of drug was filled in the capillary and inserted into the sample holder of the melting point apparatus. The temperature at which the drug substance started melting was recorded. The experiment was performed in triplicate.

Identification by FT-IR: The FT-IR spectrum of the procured sample drug was compared with a reference-IR spectrum of pure drugs.

B. Compatibility Studies:

FT-IR Spectroscopy: The spectrum of the drug, HPMC E5, and PEG-4000 were separately recorded using an FTIR spectrophotometer (Shimadzu Corporation, Japan) to study the chances of interaction between the drug and PEG-

4000. Prepared samples were scanned over the wavelength range of 7800 to 350cm^{-1} to record the spectrums and were analyzed for compatibility.

Preparation of Solid Dispersion (SDP): The composition of solid dispersion in different ratios is given in **Table 1.**

TABLE 1: CONTENT OF FORMULATION OF SOLID DISPERSION AND PHYSICAL MIXTURE

Formula Code	Ratio	Drug+ PEG4000
PM1	1:1	Drug+ PVPK30
PM2	1:2	
PM3	1:3	
PM4	1:1	
PM5	1:2	Drug+ PEG4000
PM6	1:3	
SD1	1:1	
SD2	1:2	
SD3	1:3	Drug+PVPK30
SD4	1:1	
SD5	1:2	
SD6	1:3	Drug+ PEG4000

Preparation by Physical Mixture: Physical mixture was prepared by taking the drug along with the polymer (PEG 4000 or PVPK30) taken as a hydrophilic polymeric carrier in the ratio (drug: polymer) of 1:1, 1:2, and 1:3 w/w and triturated together in a glass mortar. The resultant mixture was then crushed, sieved, and stored in a desiccator for further treatment.

Preparation by Solvent Evaporation: Solid dispersion of Risperidone was prepared by a solvent evaporation method using PEG 4000 or PVP-K30 as a hydrophilic polymeric carrier in the ratio (drug: polymer) of 1:1, 1:2, and 1:3.

The weighed amount of drug and carrier was dissolved in a minimum quantity methanol in a beaker to get a clear solution and further stirred. The solvent was then evaporated in a vacuum oven at 50°C. The solid mass was crushed, passed through a sieve, and stored in a desiccator for further studies.

Evaluation of Solid Dispersion:

Differential Scanning Calorimetry (DSC) Analysis: To determine the thermal behaviour, crystallinity of the drug and solid dispersion, DSC thermograms of Risperidone and optimized solid dispersion were recorded using a DSC (Shimadzu, Koyoto Japan) at a heating rate of 10°C/minute.

Percent Yield: It is estimated to identify the efficacy of the method used for preparation. The percent practical yield of the physical mixture and solid dispersion prepared with the solvent evaporation method was separately determined using the following equation:

$$\% \text{ Practical Yield} = \text{Practical mass} \times 100 / \text{Theoretical mass (drug + polymer)}$$

Percent Drug Content: Accurately weighed quantity of physical mixture and solid dispersion of drug equivalent to 4mg was dissolved in methanol. The solution was then filtered, suitably diluted, and scanned using a wavelength of 236nm to determine percent drug content using the following equation:

$$\% \text{ Drug Content} = \text{Practical drug content} \times 100 / \text{Theoretical drug content}$$

Percent Drug Dissolution Study: The drug dissolution studies of physical mixture and solid dispersion of drugs were performed separately using USP type II apparatus (paddle) in phosphate buffer pH 6.8 as dissolution medium. Solid dispersion equivalent to 4mg was added to 500 ml of dissolution medium at 37.0 ± 0.5°C and stirred at 50rpm. A sample of 5ml was collected at 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, and 60 min, and an equal volume of fresh medium was added to maintain the sink condition. Samples were filtered using a membrane filter, diluted suitably, and analyzed at a wavelength of 236nm against a blank.

Scanning Electron Microscopy (SEM): To study the surface morphology of solid dispersion, scanning electron microscopy was used.

Formulation Development of Fast Dissolving Buccal Films (FDBFs): Formulation of FDFs containing Solid dispersion of drug- FDBFs containing selected solid dispersion of Risperidone were formulated using the solvent casting method. The solution to be cast was prepared by dissolving an equivalent weighed amount of solid dispersion of the drug, HPMC-E5 (40- 45% w/w) and PEG 400 (10-15% w/w) in 10ml of distilled water with continuous stirring on a magnetic stirrer for 30 min. Further, the required amount of Croscarmellose (1-5% w/w) and citric acid (1% w/w) was gradually added to the solution until a clear solution was obtained.

The solution was kept for 2 hours to remove the entrapped bubbles. The resulting solution was then cast on a petri dish and allowed to dry completely in the vacuum oven at 50°C to form the film. The dried films were carefully separated from the petri dish and cut into the desired film.

Optimization of FDFs using Quality by Design (QbD) Technique:

Assigning of QTPP and CQA: The QbD approach helped in the appropriate selection and assignment of QTPP surrounding the proactive summary for using the optimum benefits of the developed formulation. Pharmaceutical development of fast dissolving films containing Risperidone begins with allocating critical process and formulation characteristics through the QTPP. The patient-centric approach mainly focuses on the safe and efficacious use of fast dissolving film that will allow the rapid onset of action with patient compliance. The CCP for a film should be robust, easy to reproduce, and obtain a product with the desired specification. Each CPP was individually positioned as a high, medium, or low-risk(s) level thinking about the possibility of risk and severity of the influence associated with the CQAs.

Risk Assessment: Risk Assessment aims to study the effect of critical material attributes (CMA) or CPPs on CQAs of fast dissolving films. **Fig. 1** shows an Ishikawa fish-bone diagram made to enumerate the possible high-risk elements that affect the final quality of the formulation. The list includes the essential material attributes and/or process variables for developing films containing Risperidone.

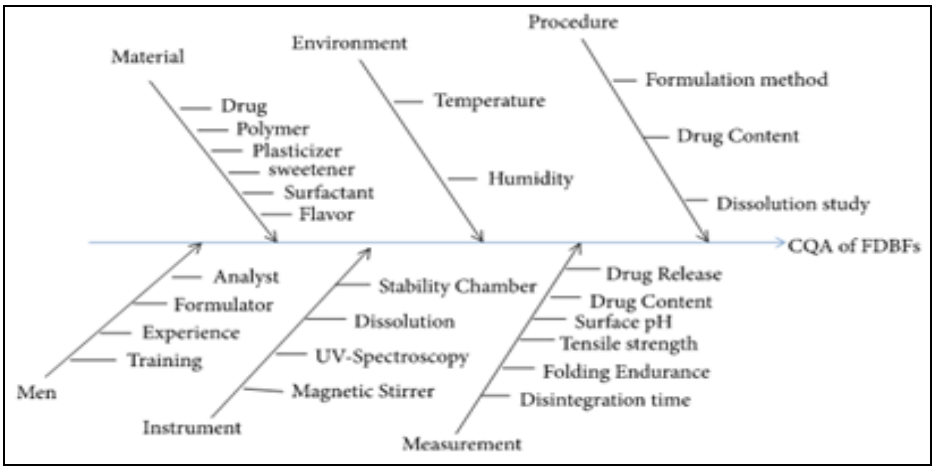

FIG. 1: ISHIKAWA FISH-BONE DIAGRAM FOR THE FORMULATION OF FDF CONTAINING RISPERIDONE

Design of Experiments: Formulation of Risperidone FDBFs were optimized by using Box Behnken Design (response surface methodology) by applying Design-Expert® -13 for formulating the FDBFs with the desired and optimum properties. The design-build information is shown in **Table 2**, list of independent variables is shown in **Table 3**, list of response or dependent variables is shown in **Table 4** and experimental designs for Risperidone FDBFs is shown in **Table 5.**

TABLE 2: DESIGN-BUILD INFORMATION USING DESIGN-EXPERT®-13

Parameters	Remarks
Study type	Response Surface Methodology
Design type	Box Behnken Design
Model	Quadratic
Subtype	Randomized
Runs	17

TABLE 3: LIST OF INDEPENDENT VARIABLES (FACTORS) SELECTED IN EXPERIMENTAL DESIGN

S. no.	Independent variables	Level of variation (%w/w)		
		Low	Medium	High
1.	Concentration of HPMC-E5(A)	45	50	55
2.	Concentration of Propylene glycol (B)	10	15	20
3.	Concentration of Croscarmellose (C)	1	3	5

TABLE 4: LIST OF RESPONSE OR DEPENDENT VARIABLES SELECTED IN EXPERIMENTAL DESIGN

Sr. no.	Response or dependent variables	Units
1.	Percentage drug dissolution (R1)	%
2.	Disintegration time(R2)	Seconds
3.	Tensile strength (R3)	Kg/mm^2

TABLE 5: BOX-BEHNKEN EXPERIMENTAL DESIGN FOR RISPERIDONE FILM

Sr. no.	Run	F.C	HPMC-E5 (A) %	PEG400(B) %	Croscarmellose (C) %
1	14	R1	45	17.5	1
2	16	R2	50	20	1
3	4	R3	50	15	1
4	8	R4	55	17.5	1
5	5	R5	45	20	3
6	15	R6	45	15	3
7	1	R7	50	17.5	3
8	6	R8	50	17.5	3
9	7	R9	50	17.5	3
10	9	R10	50	17.5	3
11	12	R11	50	17.5	3
12	10	R12	55	20	3
13	17	R13	55	15	3
14	11	R14	45	17.5	5
15	3	R15	50	20	5
16	2	R16	50	15	5
17	13	R17	55	17.5	5

The concentration of HPMC-E5 (A), the concentration of PEG 400 (B), and the concentration of Croscarmellose (C) were selected as three independent variables (factors). Folding Endurance (R1), Disintegration Time (R2), and Tensile Strength (R3) were selected as dependent or response variables (factors).

Based on the preliminary studies, the concentration of independent variables was set to vary between 45-55% w/w for HPMC-E5, 10-15% w/w for PEG 400 and 1- 5% w/w for Croscarmellose sodium. Subsequently, the experimental Box Behnken design was analyzed for various models like quadratic, linear, 2FI and means to find out the best fit model on the basis of responses of the dependent variables were carried out. Further, statistical validity using ANOVA, 3D-response surface plots and cube plots were established to find the compositions of optimized formulation based on the changes observed in the values response variables.

Evaluation of Fast Dissolving Films:

Differential Scanning Calorimetry (DSC) Analysis: To determine the thermal behaviour, nature of the solid dispersion and film DSC thermogram was recorded using a DSC (Shimadzu, Koyoto Japan) at a heating rate of 10°C/minute.

Uniformity of Mas: It was determined by individually weighing 5 randomly chosen films on a weighing balance. Films (4 cm^2) were cut from different places of the casted films and the average mass was calculated.

Thickness: A micrometer screw gauge was used to determine the thickness of the film. The thickness of film should be in range 5-200µm. The thickness was evaluated at five different locations (four corners and one at centre) to confirm uniformity in the thickness of film as the accuracy of dose distribution in the film is directly proportional to it.

