

Formulation and Evaluation of Mouth Dissolving Film of Risperidone

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Abstract: Schizophrenia is a severe, disabling disorder that affects about 1% of the world's population, which is associated with a high risk of suicidality, with a frequently reported modal rate of suicide rate being approximately 10%. Risperidone is effective for treating the positive and negative symptoms of schizophrenia compared to first generation antipsychotics. But oral administration of Risperidone has drawbacks such as hepatic first pass metabolism which is overcome by means of mouth dissolving film formulation. In the present study, Risperidone fast dissolving films were formulated by solvent-casting method containing HPMC E5 as polymer and Propylene glycol as plasticizer. All films prepared were smooth and elegant in appearance and showed no visible cracks; were uniform in thickness, weight and drug content. Formulation A2 is considered as the optimized formulation as it showed good % elongation (120%), good folding endurance (185), faster disintegration rate (13 sec.) and maximum in vitro drug release (93.57%) within 10 mins. No significant changes were observed during stability studies for the optimized formulation. It was concluded that Risperidone fast dissolving oral films can be formulated as a potentially useful tool for an effective treatment of Schizophrenia with improved bioavailability, rapid onset of action and with increased patient compliance.

Keywords: Schizophrenia, Risperidone, mouth dissolving film, HPMC E5 LV, Propylene glycol.

1. Introduction:

Despite of so much of advancements in various delivery system developed for administration of various drugs through different routes such as oral, parenteral, transdermal, nasal, etc., the oral route is considered as the most convenient and the preferred route of administration. ^[1] More than 70% of drugs are available in the market in the form of oral drug delivery system due to pain avoidance, more patient compliance, ease of administration, patient friendly and versatility (to accommodate various types of drug candidates). But, dysphagia is commonly found among all age groups. Due to this problem, approximately 50% of population, mainly paediatric and geriatric patients, tend to avoid taking oral solid dosage preparations due to fear of choking. ^[2] Keeping the ease of administration and swallowing in mind, pharmaceutical research has led to the development of fast-dissolving drug delivery system. ^[3, 4]

Research in the oral drug delivery segment has led to evolution of dosage forms from simple conventional tablets/capsules to modified release tablets/capsules to oral disintegrating tablet to wafer to the recent development of fast dissolving oral films. ^[3, 4] Mouth dissolving film is one such novel approach to

increase consumer acceptance by virtue of self-administration, improved efficacy of APIs by rapidly dissolving within few seconds in oral cavity after the contact with saliva without water or chewing. ^[5] These are ultra thin postage stamp size prepared using hydrophilic polymers with an active agent and other pharmaceutical excipients. ^[3, 6, 7] These are the most advanced form of oral solid dosage form due to more flexibility and comfort. ^[8] It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa. ^[1] Mouth dissolving film has several advantages such as availability of larger surface area that leads to rapid disintegration and dissolution in the oral cavity, site specific and rapid onset of action, stability for longer duration of time, avoidance of first pass effect, no risk of choking after administration, etc. ^[3]

Risperidone (C₂₃H₂₇N₄O₂) is a benzisoxazole derivative, is a second-generation atypical antipsychotic agent indicated for the treatment of schizophrenia with reduced side effects especially extra-pyramidal symptoms. It is a dopamine antagonist possessing anti-serotonergic, anti-adrenergic and anti-histaminergic properties. It is used primarily in the management of schizophrenia, inappropriate behavior in severe dementia and manic episodes associated with bipolar I disorder. Risperidone is effective for treating the positive and negative symptoms of schizophrenia compared to first generation antipsychotics. Risperidone was approved by the United States Food and Drug Administration (FDA) in 1994 for the treatment of schizophrenia. Physicochemical properties and long half life of Risperidone make it suitable candidate for oral fast dissolving drug delivery system. ^[9, 10, 11]

2. Materials and Methods:

2.1. Materials:

Risperidone was obtained as a gift sample from Glenmark pharmaceuticals, Nashik; HPMC E-5 LV Premium and Citric acid were procured from Loba Chemie, Pvt. Ltd., Mumbai; Propylene glycol was procured from Research-Lab Fine Chem Industries, Mumbai; other ingredients like Sucralose and Potassium Dihydrogen Phosphate used were of pharmaceutical grade.

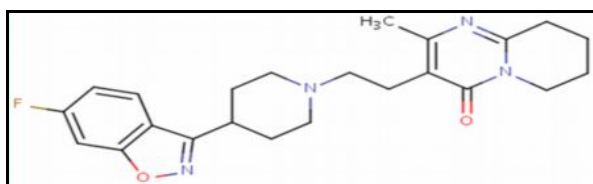


Figure 1: Chemical structure of Risperidone. ^[11]

2.2. Methods:

2.2.1. Preformulation study:

2.2.1.1. Color and Odor:

A small quantity of drug Risperidone was taken on butter paper and viewed in well illuminated place and color was observed. Very less quantity of Risperidone was smelled to get the odor.

2.2.1.2. Identification by Melting point:

The melting point of the drug was determined by capillary tube method using the melting point apparatus (Kumar industries; VMP-D).

2.2.1.3. Identification by FTIR Spectroscopy:

Risperidone disc was prepared by pressing the Risperidone with potassium bromide (KBr) in 1:99 proportions and the spectrum was recorded in range of 400-4000 cm⁻¹ using FTIR spectrophotometer (Shimadzu; 8400S, Tokyo, Japan).

2.2.1.4. Identification by UV-Visible Spectroscopy:

Drug was accurately weighed and dissolved in solvent 0.1 N HCl to obtain stock solution of 1000 μ g/ml. This solution was then suitably diluted with same solvent to get solution of concentration 100 μ g/ml and further diluted to obtain concentrations ranging from 2-20 μ g/ml. Then the UV spectrum of 10 μ g/ml was recorded over the wavelength range 200-400 nm by using double beam spectrophotometer (Shimadzu; UV 2450). Also the absorbance of all solutions was measured against 0.1N HCl as blank at the specific λ_{\max} . The calibration curve was constructed by plotting concentration (2-20 μ g/ml) versus absorbance at λ_{\max} . Same procedure was repeated by using 6.8 pH phosphate buffer.

2.2.1.5. Identification by DSC:

DSC was performed using Shimadzu Thermal Analyser; DSC-60 by taking 4 mg sample. Sample was hermetically sealed in aluminium pan and heated from ambient temperature 30⁰ C to 300⁰ C, with the heating rate of 10⁰ C/min. Inert atmosphere was provided by purging nitrogen gas flowing at 40 ml/min.

2.2.1.6. Drug-Polymer interaction studies:

FT-IR study was performed to ascertain the compatibility of the Risperidone with the selected polymer and other excipients. The physical mixture of drug, polymer and other excipients was stored for 30 days at elevated temperature and humidity conditions of 40 \pm 2⁰ C / 75 \pm 5 % RH. After 30 days, an IR spectrum of the stored sample was recorded.

2.2.2. Formulation and Development of mouth dissolving film:

Mouth dissolving film of Risperidone was prepared by solvent casting technique. Aqueous solution 'A' was prepared by dissolving HPMC-E5 LV polymer in 15 ml cool water with stirring to produce solution and kept for 24 hrs. to remove all the air bubbles and form clear solution. Aqueous solution 'B' was prepared by dissolving Risperidone, sucralose, citric acid and propylene glycol in specific proportion in 5 ml of distilled water. The aqueous solutions 'A' and 'B' were mixed and stirred for 1 hr. The solutions were cast on to glass petri plate of 9 cm diameter and were dried in the oven at 45⁰ C till a peelable film was formed. Then dried films were cut into rectangular shape pieces, with 3.0 cm² (2.0 cm \times 1.5 cm) total surface area. Desired quantity of Risperidone was 0.5 mg (dose of drug) per 3.0 cm² films. ^[12]

Table 1: Composition of mouth dissolving films of Risperidone.

Name of excipients	Different batches of mouth dissolving films of Risperidone								
	A1	A2	A3	A4	A5	A6	A7	A8	A9
HPMC-E5 LV	0.7	0.7	0.7	1.0	1.0	1.0	1.3	1.3	1.3
PG	0.15	0.18	0.21	0.15	0.18	0.21	0.15	0.18	0.21
Sucralose	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Citric Acid	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

- Each batch contains 0.5 mg drug Risperidone.

2.2.3. Evaluation of mouth dissolving films:

2.2.3.1. Physical appearance:

Films of each formulation were randomly selected and inspected visually as well as by feel or touch for texture.

2.2.3.2. Thickness:

Five films of each formulation were taken and the film thickness was measured by using micrometer screw gauge at different strategic locations (5 locations). Mean thickness and standard deviation were calculated. ^[13, 14]

2.2.3.3. Weight variation test:

For weight variation test, 10 films of every formulation were randomly selected and weighed individually to determine the average weight and standard deviation was also calculated. ^[13, 14]

2.2.3.4. Percentage moisture loss:

For moisture content test, three films of each formulation were taken. Initially, these selected films were weighed accurately and kept in desiccator containing fused anhydrous calcium chloride. After 3 days, films were removed, weighed and percentage moisture loss was calculated. Mean percentage moisture loss and standard deviation were calculated. ^[15]

The percentage moisture loss was calculated using following formula:

$$\text{Percent moisture loss} = \frac{\text{Weight loss}}{\text{Initial weight}} \times 100$$

2.2.3.5. Surface pH of films:

The surface pH of films was determined to investigate the possible side effect because of change in pH *in vivo*, since an acidic or alkaline pH may cause irritation to oral mucosa. The film to be tested was placed in a test tube and was moistened with 1.0 ml of distilled water and kept for 30 second. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibrating for 1 min. The average of three determinations for each of the formulation was taken and standard deviation was also calculated. ^[15, 16]