Percent Drug Content: The percent drug content of the film ($2cm^2$) containing the equivalent of 4mg of drug was separately measured by dissolving it in phosphate buffer pH 6.8. Samples were filtered, diluted and analyzed for percentage drug content by double beam UV visible spectrophotometer at 236nm.

Folding Endurance: The brittleness of a film is determined by folding endurance, whereby the film (2 x 2 cm) was folded at the same place several times until it cracked.

Surface pH Test: This test was performed to determine the surface pH of the film as changes in the pH of the film can cause irritation to the oral mucosa. A combined pH electrode was used to determine the surface pH of the film (7 or close to neutral). The pH was determined by wetting the film in water. This study was done on three films of each formulation and their mean SD was calculated.

Tensile Strength: It is referred to as the maximum stress applied to a point at which the film specimen breaks. Tensile strength was calculated using the formula:

Tensile strength = Load at failure × 100 / Film thickness × Film width

Percent Elongation: Hounsfield universal testing machine was used to determine the deformation of the film until it breaks down.

Percent Elongation = Increase in length of film × 100 / Initial length of film

Disintegration Time: Disintegration time of an oral film is the time taken for the film to break or disintegrate in the presence of water or saliva. This test was done by dipping the film in 20 ml phosphate buffer pH 6.8 in a beaker and periodically shaking it to note when the film starts to break or disintegrate.

Percentage Moisture Loss: This study was performed to determine the physical stability and integrity of the film by weighing the cut films (2 x2 cm). These films were stored for 72 hours in a desiccator (containing fused anhydrous calcium chloride) and then weighed to measure the percentage moisture loss of films using the formula:

Percent moisture loss = (Initial weight - Final weight) × 100 / Initial weight

***In-vitro* Drug Dissolution Studies:** Dissolution is the quantity of the drug substance which goes into the solution per unit time under standard common conditions of liquid/solid interface, temperature, and solvent concentration.

The USP type II apparatus (paddle) was used for dissolution testing. The dissolution medium, phosphate buffer pH 6.8 maintained at 37± 0.5ºC at 50 rpm was used to study the dissolution of the API from the film.

X-Ray Diffraction: This was performed using an X-ray powder diffractometer to study the drug's and film's crystalline behavior. The study involved subjecting the drug to X-ray diffraction analysis, and XRD patterns were reported over the 2θ range at a scanning rate of 10°/min.

Scanning Electron Microscopy (SEM): Scanning electron microscopy was used to study the surface morphology of film consisting of drug and excipients.

***Ex-vivo* Permeation Study:** Franz diffusion cell was used for the *ex-vivo* permeation study of the film (2x2cm) using a membrane of oral sheep mucosa collected from the slaughterhouse. Phosphate buffer pH 6.8 was used as a diffusion medium in the receptor compartment maintained at 37±0.5ºC. The film was fixed on the sheep oral mucosa membrane at mid of the receptor and donor compartment. Further, aliquots of 1ml were collected at 2, 4,6,8,10,12 and 14 min. To maintain the volume of the diffusion medium, 1 ml of phosphate buffer pH 6.8 was added every time a sample was collected. Collected aliquots were filtered and analyzed by a double beam UV visible spectrophotometer at 236 nm against a blank.

Stability Studies: Stability studies for the film of Risperidone were carried out at room temperature for 90 days. Samples were collected on 0, 30, 60, and 90 days and analyzed based on appearance, folding endurance, disintegration time, and tensile strength.

RESULTS AND DISCUSSION:

Preformulation Studies:

Physical Characterization of Risperidone:

TABLE 6: PHYSICAL CHARACTERIZATION OF RISPERIDONE

Sr. no.	Test	Observation
1	Color	White Powder
2	Odor	Odorless
3	Surface Nature	Crystalline

Solubility Analysis:

TABLE 7: SOLUBILITY ANALYSIS

Sr. no.	ingredients	Solubility (µg/ml)
1	water	30
2	Phosphate buffer	106
3	Methanol	203
4	Solid dispersion+water	144

Melting Point:

TABLE 8: MELTING POINT DETERMINATION

Sr. no.	Reported Melting Point	Observed Melting Point (ºC)	Mean
1.		171	172
2.	170-172	172	
3.		172	

Identification by FTIR: Drug was characterized by FTIR spectroscopy, and the spectrum was recorded using FTIR Spectrophotometer. The spectrum of Risperidone is shown in **Fig. 2** with a scanning range of 4000 to 500 cm^{-1}.

The FTIR spectrum of Risperidone showed major peaks at 2943.37 and 2743.37cm^{-1} (C-H stretch), 1643.35 cm^{-1} and 1612.49 cm^{-1} (C=C stretch) and 1130 cm^{-1} (C-F stretch).

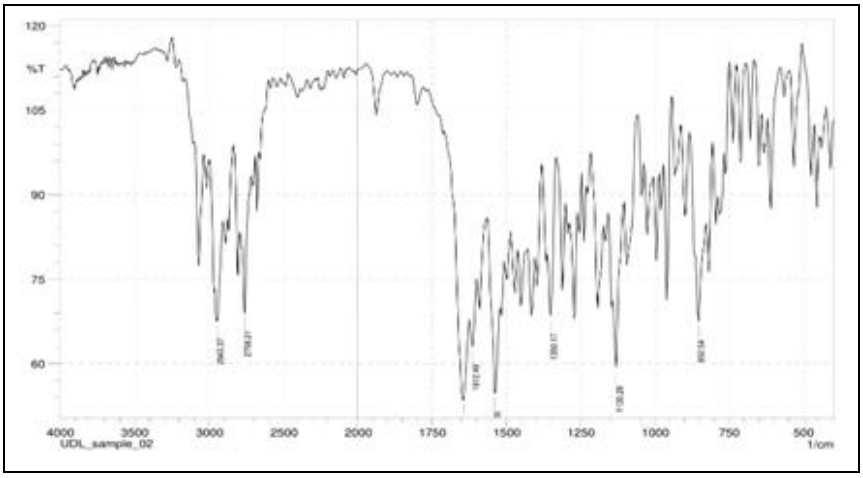

FIG. 2: FTIR OF RISPERIDONE

Compatibility Studies: Compatibility study was done by FTIR Analysis of drug with PEG 4000 and HPMC E5. No incompatibility was found between the drug and the excipients as shown in **Fig. 3, 4.**

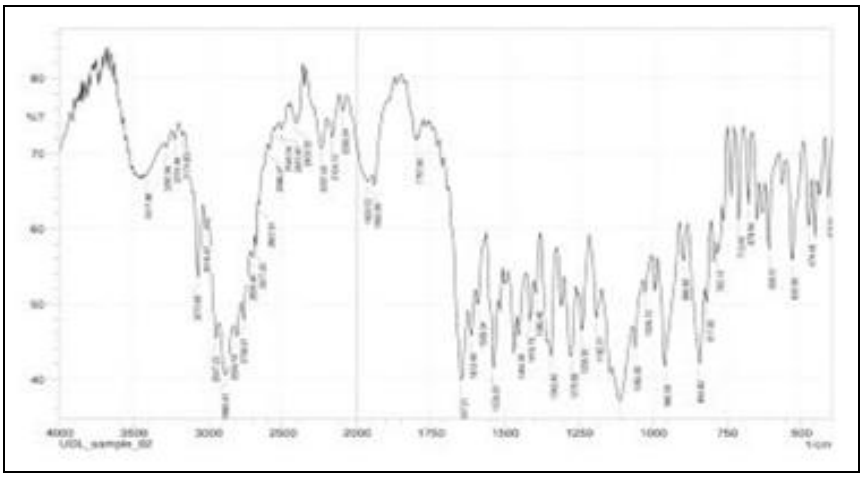

FIG. 3: FTIR OF DRUG AND PEG4000

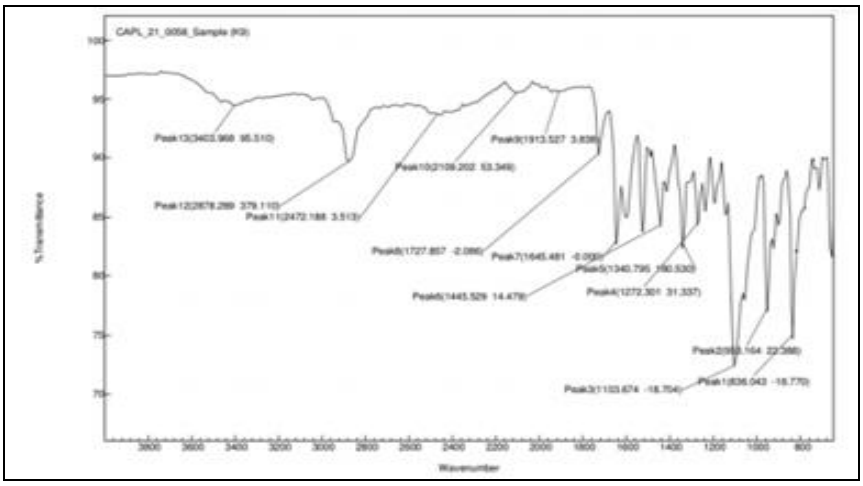

FIG. 4: FTIR OF DRUG AND HPMC E5

Evaluation of Solid Dispersion:

Differential Scanning Calorimetry (DSC) Analysis: DSC thermogram of Risperidone showed a prominent endothermic peak at 171.12ºC. The high intensity of peak reveals the highly crystalline nature of the drug as shown in **Fig. 5.** DSC thermogram of SD1 showed an endothermic peak at 164.31ºC in comparison with the thermogram of pure drug as shown in **Fig. 6**. Thus, it indicates the depression in crystalline nature of Risperidone.