2.2.3.6. Drug content uniformity:

Content uniformity is determined by estimating the API content in individual strip. Three films from each formulation were took and individually dissolved in 50 ml of 6.8 pH phosphate buffer to give solutions of 10µg/ml concentration. These solutions were filtered and absorbance of each solution was recorded at 276 nm (λ max of Risperidone) using the placebo patch (patch without drug) solution as a blank. The percentage drug content was determined. Mean of the percentage drug content and standard deviations were calculated. The Limit of content uniformity is 85-115%. ^[1, 16]

2.2.3.7. Disintegration time:

The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Although, no official guidance is available for oral fast disintegrating films/strips, this may be used as a qualitative guideline for quality control test or at development stage. This test is carried out using the disintegration apparatus. Three films from each formulation were taken and performed disintegration test by placing the films in the cylindrical glass tube of disintegration apparatus containing 6.8 pH phosphate buffer. The time at which film disintegrated is noted. Mean and standard deviation were calculated. Normally disintegration time for fast dissolving oral films is 5-30 seconds. ^[1]

2.2.3.8. Folding endurance:

Three films of each formulation of 1 cm² (1 × 1 cm) were cut by using sharp blade. Folding endurance was determined by repeatedly folding a small strip of film at the same place till it break. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance. The mean value of three readings and standard deviation were calculated. ^[14, 17]

2.2.3.9. Tensile strength:

Tensile strength of the film was checked by Universal Tensile Strength Testing Machine (LS5, Lloyd Instruments Limited, UK) equipped with a 500 N load cell. Test was conducted under normal laboratory conditions. The film of 400 mm² was randomly selected and ASTM D-882 method was used to perform the test. The lower clamp was held stationary and the film was pulled apart by the upper clamp at a speed of 50 mm/min. The force of the film at the point, when the film broke was recorded. Nexygen Plus 3 software was

used for data collection and performance of calculations. The experiment was performed in triplicate and average values were reported. ^[17, 18]

The tensile strength at break value was calculated using formula:

$$\text{Tensile strength} = \frac{\text{force at break(N)}}{\text{Initial cross sectional area (mm}^2\text{)}}$$

2.2.3.10. Percent elongation:

When stress is applied, a strip sample stretches referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. ^[3, 17]

$$\% \text{ elongation} = \frac{\text{Increase in length of strip}}{\text{Initial length of strip}} \times 100$$

2.2.3.11. Dissolution test:

Dissolution testing performed in pH 6.8 phosphate buffer (dissolution media) using the standard basket apparatus at $37 \pm 0.5^\circ \text{C}$ and 50 rpm. A single film was placed in 500 ml dissolution media. 5 ml of samples were withdrawn at suitable time intervals and replaced with fresh dissolution medium. Then samples were determined using UV visible spectrophotometer at 276 nm and cumulative drug release was calculated. ^[17, 19]

2.2.3.12. Ex Vivo drug permeation study:

The optimized formulation was subjected to permeation studies through the sheep oral mucosa. The permeation of Risperidone across sheep oral mucosa was carried out using Franz diffusion cell. A 3.20 cm^2 film of optimized formulation was placed on the oral mucosa. Receptor compartment contained 16.5 ml simulated saliva solution of pH 6.8, while donor compartment was filled with 1 ml simulated saliva of pH 6.8. The cell contents were stirred using magnetic bead at $37 \pm 1^\circ \text{C}$. Aliquots of 1 ml were withdrawn at regular intervals (every 5 min.) for 30 min. and filtered. The amount of drug permeated was quantified using UV visible Spectrophotometric method of analysis with the help of standard curve of drug; absorbance was measured at 276 nm. ^[15]

2.2.3.13. Buccal mucosa sensitivity test:

The final optimized formulation was subjected for oral mucosa sensitivity test to check whether there is any irritation has occurred or not after dissolving film in mouth. After completion of the diffusion experiment, oral mucosa was repeatedly washed with 6.8 pH phosphate buffer. Small portion of the mucosa was fixed in 10% buffered formalin solution and dehydrated. Sections were taken by microtome at $4 \mu\text{m}$ perpendicular to the epithelial surface, stained with haematoxylin eosin (HE) and examined under digital microscope to evaluate any histological changes in the epithelium and the adjacent connective tissue. Control oral mucosa was also treated and examined similarly. ^[20]

2.2.3.14. Accelerated stability studies:

The stability studies were conducted according to ICH guidelines to investigate the effect of - temperature, relative humidity on drug in formulation. Final optimized formulation was subjected to aggravated conditions of temperature and relative humidity by wrapping it in aluminium foil and packaging it in glass container. The films were kept in stability chamber, at $40 \pm 2^\circ \text{C}$ temperature and $75 \pm 5\% \text{ RH}$ for 3 months. ^[21] After 1, 2 and 3 months, films were tested for:

1. Change in the appearance.
2. Change in the disintegration time.
3. Change in the surface pH.
4. Change in the folding endurance.

3. Result And Discussion:

3.1. Preformulation study:

3.1.1. Color and Odor:

Risperidone was observed and found to be white in color and odorless.

3.1.2. Identification by Melting point:

The melting point of Risperidone was taken in triplicate and mean value was found to be 169-171⁰ C.

3.1.3. Identification by FTIR Spectroscopy:

The obtained IR spectra of drug sample matched with the standard IR spectra of Risperidone (Fig. 2).

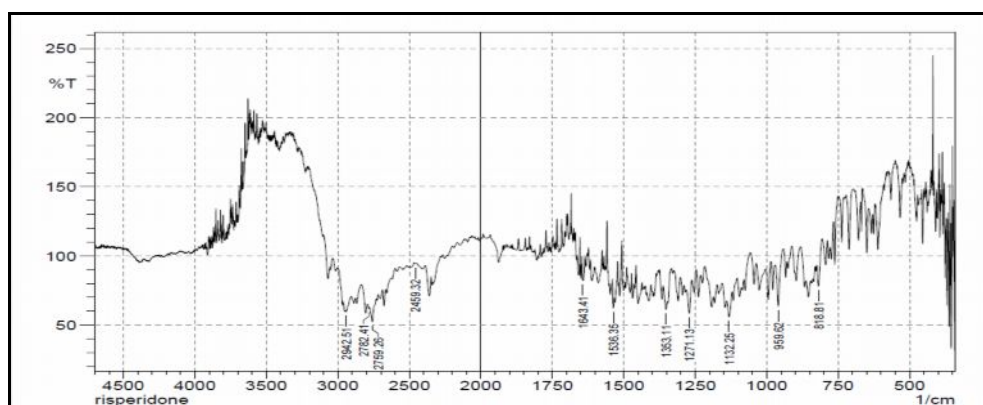


Figure 2: IR spectrum of Risperidone (pure drug).

Table 2: Reported and observed principal peaks of Risperidone in IR spectrum

Type of vibration	Observed frequencies (cm ⁻¹)	ported Frequencies ^[22] (cm ⁻¹)
C-H bending (Aromatic)	818.81	900-690
Aromatic	1643.41	1600, 1475
C-F (Fluoride)	1271.13, 1132.25, 1353.11, 1060.88	1400-1000
C-N (Amines)	1353.11, 1060.88	1350-1000
C=O (Amide)	1643.41	1680-1630
C=N (Imines, Oximes)	1643.41	1690-1640
C-H stretching (Alkanes)	2942.51, 2782.41, 2759.26	3000-2850

3.1.4. Identification by UV-Visible Spectroscopy:

The maximum absorbance of Risperidone was found at 274 nm in 0.1N HCl and 276 nm in 6.8 pH phosphate buffer which are shown in Fig. 3, 5. A linear relationship was obtained in Beer-Lamberts plot of Risperidone which is shown in Fig. 4, 6.

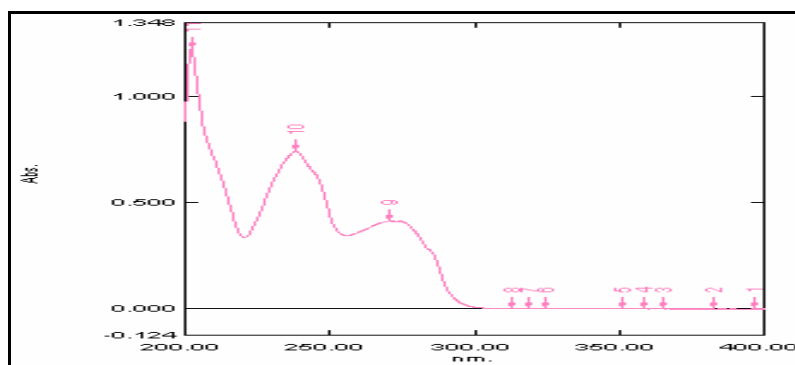


Figure 3: UV spectrum of Risperidone in 0.1N HCl

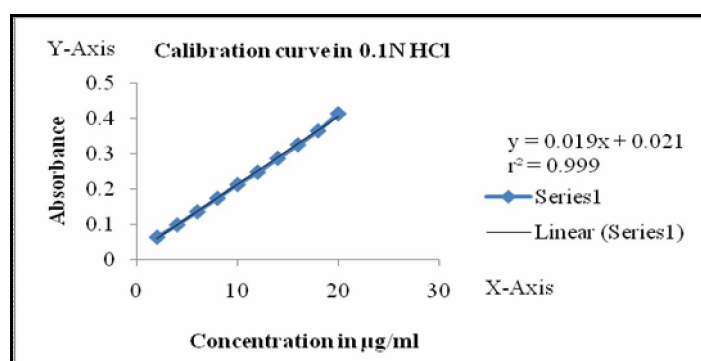


Figure 4: Calibration curve of Risperidone in 0.1N HCl.