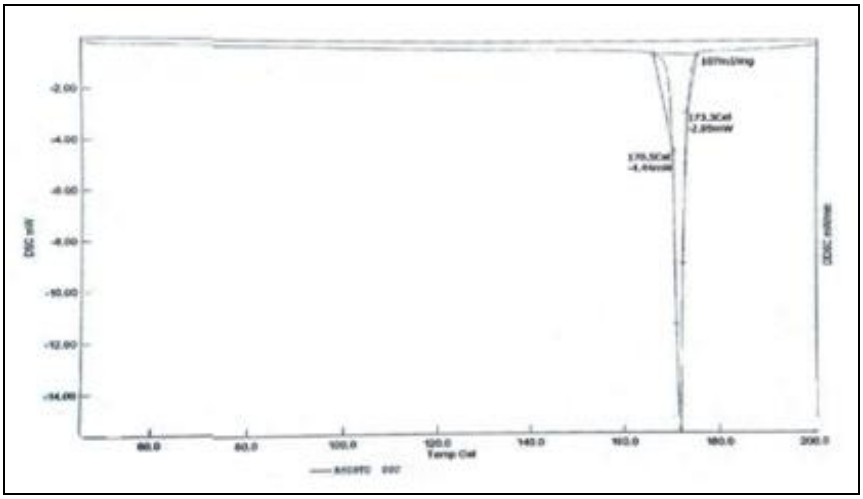

FIG. 5: DSC THERMOGRAM OF RISPERIDONE

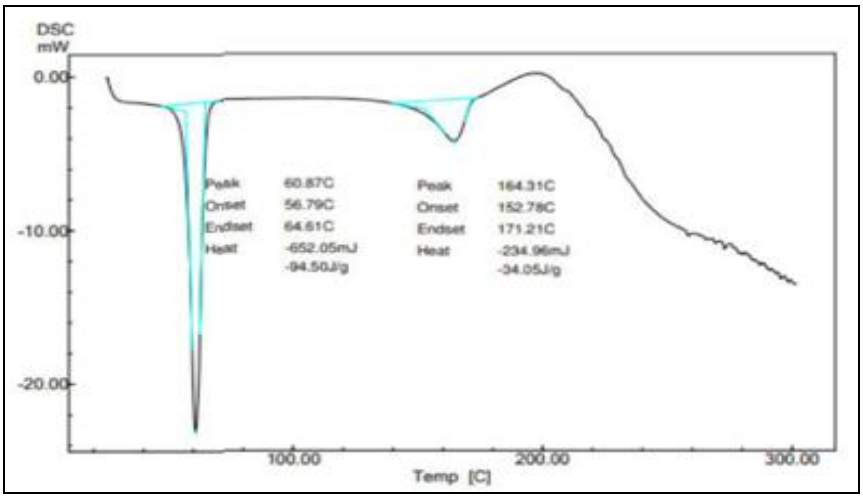

FIG. 6: DSC THERMOGRAM OF SD1

Percent Yield: The calculated data of percent practical yield of SDPs of drugs prepared by physical mixture and solvent evaporation are shown in **Table 9** and **10.** It showed an increased yield for SDPs prepared by a solvent evaporation method using drug and PEG 4000 in the ratio of 1:1.

TABLE 9: RESULTS OF PERCENT YIELD OF PHYSICAL MIXTURE (N=3)

Physical Mixture					
Polymer	**Ratio**	**Percent Yield (%)**			**Mean±S.D**
		1	2	3	
PEG4000	1:1	95.84	94.23	95.12	95.06±0.8064
	1:2	92.45	93.12	92.12	92.56±0.5095
	1:3	94.23	94.12	93.67	94.00±0.2967
PVPK30	1:1	87.34	90.01	89.56	88.97±1.4294
	1:2	89.23	88.02	89.45	88.9±0.77
	1:3	90.21	91.54	90.65	90.8±0.6775

TABLE 10: RESULTS OF PERCENT YIELD OF SOLVENT EVAPORATION METHOD (N=3)

Solvent Evaporation Method					
Polymer	**Ratio**	**Percent Yield (%)**			**Mean±S.D**
		1	**2**	**3**	
PEG4000	1:1	97.43	96.84	97.34	97.20±0.3178
	1:2	93.12	94.76	92.58	93.48±1.1353
	1:3	95.40	96.00	95.34	95.58±0.3649
PVPK30	1:1	91.32	90.49	89.56	90.45±0.8804
	1:2	92.12	91.87	92.65	92.21±0.3982
	1:3	94.87	94.37	94.88	94.70±0.2916

Percent Drug Content: The percent drug content for SDP of the drug is shown in **Tables 11** and **12.** The drug content of the prepared solid dispersions was found to be in the range which meets the criteria of United States Pharmacopeia content uniformity (98-102%). The results indicated that applying the solvent evaporation method was the best method for preparing solid dispersions with high content uniformity.

TABLE 11: RESULTS OF DRUG CONTENT OF PHYSICAL MIXTURE (N=3)

Physical Mixture					
Polymer	**Ratio**	**Drug Content (%)**			**Mean±S.D**
		1	**1**	**3**	
PEG4000	1:1	100.00	100.00	101.23	100.26±0.8655
	1:2	97.47	97.47	98.23	98.05±0.5141
	1:3	99.45	99.45	99.22	99.55±0.3897
PVPK30	1:1	97.99	97.99	98.87	98.40±0.4430
	1:2	98.56	98.56	99.61	99.13±0.5316
	1:3	99.11	99.11	100.11	99.33±0.6925

TABLE 12: RESULTS OF DRUG CONTENT OF SOLVENT EVAPORATION METHOD (N=3)

Solvent Evaporation Method					
Polymer	**Ratio**	**Drug Content (%)**			**Mean±S.D**
		1	**1**	**3**	
PEG4000	1:1	102.45	101.00	103.98	102.47±1.4901
	1:2	99.45	100.78	99.99	100.07±0.6689
	1:3	101.04	102.00	101.12	101.38±0.5326
PVPK30	1:1	98.03	98.81	97.95	98.26±0.4751
	1:2	99.78	98.99	100.05	99.60±0.5508
	1:3	100.23	101.34	99.56	100.37±0.8990

***In–vitro* Dissolution Studies:** SDPs were prepared successfully using a physical mixture and solvent evaporation method to determine the perfect combination with respect to increasing the drug dissolution characteristics of the drug in comparison with its pure form. Results revealed a maximum increase in the drug dissolution using both the methods for a drug: polymer ratio of 1:1 as compared to 1:2 & 1:3. Studies also revealed that the SDPs prepared with the solvent evaporation method showed a significant increase in the drug dissolution as compared to the physical mixing and pure form of the drug. Thus, SDPs prepared with a drug to polymer ratio of 1:1 using solvent evaporation method were found to be the best and selected for further studies and characterization. **Fig. 7** and **Fig. 8** show drug release profiles of Risperidone Physical Mixture and Drug release profiles of Solid Dispersion, respectively.

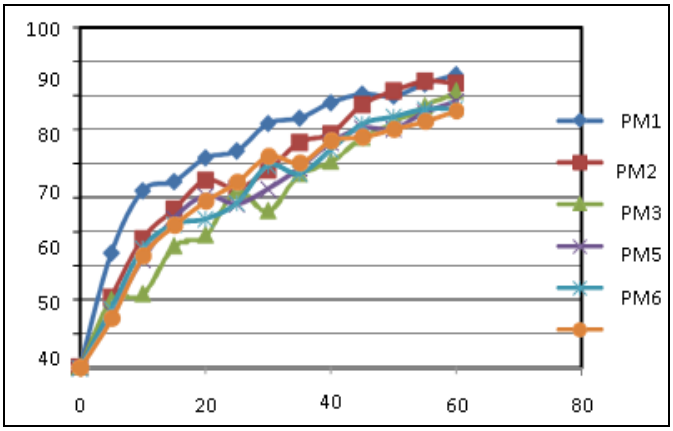

FIG. 7: DRUG RELEASE PROFILES OF RISPERIDONE PHYSICAL MIXTURE

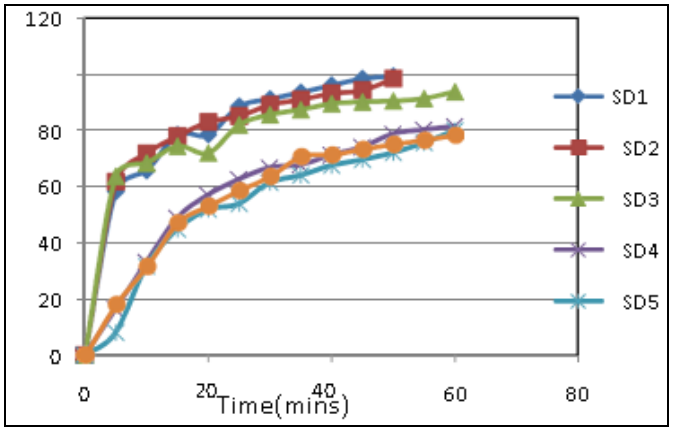

FIG. 8: DRUG RELEASE PROFILES OF SOLID DISPERSIONS

Scanning Electron Microscopy (SEM): SEM image of the selected solid dispersion drug is shown in **Fig. 9**, thus confirming its amorphous nature.

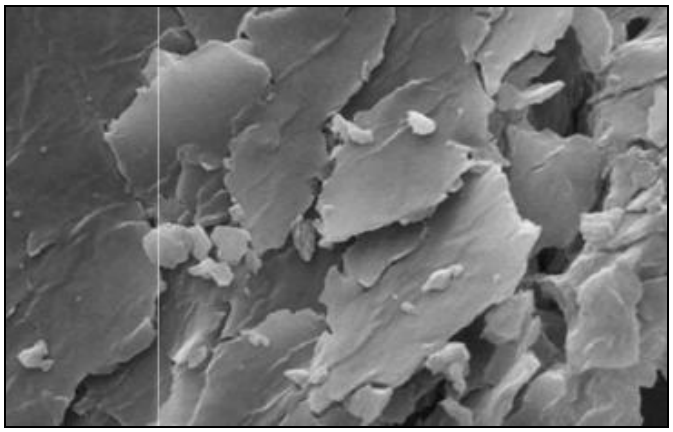

FIG. 9: SEM OF SD1

Variables Affecting the Dissolution Profile:

Effect of Solid Dispersion Formation: Fig. 10 shows the effect of solid dispersion formation on the release of Risperidone. It was seen that the release of Risperidone increased significantly when it was formulated as a solid dispersion. 99.06% of the drug was released from the solid dispersion at 50 minutes compared with 65.10% of drug release in 60 min when it is found in free form.

The increased dissolution rate from solid dispersion may be due to a reduction in particle size to the molecular level when the carrier brings the drug into the dissolution medium. PEG 4000 also helped by providing a large surface area for dissolution by preventing the aggregation of finer drug particles. Adding a carrier polymer also inhibits the drug's crystal growth, which facilitates faster dissolution.

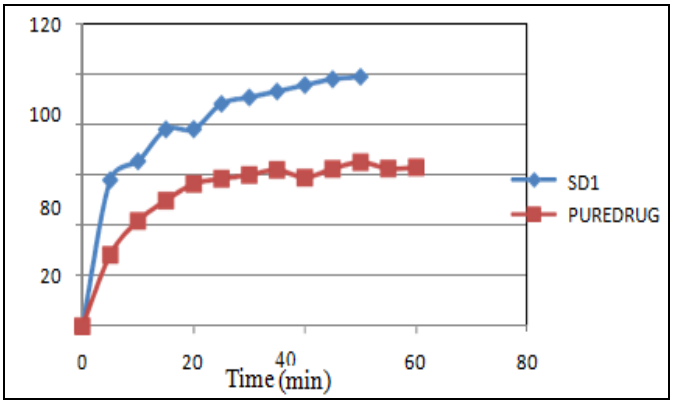

FIG. 10: THE EFFECT OF SOLID DISPERSION FORMATION ON THE RELEASE PROFILE

Effect of Polymer Type: Formulations SD1 and SD4 were used to study the effect of polymer type on the release of drug from solid dispersion where PEG4000 and PVP K30 were used in SD1and SD4, respectively in the ratio 1:1. It was observed that 99.03% of drug was released from SD1 at 50 min where as 81.32% drug was released from SD4 at 60 min. From the results, the release of drug from solid dispersion containing PEG4000 was found to be greater as compared to solid dispersion, which had PVP K30; this may be because of the more water soluble and hydrophilic nature of PEG4000.

Comparison between Physical Mixture and Solvent Evaporation Method: Fig. 11 compares a physical mixture and solvent evaporation method. It was observed that 86.04% of the drug was released at 60 min from solid dispersion PM1 made as a physical mixture, whereas 99.03% drug was released at 60 min from solid dispersion SD1 made by a solvent evaporation method. The results concluded that more drug release was from solid dispersion made by solvent evaporation method than a physical mixture.

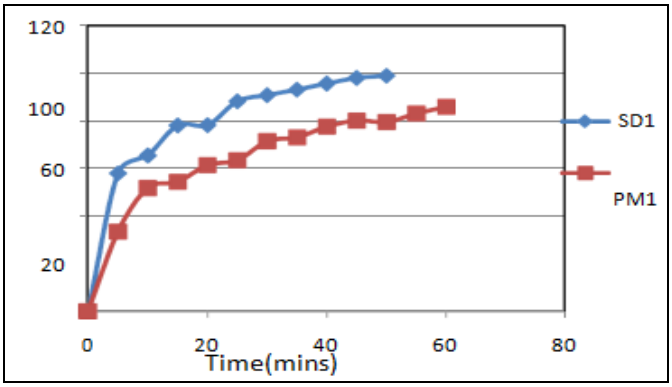

FIG 11: COMPARISON BET WEEN PHYSICAL MIXTURE AND SOLVENT EVAPORATION METHOD

Formulation development of fast dissolving oral films (FDBFs):

Preliminary Selection of Formulation Additives:

Selection of Suitable Method of Preparation: The solvent casting method was chosen, as the films prepared by the solvent casting method showed good physical appearance and better mechanical strength properties. In the solvent casting method, the solution of the drug, film forming agent and other excipients was prepared, followed by casting of solution on a petri plate.

Selection of the Suitable Film-forming agent: Among the different film forming agents, such as HPMC (E3, E5& E15) used to prepare blank films, HPMC-E5 was selected as the most preferred film-forming agent.

Blank FDBFs which were prepared by using HPMC E5 had shown better physical appearance, optimum mechanical strength and fast disintegrating profile.

Selection of the Suitable Plasticizer: Based on the preliminary observations, PEG 400 was found to be a comparatively suitable plasticizer because it produced films with good flexibility and optimum plasticity in the normal concentration range as compared to others.

Selection of the Disintegrating agent – Preliminary, two disintegrating agents, Croscarmellose and SSG were used to prepare the blank FDBFs. Croscarmellose was found to be suitable out of the two because it produced films that underwent disintegration rapidly compared to others.

Formulation of FDBFs Containing SDPs of Risperidone: Films containing selected SDP were separately prepared by using the solvent casting method with selected formulation additives. Each FDBF contained SDP of the equivalent of 4mg of Risperidone. The casting solution was prepared in distilled water without the use of organic solvent and was casted on a fabricated glass mould to yield films (2cm x 2cm).

Optimization of FDBFs using Quality by Design (QbD) Technique: The CQAs of Risperidone FDBF were investigated using the QbD approach. The prime considerations were given to those parameters which significantly influence the quality of film formulation. Accordingly, the CQAs of fast dissolving buccal film of Risperidone which was identified, include tensile strength, folding endurance and disintegration time. Box Behnken was used as a screening design to determine the impact of each independent variable on selected respective responses. Quality Target Product Profile QTPP was utilized to identify critical quality attributes and desired dosage form of Risperidone (FDBF). Risperidone FDBF was developed to manage and treat hypertension or high blood pressure. QTPP of Risperidone involves safe and effective administration of the film that helps in fast drug action and improves patient compliance. The method used to prepare FDBFs was powerful and could be easily reproduced; hence product meets the critical quality attributes. **Table 13** enlists the QTPP with justifications for their selection.

TABLE 13: QUALITY TARGET PRODUCT PROFILE (QTPP) EARMARKED FOR FAST DISSOLVING BUCCAL ORAL FILM OF RISPERIDONE

QTPP	Target	Justification
Dosage form	Buccal Film	Pharmaceutical requirement; equivalence same dosage form
Route of administration	Buccal Cavity	Recommended route for drug delivery of Risperidone to enhance *in-vitro* drug dissolution and by pass the first pass metabolism
Dosage strength	4mg	Unit dose of Risperidone incorporated into a single formulation of FDBF
Dosage Type	Fast dissolving buccal film (FDBF)	Faster onset of action leading to increased therapeutic efficacy.
Packaging	Polyethylene strip	Same pack aging according to pharmaceutical requirement
Stability	At least 90 days at room temperature	To maintain therapeutic efficacy of the drug during stipulated storage time period
Alternative routes of administration	None	Alternative method of administration not present

Construction of Ishikawa Diagram the Ishikawa diagram was constructed to structure the risk analysis operation to determine the causes and sub-causes affecting the CQAs.

A process of risk assessment was performed to identify high-risk factors which may have an effect on the CQAs of films; it comprises critical materials attributes (CMA's) and CPPs.

Fig. 1 illustrates Ishikawa (fish-bone) diagram for Risperidone FDBFs. Risk assessment studies concluded that, among the several processes and parameters set for formulation screened, the following parameters such as concentration of polymer (A), the concentration of plasticizer (B) and concentration of super disintegrant (C) were reported to be critical due to high risk which was associated on the final CQA's like Folding Endurance (R1), Disintegration time (R2) and Tensile Strength (R3).

Further, in the preparation of fast dissolving, Risperidone film solvent-casting method was employed without the usage of any sophisticated instrument/equipment in the laboratory; hence no such parameters related to the process were known to have a pronounced effect on the formulation during all experimentation run. Citric acid used as a saliva stimulating agent at a concentration of 2% showed negligible risk. Design of Experiments Formulation of Risperidone FDFs was separately optimized by using Box Behnken design (response surface methodology) by applying software Design-Expert® -13.

A total of 17 trials for each experimental design were run in a randomized fashion to avoid chances of bias. The effect of different levels (low, medium, and high) of independent variables (concentration of polymer HPMC-E5 (A), concentration of PEG 400 (B), and concentration of super disintegrant Croscarmellose (C)) on the response variable (Folding Endurance (R1), Disintegration time (R2) and Tensile Strength (R3)) were investigated. Further, the experimental design of Box-Behnken was analyzed for various models like quadratic, linear, 2FI, and mean to find out the best fit model on the basis of responses of the dependent variables.

The effects of independent variables over the response or dependent variables are shown in **Table 14**. Further, statistical validity was performed using the ANOVA test to create linear equations, R2, adjusted R2, predicted R2, standard deviation, and % coefficient of variance.

TABLE 14: EFFECTS OF INDEPENDENT VARIABLE SON RESPONSE VARIABLES FOR FDBFS

Batch No.	Independent variables			Response Variables		
	(A)%	(B)%	(C)%	(no.)	(Sec)	(Kg/mm^2)
R1	45	17.5	1	140	29	2.67
R2	50	20	1	165	33	3.57
R3	50	15	1	150	39	3.3
R4	55	17.5	1	179	45	3.79
R5	45	20	3	146	25	2.88
R6	45	15	3	135	32	2.52
R7	50	17.5	3	155	36	3.41
R8	50	17.5	3	156	36	3.43
R9	50	17.5	3	158	37	3.49
R10	50	17.5	3	156	37	3.48
R11	50	17.5	3	157	37	3.45
R12	55	20	3	189	47	3.91
R13	55	15	3	171	50	3.69
R14	45	17.5	5	142	27	2.6
R15	50	20	5	167	34	3.5
R16	50	15	5	149	37	3.33
R17	55	17.5	5	177	45	3.75

Various graphical plots such as probability plot, interaction plot, contour plot, 3D response surface plot, and cube plot were prepared and studied separately for each response variable using Design-Expert® -13, and out of that 3D surface plot and cube plot were selected to describe further the effects of independent variables over the dependent variables.

Effects of Independent Variables on Folding Endurance (R1): The effects of independent variables (A, B, & C) on the folding endurance (R1) were determined and recorded in the form of 3D surface plots and cube plots, as shown in **Fig. 12** & **13** and **14** respectively. In a polynomial equation, positive sign indicates a synergistic effect and a negative sign indicates an antagonistic effect.

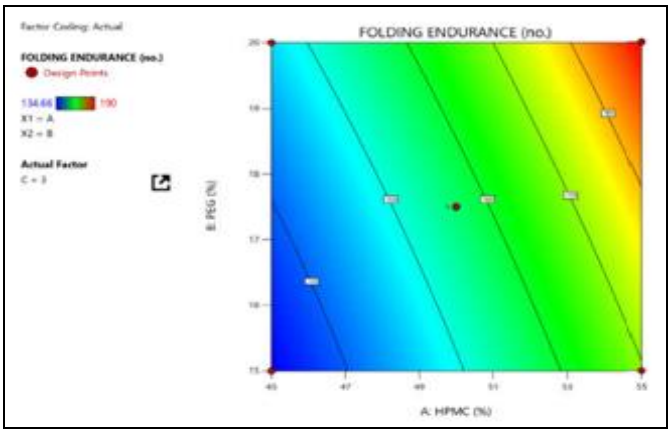

FIG. 12: CONTOUR PLOT FOR FOLDING ENDURANCE

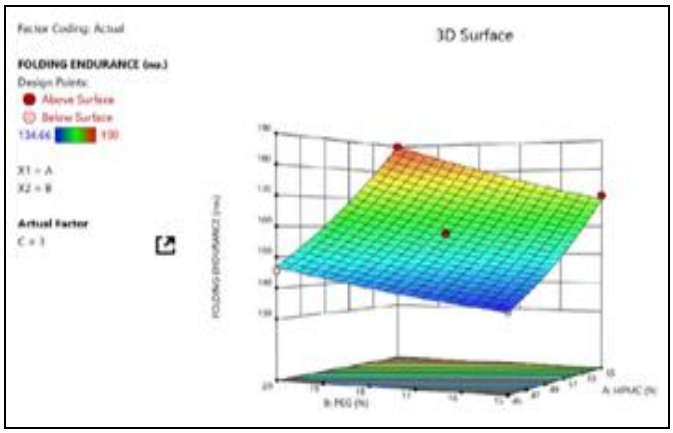

FIG. 13: 3D SURFACE PLOT OF EFFECT OF A & BON FOLDING ENDURANCE

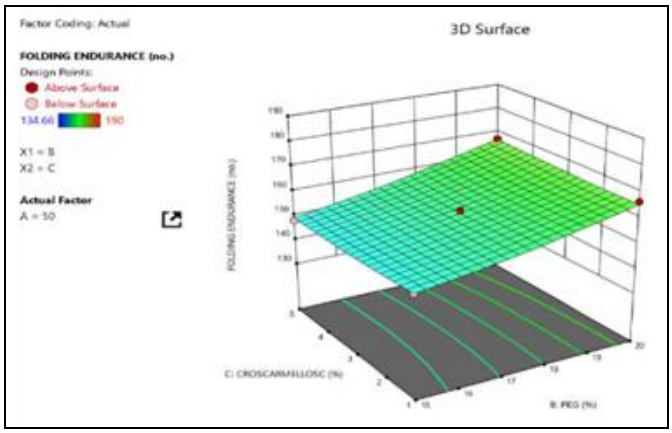

FIG. 14: 3DSURFACEPLOT OF EFFECT OF B &C ON FOLDING ENDURANCE

The polynomial equation for folding endurance is: 156.40 +19.13 * A +7.75 * B +0.1250 * C +1.75 * AB -1.00 * AC +0.7500 * BC +2.80 *A2 +1.05* B2 +0.3000 *C2.