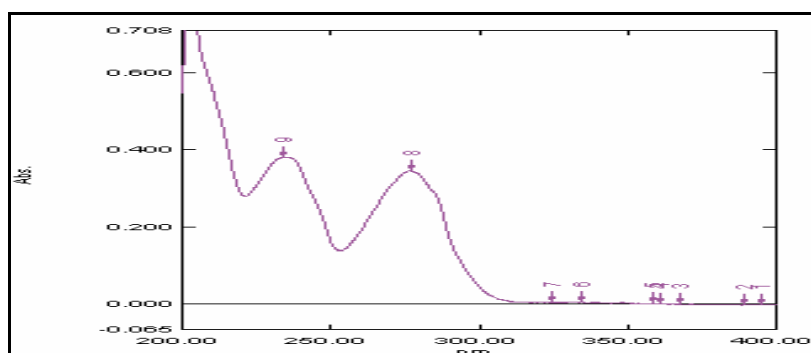


Figure 5: UV spectrum of Risperidone in 6.8 pH phosphate buffer.

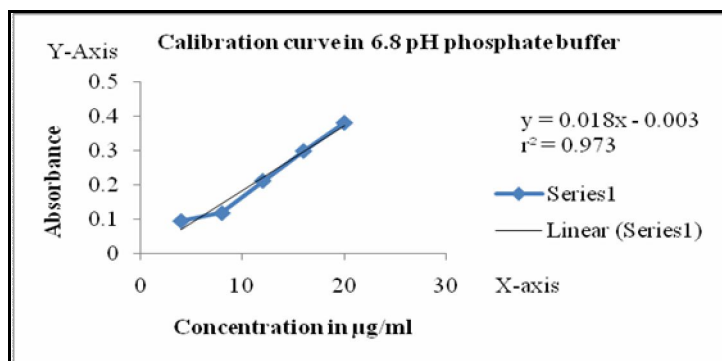


Figure 6: Calibration curve of Risperidone in 6.8 pH phosphate buffer.

3.1.5. Identification by DSC:

A sharp exothermic peak was observed of the drug at 167.48°C , corresponding to its melting point (169°C - 171°C).

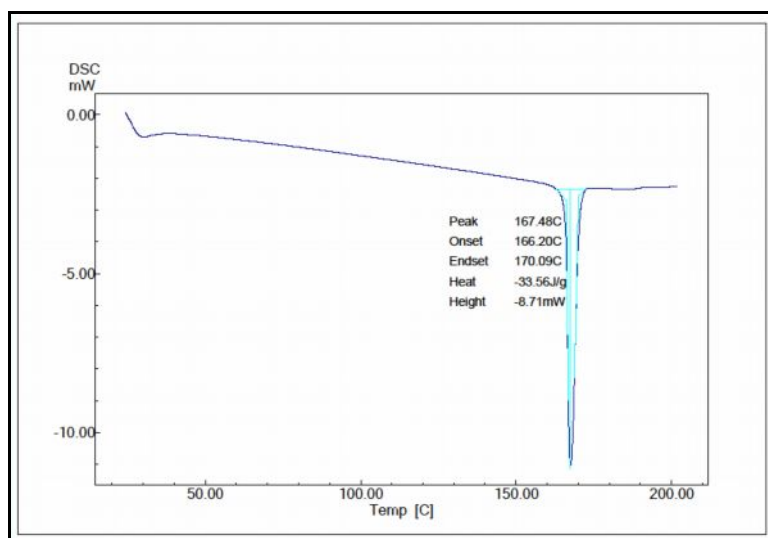


Figure 7: Thermogram of pure drug Risperidone.

3.1.6. Drug-Polymer interaction studies:

Drug-excipients interaction study showed no interaction between Risperidone and selected polymers as there was no significant shift of peaks in IR spectrum. Also the characteristic peaks of drug Risperidone were observed in drug-excipients mixture sample. It was concluded that the selected excipients were compatible with Risperidone and hence used for formulation of mouth dissolving film of Risperidone.

3.2. Evaluation of mouth dissolving films:

3.2.1. Physical appearance:

All patches from A1-A9 were found to be smooth in nature and had good appearance.

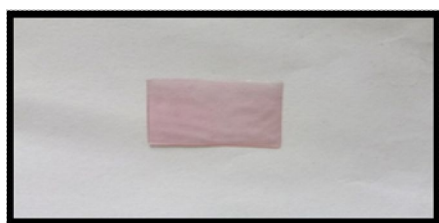


Figure 8: Mouth dissolving film of Risperidone

Table 3: Evaluation of physicochemical parameters of Risperidone films.