Results indicated an increased value of folding endurance with an increase in the concentration of both HPMC-E5 and PEG 400, indicating that the optimum combination of the polymer and plasticizer significantly influences the folding endurance.

Croscarmellose had not shown any significant variation over the folding endurance of the FDBFs.

The optimized values of folding endurance were found to be 155.514 times indicating an improved mechanical strength and good flexibility of the FDBFs at higher concentrations of HPMC-E5 and PEG 400. The statistical data of regression analysis and ANOVA test for folding endurance (R1) are shown in **Table 15**.

The Predicted R^2 of 0.9735 and the Adjusted R^2 of 0.9931 were found to be in reasonable agreement with each other; i.e., the difference was less than 0.2.

The adequate precision that measures signal to noise ratio was 57.358. A ratio greater than 4 is desired; hence a quadratic model can be used to navigate the design space.

TABLE 15: REGRESSION ANALYSIS OF QUADRATIC MODEL FOR FOLDING ENDURANCE

Std. Dev.	1.22	R^2	0.9970
Mean	158.35	Adjusted R^2	0.9931
C.V.%	0.7716	Predicted R^2	0.9735
		Adequate Precision	57.3580

Effects of Independent Variables on Disintegration Time (R2): The effects of independent variables (A, B & C) on the disintegration time (R2) were determined for FDBF and recorded in the form of 3D surface plots and cube plots as shown in **Fig. 15** & **16** and **17** respectively. In a polynomial equation, positive sign indicates a synergistic effect, and a negative sign indicates an antagonistic effect.

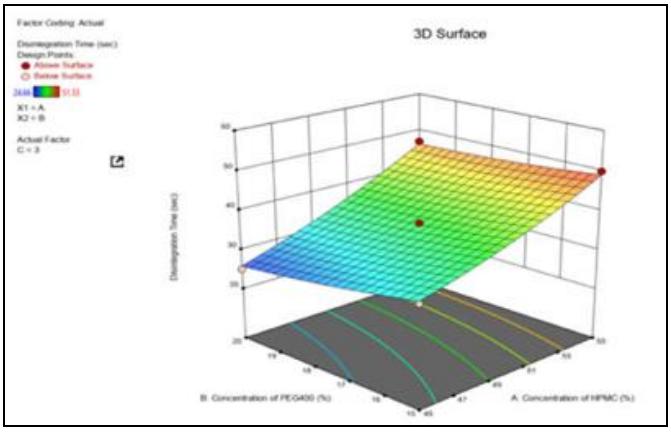

FIG. 15: 3DSURFACEPLOT OF EFFECT OF A & BO DISINTEGRATION TIME

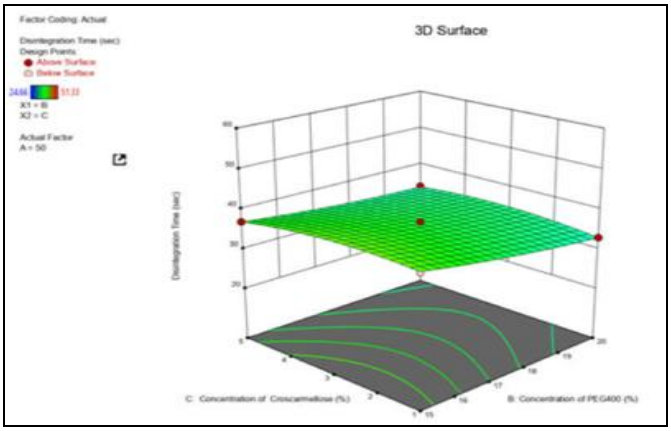

FIG. 16: 3DSURFACE PLOT OF EFFECT OF B & C ON DISINTEGRATION TIME

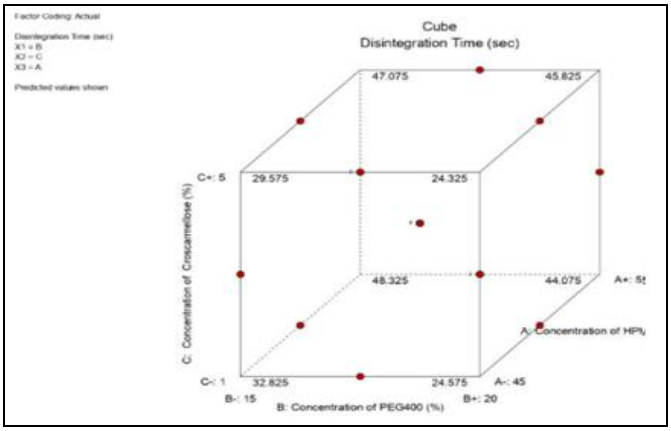

FIG. 17: CUBE PLOT OF EFFECT ON A, B & C ON DISINTEGRATION TIME

The polynomial equation for disintegration time is: +36.60+9.25* A-2.37*B 7.3750* C+1.0000* AB+0.5000* AC+0.7500* BC+1.32* A^2+0.5750* B^2- 1.42* C^2.

Results indicated a decrease in disintegration time with an increase in the concentration of Croscarmellose and PEG 400, while an increase in disintegration time with increase in the concentration of HPMC-E5.

Generally, an increase in the disintegration time is seen with increase in the concentration of a polymer. However, HPMC-E5 being a hydrophilic polymer in combination with PEG 400 does not show a prominent effect on disintegration time. The optimized disintegration time value was 33.0142 seconds, indicating the fast disintegration of the FDBFs at higher concentrations of Croscarmellose and PEG 400. The statistical data of regression analysis for disintegration time (R2) is shown in **Table 16.**

The Predicted R^2 of 0.9976 and the Adjusted R^2 of 0.9821 were in reasonable agreement with each other, i.e.; the difference was less than 0.2. The Adequate Precision was found to be 32.88; hence a Quadratic model can be used to navigate the design space.

TABLE 16: REGRESSION ANALYSIS OF QUADRATIC MODEL FOR DISINTEGRATION TIME

Std. Dev.	0.9220	**R^2**	0.9922
Mean	36.82	Adjusted R^2	0.9821
C.V.%	2.50	Predicted R^2	0.9976
		Adequate Precision	32.8805

Effects of Independent Variables on Tensile Strength (R3): The effects of independent variables (A, B, & C) on the tensile strength (R3) were determined separately and recorded in the form of 3D surface plots and cube plots, as shown in **Fig. 18** & **19** and **20** respectively. In a polynomial equation, a positive sign indicates a synergistic effect, and a negative sign indicates an antagonistic effect.

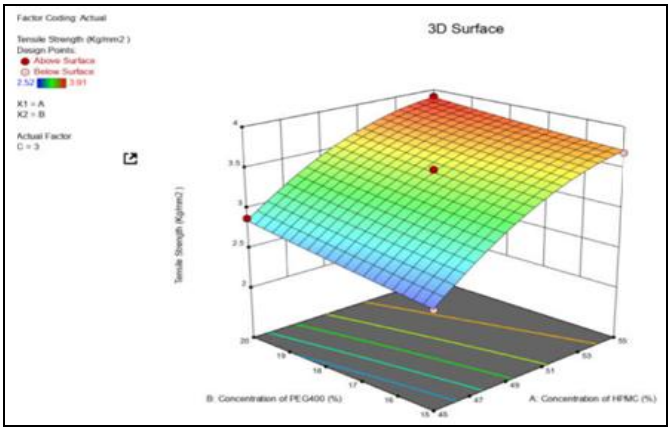

FIG. 18: 3D SURFACEPLOTOFEFFECT OF A & B ON TENSILE STRENGTH

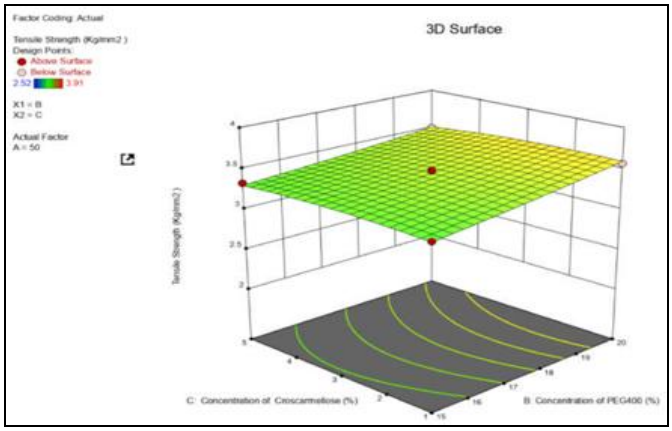

FIG. 19: 3D SURFACE PLOT OF EFFECT OF B & C ON TENSILE STRENGTH

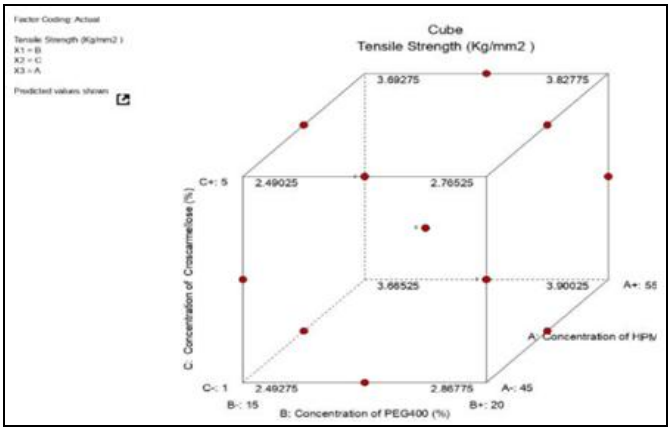

FIG. 20: CUBE PLOT OF EFFECT OF A, B, C ON TENSILE STRENGTH

The polynomial equation for tensile strength is: 3.452 + 0.55875 * A + 0.1275 * B -0.01875 * C +0.035 * AB + 0.0075 * AC -0.025 * BC - 0.21225 *A2 - 0.01025 * B2 -0.03725 * C^2.

Results suggested an increased tensile strength value with an increase in the concentration of both HPMC-E5 and PEG 400. However, the optimum combination of HPMC-E5 and propylene glycol significantly affects the tensile strength.

The change in concentration of Croscarmellose had not shown any significant variation over the tensile strength of the FDBFs, indicating the improved mechanical strength of the FDBFs at higher concentrations of HPMC-E5 and PEG 400. The statistical data of the ANOVA test for tensile strength (R3) is shown in **Table 17**. The Predicted R^2 of 0.9769 and the Adjusted R^2 of 0.9935 were in reasonable agreement with each other; i.e., the difference was less than 0.2. The Adequate Precision was found to be 52.429; hence the Quadratic model can be used to navigate the design space.

TABLE 17: REGRESSION ANALYSIS OF QUADRATIC MODEL FOR TENSILE STRENGTH

Std. Dev.	0.0341	**R^2**	0.9971
Mean	3.34	Adjusted R^2	0.9935
C.V.%	1.02	Predicted R^2	0.9769
		Adequate Precision	52.4293

The optimized values of independent and dependent or response variables were obtained based on the results and observations of formulation optimization using Box Behnken design on Design-Expert® -13. Further,

formulations of FDBFs were validated using an optimized concentration of independent variables, and validated results for Risperidone FDBFs are shown in **Table 18**. Validated values of response variables were found to be close to that of the optimized values depending on the statistical analysis. Further, the optimized formula for Risperidone FDBFs is shown in **Table 19.**

TABLE 18: VALIDATED VALUES OF INDEPENDENT VARIABLES AND RESPONSE VARIABLES FOR RISPERIDONE FDBF

Type of Variable	Variables	Optimized Value	Validated Value(n=3)
Independent	HPMC-E5: A(%w/w)	49.236	49.23
	Propylene glycol: B(%w/w)	20	20
	Croscarmellose: C(%w/w)	5.00	5.00
Response or Dependent	Folding endurance: R1 (no.)	163.776	164.41±0.8100
	Disintegration time: R2 (Seconds)	31.270	32.66±0.5773
	Tensile strength: R3 (Kg/mm^2)	3.423	3.416±0.0115

TABLE 19: OPTIMIZED FORMULA FOR RISPERIDONE FDBF (FF) BASEDON BOX-BEHNKENDESIGN

S. no.	Name of Ingredients	Quantity (for 5 films of 2cm^2)
1.	SDP (1:1) drug to polymer ratio	47.49mg (equivalent to 4mg of Risperidone)
2.	HPMC-E5	196.92mg
3.	Propylene glycol	80mg
4.	Croscarmellose	20mg
5.	Citric acid	6mg
6.	Sodium saccharin	31.5mg
7.	Distilled water	Q.S to 10ml

Evaluation of Fast Dissolving Buccal Films:

DSC Analysis: Fig. 21 shows the DSC analysis of the optimized film (FF). It is seen that the original peak of drug disappears from the thermogram of formulation, and endotherm is seen to broaden and slightly shift to a lower temperature. The absence of a Risperidone peak at 171ºC provides evidence of complete amorphization of Risperidone.

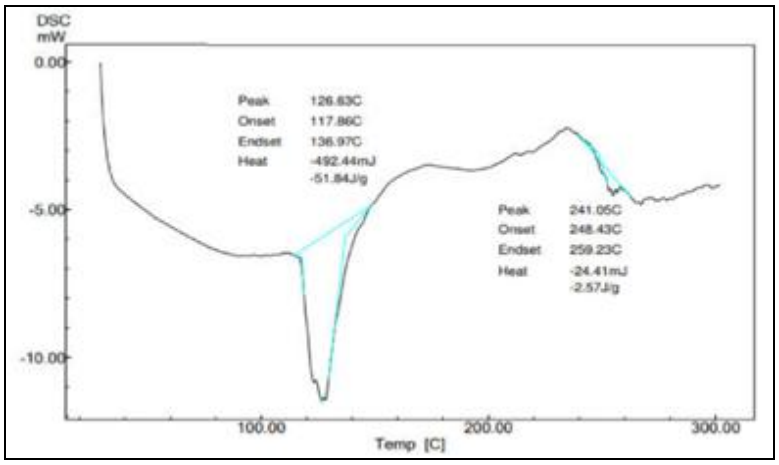

FIG. 21: DSC OF FF

Uniformity of Mass: The data for uniformity of mass of films is shown in **Table 20**. The mass of the film cut from different places was found to be uniform.

TABLE 20: DATA OF UNIFORMITY OF MASS (N=3)

Formula Code	Uniformity of mass of 2 cm^2 of film			Mean (mm) ±SD	Formula Code	Uniformity of mass of 2cm^2 of film			Mean (mm) ±SD
	Film 1	Film 2	Film 3			Film 1	Film 2	Film 3	
R1	77.74	78.33	77.89	77.98±0.3066	R10	79.53	78.30	78.21	78.68±0.7374
R2	78.18	78.45	77.99	78.20±0.2311	R11	78.69	78.50	77.98	78.39±0.3675
R3	77.56	77.98	78.45	77.99±0.4452	R12	77.71	77.91	78.31	77.97±0.3055
R4	76.99	78.23	78.45	77.89±0.7871	R13	78.45	78.30	78.40	78.38±0.0763
R5	78.23	78.36	77.99	78.19±0.1877	R14	79.11	79.01	78.68	78.93±0.2250

R6	77.65	77.78	78.42	77.95±0.4121	R15	78.48	78.57	77.97	78.34±0.3235
R7	79.02	78.48	78.12	78.54±0.4529	R16	77.79	78.34	78.47	78.2±0.3609
R8	77.80	77.98	78.34	78.04±0.2749	R17	78.43	77.89	78.58	78.3±0.3629
R9	78.40	78.38	78.56	78.44±0.0986	FF	78.60	78.56	77.95	78.37±0.3642

Thickness: The data of the determination of thickness of FDBFs are shown in **Table 21**. Results revealed an increase in the thickness of FDBF's with an increase in the concentration of HPMC-E5 and PEG 400. The thickness of the film cut from the different places was found to be uniform.

TABLE 21: DATA OF DETERMINATION OF THICKNESS (N=3)

Formula Code	Thickness of FDBFs			Mean (mm) ± SD	Formula Code	Thickness of FDBFs			Mean (mm) ± SD
	Film 1	Film 2	Film 3			Film 1	Film 2	Film 3	
R1	0.11	0.10	0.09	0.10±0.01	R10	0.13	0.11	0.11	0.11±0.0115
R2	0.11	0.13	0.11	0.11±0.0115	R11	0.11	0.11	0.12	0.11±0.0057
R3	0.12	0.11	0.11	0.11±0.0057	R12	0.15	0.16	0.15	0.15±0.0057
R4	0.16	0.15	0.16	0.15±0.0057	R13	0.14	0.16	0.15	0.15±0.01
R5	0.09	0.11	0.11	0.10±0.0141	R14	0.09	0.09	0.11	0.09±0.0115
R6	0.11	0.10	0.10	0.10±0.0057	R15	0.13	0.11	0.11	0.11±0.0115
R7	0.12	0.12	0.13	0.12±0.0057	R16	0.11	0.11	0.12	0.11±0.0057
R8	0.11	0.11	0.11	0.11±0	R17	0.15	0.15	0.15	0.15±0
R9	0.12	0.13	0.12	0.12±0.0057	FF	0.12	0.11	0.11	0.11±0.0057

Percent Drug Content: The data for determining the percent drug content of FDBFs are shown in **Table 22**. Overall results suggested the good uniformity of content in the FDBFs.

TABLE 22: DATA OF DETERMINATION OF PERCENT DRUG CONTENT (N=3)

Formula Code	Percent drug content of FDBFs			Mean (mm) ± SD	Formula Code	Percent drug content of FDBFs			Mean (mm) ± SD
	Film 1	Film 2	Film 3			Film 1	Film 2	Film 3	
R1	98.45	98.99	99.34	98.92±0.4483	R10	100.01	100.34	100.40	100.25±0.21
R2	99.23	100.11	99.22	99.52±0.5109	R11	99.78	99.23	99.12	99.37±0.3536
R3	98.56	100.78	100.71	100.01±1.2619	R12	98.77	100.02	99.81	99.53±0.6693
R4	101.79	100.58	100.81	101.06±0.6425	R13	100.36	101.81	101.90	101.35±0.8643
R5	99.23	99.78	99.98	99.66±0.3883	R14	99.61	99.77	100.92	100.1±0.7146
R6	100.10	99.81	99.02	99.64±0.5589	R15	101.29	100.89	101.76	101.31±0.4354
R7	101.89	100.06	100.59	100.84±0.9416	R16	99.96	100.67	99.45	100.02±0.6127
R8	99.39	99.71	98.19	99.09±0.8013	R17	101.65	99.85	100.79	100.76±0.9002
R9	98.81	99.98	99.12	99.30±0.6061	FF	99.45	100.67	100.80	100.30±0.7447

Folding Endurance: The data of determination of folding endurance of FDBFs are shown in **Table 23**. Results suggested an increased value of folding endurance on increasing the concentration of HPMC-E5 and PEG 400.

TABLE 23: DATA OF DETERMINATION OF FOLDING ENDURANCE (N=3)

Formula Code	Folding endurance of FDBFs			Mean (mm)±SD	Formula Code	Folding endurance of FDBFs			Mean(mm)±SD
	Film 1	Film 2	Film 3			Film 1	Film 2	Film 3	
R1	140	138	141	139.66±1.5275	R10	156	155	158	156.33±1.5275
R2	165	168	166	166.33±1.5275	R11	159	156	157	157.33±1.5275
R3	149	151	151	150.33±1.1547	R12	191	190	189	190±1
R4	177	180	179	178.66±1.5275	R13	170	172	170	170.66±1.1547
R5	145	146	146	145.66±0.5773	R14	142	143	141	142±1.0
R6	134	136	134	134.66±1.1547	R15	167	167	167	167±0
R7	153	156	155	154.66±1.5275	R16	149	148	147	148±1.0
R8	156	154	158	156±2	R17	177	179	180	178.66±1.5275
R9	157	158	158	157.66±0.5773	FF	164.40	165.23	163.61	164.41±0.8100

Surface pH: The data for determining the surface pH of FDBFs are shown in **Table 24**. Results of the study indicated an almost neutral pH of the FDBFs, which revealed no chances of irritation to the oral mucosa after its administration.