FC	Thickness (mm)	Weight uniformity (mg)	Moisture content loss (%)	Surface pH
A1	0.15 ± 0.04	30.8 ± 1.47	9.89 ± 0.19	6.51 ± 0.03
A2	0.15 ± 0.03	31.8 ± 1.39	6.45 ± 0.20	6.99 ± 0.01
A3	0.16 ± 0.03	32.5 ± 1.77	3.19 ± 0.15	6.69 ± 0.03
A4	0.16 ± 0.02	38.6 ± 1.68	8.74 ± 1.30	6.37 ± 0.03
A5	0.16 ± 0.01	40.8 ± 1.01	4.95 ± 0.07	7.01 ± 0.02
A6	0.17 ± 0.03	42.1 ± 1.59	7.87 ± 1.42	7.04 ± 0.02
A7	0.18 ± 0.03	50.3 ± 1.55	5.96 ± 0.06	6.55 ± 0.01
A8	0.18 ± 0.02	51.0 ± 1.63	5.11 ± 1.03	6.80 ± 0.02
A9	0.19 ± 0.02	52.7 ± 1.49	5.69 ± 0.05	6.97 ± 0.06

Table 4: Evaluation of physicochemical parameters of Risperidone films.

FC	Drug content uniformity (mg)	Disintegration time (Sec.)	Folding endurance
A1	0.47 ± 0.010	10 ± 1.00	178 ± 1.02
A2	0.49 ± 0.017	13 ± 0.58	185 ± 1.45
A3	0.50 ± 0.010	17 ± 0.58	220 ± 2.03
A4	0.48 ± 0.038	19 ± 0.58	247 ± 1.94
A5	0.49 ± 0.017	20 ± 0.58	259 ± 2.13
A6	0.51 ± 0.021	23 ± 0.57	276 ± 1.92
A7	0.47 ± 0.010	27 ± 1.00	280 ± 1.45
A8	0.51 ± 0.015	32 ± 1.00	289 ± 1.78
A9	0.46 ± 0.030	40 ± 0.57	297 ± 1.52

3.2.2. Tensile strength:

The tensile strength of optimized formulation was 9.150 N/mm². It was found that tensile strength increased with an increasing amount of HPMC-E5 LV and increasing amount of PG. The value showed that the mechanical strength of films was enough to bear stress during transport and administration of films.

3.2.3. Percent elongation:

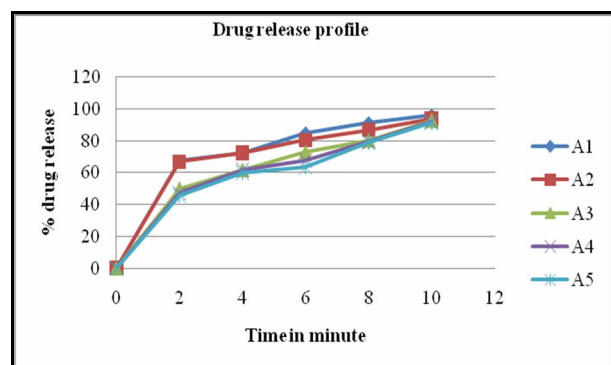
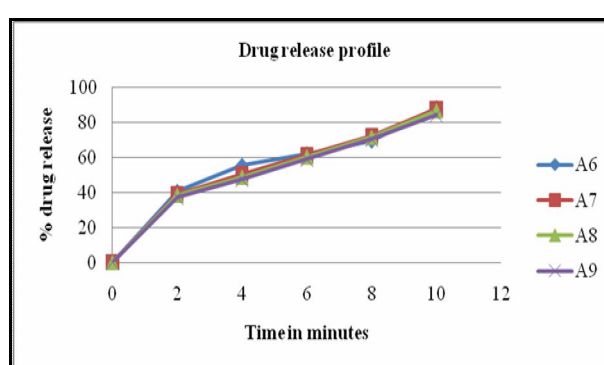
The percentage elongation of optimized formulation was 120%. Generally elongation of film increases as the plasticizer content increases.

3.2.4. Dissolution test (*In Vitro* drug release studies):

In-vitro drug release study results showed that as the concentration of polymer increases, drug release from mouth dissolving films decreases. An immediate drug release was successfully observed for all HPMC films.

Table 5: Percent drug release of Risperidone films.

Time (Minutes)	A1	A2	A3	A4	A5	A6	A7	A8	A9
0	0	0	0	0	0	0	0	0	0
2	67.22	66.66	50	47.22	45.55	40.55	38.88	38.33	37.22
4	72.33	72.33	61.61	61.58	59.9	55.40	50.38	48.71	47.59
6	84.72	80.27	72.77	67.75	63.27	62.06	61.44	60.31	59.17
8	91.11	86.61	80.16	79.52	78.89	69.34	72.05	71.46	70.31
10	95.88	93.57	92.61	91.97	91.33	88.35	87.75	86.60	84.33

**Figure 9: Comparative *in vitro* drug dissolution profiles of Risperidone films (A1-A5).****Figure 10: Comparative *in vitro* drug dissolution profiles of Risperidone films (A6-A9).**

Kinetics of drug release:

The coefficient of regression value was found to be highest for Zero order model. By fitting in the Korsmeyer-Peppas equation the release kinetics follows quassi-Fickian kinetics. The diffusion exponent n value was found to be less than 0.5 for all the formulations; indicating quassi-Fickian diffusion of drug through the films.