TABLE 24: DATA OF DETERMINATION OF SURFACE pH (N=3)

Formula Code	Surface pH of FDBFs			Mean (mm) ±SD	Formula Code	Surface pH of FDBFs			Mean (mm) ±SD
	Film 1	Film 2	Film 3			Film 1	Film 2	Film 3	
R1	6.78	6.65	6.69	6.70±0.0665	R10	6.76	6.80	6.78	6.78±0.02
R2	6.66	6.80	6.74	6.73±0.0702	R11	6.67	6.76	6.78	6.73±0.0585
R3	6.77	6.73	6.65	6.71±0.0611	R12	6.79	6.68	6.76	6.74±0.0568
R4	6.63	6.78	6.72	6.71±0.0754	R13	6.71	6.78	6.65	6.71±0.0650
R5	6.74	6.71	6.66	6.70±0.0404	R14	6.76	6.65	6.78	6.73±0.07
R6	6.67	6.75	6.69	6.70±0.0416	R15	6.80	6.68	6.74	6.74±0.06
R7	6.79	6.73	6.76	6.76±0.03	R16	6.76	6.75	6.64	6.71±0.0665
R8	6.66	6.78	6.69	6.71±0.06245	R17	6.69	6.70	6.78	6.72±0.0493
R9	6.72	6.78	6.65	6.71±0.0650	FF	6.69	6.70	6.70	6.69±0.0577

Tensile Strength: The data for determining tensile strength of FDBFs are shown in **Table 25.** Results showed a significant increase in the value of tensile strength with an increase in the concentration of HPMC-E5 and PEG 400. It also revealed the good mechanical strength of FDBFs against rupture and breaks.

TABLE 25: DATA OF DETERMINATION OF TENSILE STRENGTH (N=3)

Formula Code	Tensile strength of FDBFs			Mean (mm) ± SD	Formula Code	Tensile strength of FDBFs			Mean (mm) ± SD
	Film 1	Film 2	Film 3			Film 1	Film 2	Film 3	
R1	2.70	2.69	2.64	2.67±0.0321	R10	3.47	3.53	3.46	3.486±0.0378
R2	3.54	3.60	3.59	3.57±0.0321	R11	3.43	3.5	3.44	3.456±0.0378
R3	3.32	3.29	3.29	3.3±0.0173	R12	3.9	3.89	3.94	3.91±0.0264
R4	3.8	3.78	3.81	3.796±0.0152	R13	3.7	3.68	3.71	3.696±0.0152
R5	2.91	2.89	2.87	2.88±0.02	R14	2.62	2.59	2.59	2.6±0.0173
R6	2.52	2.54	2.51	2.523±0.0152	R15	3.49	3.54	3.51	3.513±0.0251
R7	3.4	3.39	3.44	3.41±0.0264	R16	3.32	3.32	3.35	3.33±0.0173
R8	3.42	3.42	3.45	3.43±0.0173	R17	3.76	3.74	3.77	3.75±0.0152
R9	3.46	3.52	3.5	3.493±0.0305	FF	3.43	3.41	3.41	3.41±0.0115

Percent Elongation: The data of determination of percent elongation of FDBFs are shown in **Table 26**. Results suggested the increase in the mechanical strength of FDBFs with increasing the concentration of HPMC-E5 and PEG 400.

TABLE 26: DATA OF DETERMINATION OF PERCENT ELONGATION (N=3)

Formula Code	Percent elongation of FDBFs			Mean(mm) ± SD	Formula Code	Percent elongation of FDBFs			Mean (mm) ± SD
	Film 1	Film 2	Film 3			Film 1	Film 2	Film 3	
R1	12.13	12.18	12.22	12.17±0.0450	R10	15.99	16.23	16.11	16.11±0.12
R2	16.33	16.14	16.32	16.26±0.1069	R11	16.23	16.34	16.22	16.26±0.0665
R3	16.42	16.31	16.41	16.38±0.0608	R12	18.34	18.23	18.40	18.32±0.0862
R4	19.55	19.23	18.78	19.18±0.3868	R13	19.33	19.11	19.39	19.27±0.1474
R5	11.89	11.99	11.90	11.92±0.0550	R14	12.08	12.20	2.17	12.15±0.0624
R6	12.10	12.03	12.11	12.08±0.0435	R15	16.36	16.41	16.44	16.40±0.0404
R7	15.89	17.13	17.25	16.75±0.7522	R16	12.04	12.14	12.14	12.10±0.0577
R8	16.22	16.43	16.12	16.25±0.1582	R17	19.45	19.36	18.97	19.26±0.2551
R9	16.56	16.45	16.33	16.44±0.1150	FF	16.25	16.38	16.19	16.27±0.0971

Disintegration time: The data of the determination of disintegration time study of FDBFs are shown in **Table 27**. Results showed a significant decrease in disintegration time with an increase in the concentration of Croscarmellose and PEG 400.

TABLE 27: DATA OF DETERMINATION OF DISINTEGRATION TIME (N=3)

Formula Code	Disintegration of FDBFs			Mean (mm)±SD	Formula Code	Disintegration of FDBFs			Mean (mm)±SD
	Film 1	Film 2	Film 3			Film 1	Film 2	Film 3	
R1	29	28	29	28.66±0.5773	R10	37	37	37	37±0
R2	33	31	34	32.66±1.5275	R11	36	36	38	36.66±1.1547
R3	38	40	37	38.33±1.5275	R12	46	45	48	46.33±1.5275
R4	45	44	45	44.66±0.5773	R13	50	51	53	51.33±1.5275
R5	25	23	26	24.66±1.5275	R14	27	27	28	27.33±0.5773
R6	30	32	31	31±1	R15	33	32	34	33±1
R7	36	36	35	35.66±0.5773	R16	37	35	37	36.33±1.1547
R8	35	37	36	36±1	R17	45	44	46	45±1
R9	38	36	35	36.33±1.5275	FF	32	33	32	32.66±0.5773

Percent Moisture Loss: The data of the determination of percent moisture loss of FDBFs are shown in **Table 28.**

TABLE 28: DATA OF DETERMINATION OF PERCENT MOISTURE LOSS (N=3)

Formula Code	Percent moisture loss of FDBFs			Mean (mm)±SD	Formula Code	Percent moisture loss of FDBFs			Mean (mm)±SD
	Film 1	Film 2	Film 3			Film 1	Film 2	Film 3	
R1	2.34	2.39	2.31	2.34±0.040	R10	2.33	2.34	2.29	2.32±0.026
R2	2.28	2.25	2.30	2.27±0.025	R11	2.14	2.18	2.20	2.17±0.030
R3	2.45	2.37	2.40	2.40±0.040	R12	2.20	2.26	2.23	2.23±0.03
R4	2.33	2.33	2.35	2.33±0.011	R13	2.36	2.35	2.34	2.35±0.01
R5	2.41	2.39	2.43	2.41±0.02	R14	2.42	2.40	2.43	2.41±0.015
R6	2.34	2.31	2.30	2.31±0.020	R15	2.25	2.26	2.21	2.24±0.026
R7	2.22	2.24	2.26	2.24±0.02	R16	2.28	2.27	2.27	2.27±0.005
R8	2.49	2.46	2.49	2.48±0.017	R17	2.33	2.34	2.33	2.33±0.005
R9	2.50	2.48	2.50	2.49±0.011	FF	2.28	2.24	2.24	2.25±0.0230

***In-vitro* Dissolution Studies:** Overall data of determination of *in-vitro* percent drug dissolution or release studies of FDFs are shown in **Table 29, 30** & **31** and **Fig. 22**. Data of *in-vitro* percent dissolution or release studies for optimized and validated FDBFs (FF) is shown in **Table 32** and **Fig. 23**. Results showed a significant increase in percent drug dissolution with an increase in the concentration of PEG 400 and Croscarmellose. It revealed more than 95% drug dissolution up to 12 minutes and thus indicated faster and almost complete drug dissolution.

TABLE 29: *IN-VITRO* DISSOLUTION STUDIES OF R1-R6

Time (min)	Cumulative percent drug release					
	R1	R2	R3	R4	R5	R6
0	-	-	-	-	-	-
2	48.5	50	39.5	36.5	51.5	47.5
4	65.48	64.5	53.89	62.365	75.51	63.975
6	80.15	78.14	76.53	70.12	89.25	79.635
8	90.29	85.275	83.76	78.695	93.38	88.29
10	95.39	92.845	90.33	85.28	96.42	94.375
12	97.04	95.92	91.39	87.345	98.45	96.935
14			96.40	93.865		

TABLE 30: *IN-VITRO* DISSOLUTION STUDIES OF R7-R12

Time (min)	Cumulative percent drug release					
	R7	R8	R9	R10	R11	R12
0	-	-	-	-	-	-
2	43.5	41.5	44	40.5	42.5	41
4	62.93	62.415	65.44	67.405	62.425	55.41
6	81.62	80.12	76.15	83.67	82.12	69.05
8	88.31	86.295	84.25	88.33	87.315	79.185
10	90.37	89.855	89.83	91.875	91.865	83.285
12	93.39	94.39	93.39	93.91	94.41	93.325
14	98.22	97.935	97.42	97.43	97.535	96.11

TABLE 31: *IN-VITRO* DISSOLUTION STUDIES OF R13-R17

Time (min)	Cumulative percent drug release				
	R13	R14	R15	R16	R17
0	-	-	-	-	-
2	37.5	49.5	49.01	40	41.5
4	59.375	73.49	73.99	58.4	52.41
6	68.09	89.73	89.35	79.08	65.02
8	77.175	91.89	91.89	85.285	77.145
10	80.265	96.91	96.71	87.345	82.765
12	85.795	97.46	97.67	92.365	90.82
14	90.35	98.01		96.82	94.9

TABLE 32: DATA OF *IN-VITRO* % DRUG DISSOLUTION OF FF

Time (min)	Absorbance	Concentration (µg/ml)	Concentration (mg/ml)	Concentration		%CDR
				mg/5ml	mg/500ml	
0	-	-	-	-	-	-
2	0.115	3.96	0.00396	0.0198	1.98	49.5
4	0.162	5.84	0.00584	0.0292	2.92	73.49
6	0.194	7.12	0.00712	0.0356	3.56	89.73
8	0.197	7.24	0.00724	0.0362	3.62	91.39
10	0.207	7.64	0.00764	0.0382	3.82	96.40
12	0.209	7.76	0.00776	0.0388	3.88	97.45
Time (min)	**Absorbance**	**Concentration (µg/ml)**	**Concentration (mg/ml)**	**Concentration**		**%CDR**
				mg/5ml	**mg/500ml**	
0	-	-	-	-	-	-
2	0.115	3.96	0.00396	0.0198	1.98	49.5
4	0.162	5.84	0.00584	0.0292	2.92	73.49
6	0.194	7.12	0.00712	0.0356	3.56	89.73
8	0.197	7.24	0.00724	0.0362	3.62	91.39
10	0.207	7.64	0.00764	0.0382	3.82	96.40
12	0.209	7.76	0.00776	0.0388	3.88	97.45

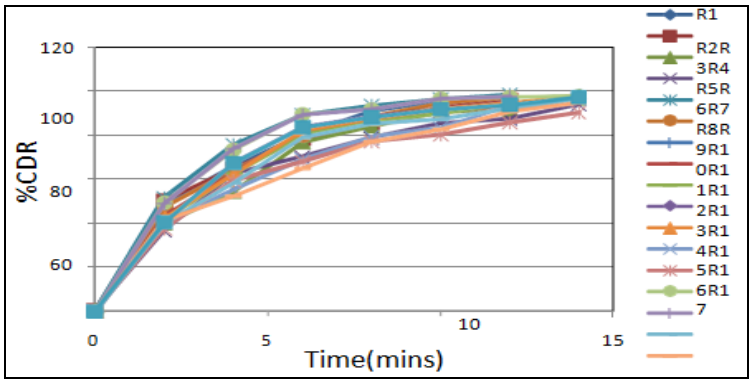

FIG. 22: *IN-VITRO* DRUG RELEASE PROFILES OF R1-R17

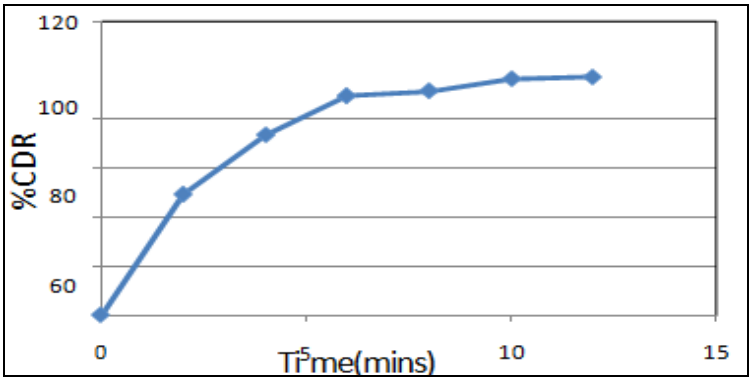

FIG. 23: *IN-VITRO* DRUG RELEASE PROFILE OF FF

X-Ray Diffraction: The X-ray diffraction spectrum of Risperidone and optimized FDBF (FF) is shown in **Fig. 24** and **25,** respectively. The sharp peaks indicate the crystalline nature of the drug, thereby conforming to the transformation of crystalline to amorphous nature of the drug in the optimized FDBF.

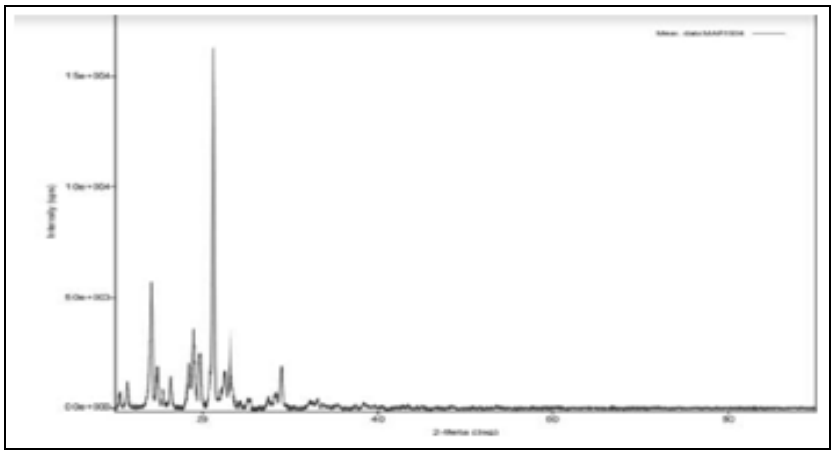

FIG. 24: XRD OF RISPERIDONE

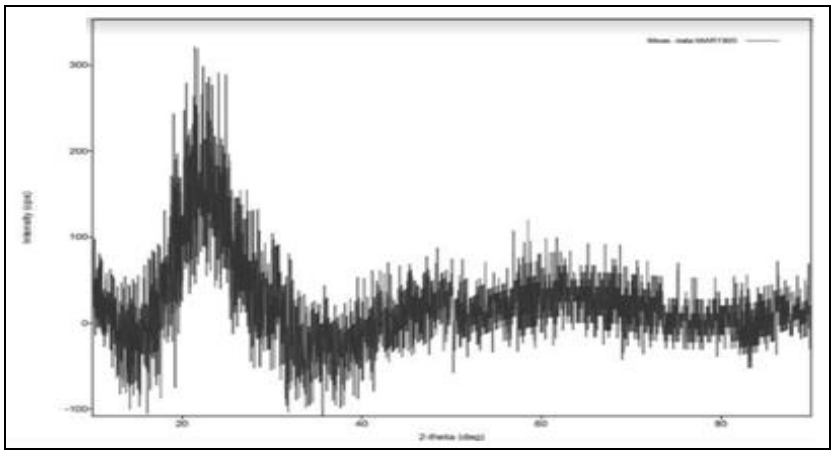

FIG. 25: XRD OF FF

Surface Morphology using SEM: The SEM image of the optimized film is shown in **Fig. 26,** indicating the smooth surface with pores of around 5-10µ. Porous structure of the film suggested increased amorphous nature of the FDBFs, which could predict rapid disintegration and dissolution. Images also revealed the absence of crystalline structures of the drug, thus confirming the suppression of crystallinity and the uniform distribution of the drug Risperidone in molecular dispersion form with polymer matrix in the form of FDBFs.

FIG. 26: SEM IMAGE OF FF

***Ex-vivo* Permeation Study:** The data for determination of *ex-vivo* permeation study of optimized and validated FDBF is shown in **Table 33** and **Fig. 27.** *Ex-vivo* permeation of FF was found to be 95.43% in 12 min, which indicated good tissue permeability of the drug from FDBF formulation.

TABLE 33: DATA OF *EX-VIVO* PERMEATION STUDY FOR FDBF

Time (min)	Absorbance	Concentration (µg/ml)	Concentration (mg/ml)	Concentration mg/5ml	Concentration mg/500ml	% CDR
0	-	-	-	-	-	-
2	0.114	3.92	0.00392	0.0196	1.96	49
4	0.147	5.24	0.00524	0.0262	2.62	65.99
6	0.17	6.16	0.00616	0.0308	3.08	77.655
8	0.187	6.84	0.00684	0.0342	3.42	86.27
10	0.202	7.44	0.00744	0.0372	3.72	93.855
12	0.205	7.56	0.00756	0.0378	3.78	95.43

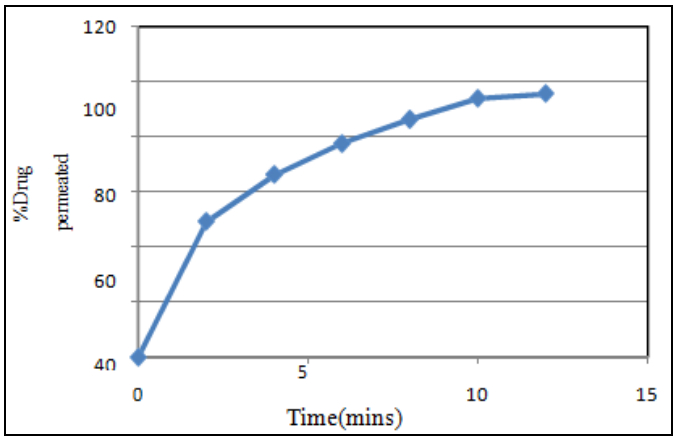

FIG. 27: *EX-VIVO* DRUG PERMEATION OF FF

Stability Study: The data of the determination of stability of optimized and validated Risperidone FDBF's is shown in **Table 33**. Observations of the study for both the storage conditions indicated good physical and chemical stability based on the physical appearance, folding endurance, disintegration time, and tensile strength up to three months.

CONCLUSION: Risperidone is an antipsychotic drug that is used to treat schizophrenia and other mood disorders. The project endeavours to formulate an oral dissolving film of Risperidone that can improve the overall solubility and dissolution characteristics. Solid dispersions were prepared by physical mixing and solvent evaporation method using PVPK30 and PEG 4000 as hydrophilic polymeric carriers to find the best method and drug-to-polymer ratio based on the increase in dissolution. SDPs prepared with solvent evaporation method with 1:1 (drug: PEG 4000) ratio were found to be comparatively better than another drug: carrier ratio. FTIR spectrum suggested the molecular dispersion of drugs with PEG 4000 with no incompatibility. DSC thermograms of SDPs indicated the depression in the intensity of crystalline endothermic peaks of the drug Risperidone in comparison with the pure samples. Percent practical yield and percent drug content of SDPs were found to be more than 98% for selected SDPs, and it suggested good efficiency of the solvent evaporation method. The solvent casting method was selected as the best suitable method using additives such as HPMC E5 (film-forming agent), PEG 400 (plasticizer), Croscarmellose (disintegrating agent), sodium saccharin (sweetening agent), and citric acid (saliva stimulating agent) which were found to be best in comparison with others. Risperidone FDBFs was optimized by using Box Behnken design (response surface methodology) by applying Design-Expert® -13 for formulating the FDBFs with the desired and optimum characteristics. The quadratic model was found to be the best fit for all three response variables and the R^2 values were more than 0.9. The films were evaluated for various parameters. FTIR spectrum of FDBFs showed major drug peaks when compared with FTIR spectrums of pure Risperidone. DSC thermograms of FDBFs indicated a decrease in the crystallinity of drugs in FDBF. The film had a thickness of 0.11±0.0057mm and showed a percent drug content of 100.30±0.7447, which showed good content uniformity without any significant variations. The Folding endurance, disintegration time, and tensile strength of the FDBFs were found to be 164.41±0.8100, 32.66±0.5773 seconds, and 3.416±0.0115 indicating good mechanical strength of FDBFs against rupture and breaks. A surface pH

of 6.69±0.0577 indicated no chances of irritation to the oral mucosa after its administration. Percent elongation and percent moisture loss of the FDBFs were found to be 16.27±0.0971 % and 2.25±0.0230 %. Results of In-vitro percent drug dissolution or release studies revealed 97.45% drug dissolution up to 12 min and thus indicated faster and almost complete drug dissolution.

In-vitro release kinetic data suggested that Risperidone films obey the Higuchi model of drug release. Stability studies were performed per ICH Q1A guidelines to assess their physical and chemical stability for up to 3 months at room temperature.

SEM and XRD analysis of FDBFs images also revealed the absence of crystalline structures of the drug, thus confirming the suppression of crystallinity and the uniform distribution of drugs in molecular dispersion form in the polymer matrix in the form of FDBFs.

Ex-vivo permeation study of FDBFs indicated 95.43% drug permeation up to 12 minutes, thus suggesting good tissue permeability of drugs from FDBF formulations. Based on the results, it was concluded that FDBF containing solid dispersion of the drug may provide the advantage of faster onset of action, enhanced dissolution, avoidance of extensive first-pass metabolism and improved patient compliance for the delivery of Risperidone.

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CONFLICTS OF INTEREST: Authors declareno conflicts of interest.

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