3.2.5. Optimization of formulation:

A 3^2 randomized full factorial design was used for optimization of Risperidone mouth dissolving film. The design was also applied to study the effect of concentration of HPMC- E5 LV and PG on physico-chemical characteristics of film. The amount (%) of film former polymer HPMC- E5 LV (X_1) and the amount (%) of plasticizer PG (X_2) were selected as independent variables, in this study. These two factors were evaluated, each at three levels. The actual units of higher, middle and lower levels of factor X_1 were 0.7%, 1.0% and 1.3% and for factor X_2 were 0.15%, 0.18% and 0.21%. The coding was +1, 0 and -1 respectively for higher, middle and lower levels of each factor. The dependent or response variables included % drug release in 10 minutes (Y_1), disintegration time in seconds (Y_2) and folding endurance (Y_3).

3.2.5.1. Effect of formulation variables on % drug release:

On applying factorial design, the quadratic model was suggested by software and found to be significant with Model F value of 179.34, p value < 0.0001 and R^2 value 0.9891 which implied that model was significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob $> F$ " less than 0.0500 indicate Model terms are significant. In this case, X_1 and X_2 are significant Model terms. The Model for response Y_1 (% drug release in 10 min.) is as follows:

$$Y_1 = + 90.27 - 3.90X_1 - 1.72X_2$$

In above equation, negative (-) sign of X_1 indicates that factor X_1 (concentration of HPMC-E5 LV) has negative effect and negative (-) sign of X_2 indicates that factor X_2 (concentration of PG) has negative effect on response Y_1 (% drug release in 10 min). That is % drug release in 10 min. decreases with increase in HPMC-E5 LV concentration and also decreases with increase in PG concentration. The release of drug was found to be dependent on swelling or gelation factor.

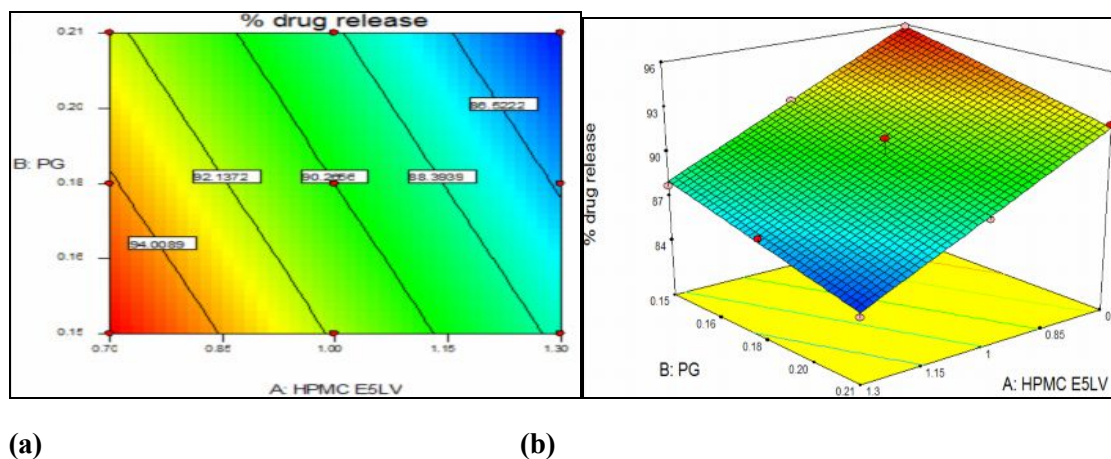


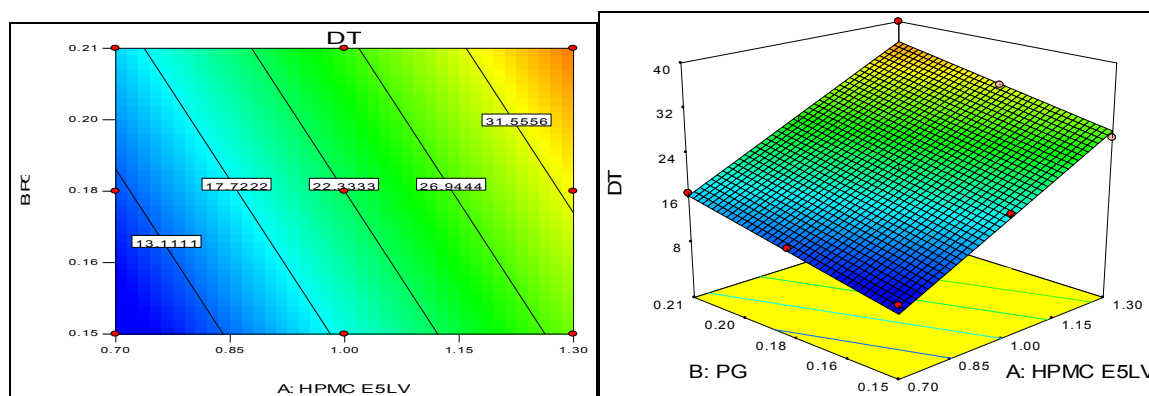
Figure 11: (a) Two dimensional contour plot (b) Three dimensional (3D) response surface plots for Y_1 (% drug release in 10 min.).

3.2.5.2. Effect of formulation variables on disintegration time:

The Model F-value of 56.61 implies the Model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of Prob $> F$ less than 0.0500 indicate Model terms are significant. In this case X_1 and X_2 are significant Model terms. Values greater than 0.10 indicate the Model terms are not significant. Following quadratic equation could describe the disintegration time response.

$$Y_2 = + 22.33 + 9.83X_1 + 4.00X_2$$

In above equation, positive (+) sign of X_1 and X_2 indicates that factor X_1 (concentration of HPMC-E5 LV) & X_2 (concentration of PG) has positive effect on response Y_2 (Disintegration time) respectively. That is disintegration time decreases with increase in HPMC-E5 LV and PG concentration.



(a)

(b)

Figure 12: (a) Two dimensional contour plot (b) Three dimensional (3D) response surface plots for Y_2 (Disintegration time).

3.2.5.3. Effect of formulation variables on folding endurance:

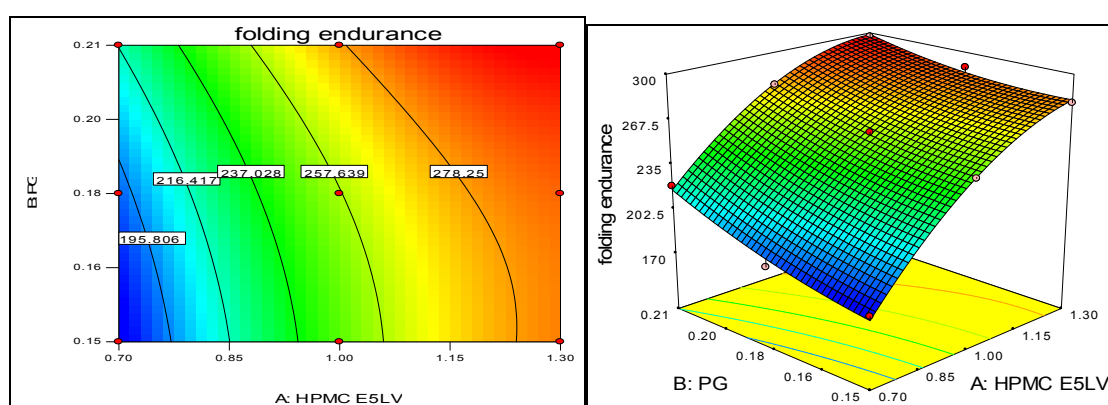
Propylene glycol acts as a plasticizer because it capable to decrease the glass transition temperature. Lowering the glass transition temperature increases chain mobility and this in turns, increase in folding endurance.

Following quadratic equation could describe the folding endurance response:

$$Y_3 = + 257.78 + 47.17X_1 + 14.67X_2 - 6.25X_1X_2 - 19.17X_1^2 + 5.33X_2^2$$

In above equation, positive (+) sign of X_1 and X_2 indicates that factor X_1 (concentration of HPMC-E5 LV) & X_2 (concentration of PG) has positive effect on response Y_3 (folding endurance) respectively. That is folding endurance increase with increase in HPMC and PG concentration. The negative (-) sign indicates negative effect on folding endurance.

The Model F-value 119.60 implies the Model is significant. There is only a 0.12% chance that a "Model F-Value" this large could occur due to noise. Values of Prob > F less than 0.0500 indicate Model terms are significant. In this case, X_1 and X_2 are significant Model terms.



(a)

(b)

Figure 13: (a) Two dimensional contour plot (b) Three dimensional (3D) response surface plots for Y_3 (Folding Endurance).

3.2.6. Ex Vivo drug permeation study:

The permeation profiles of A2 formulation, without penetration enhancer, across sheep oral mucosa are shown in Fig. 14. The apparent permeability coefficient (P_{app}), steady state flux (J_{ss}) and the steady state diffusion coefficient (D) of Risperidone through the mucosa were found to be 7.90 cm min^{-1} , $3.95 \mu\text{g cm}^2 \text{ min}^{-1}$ and $9.18 \text{ cm}^2 \text{ min}^{-1} \times 10^{-2}$ respectively.

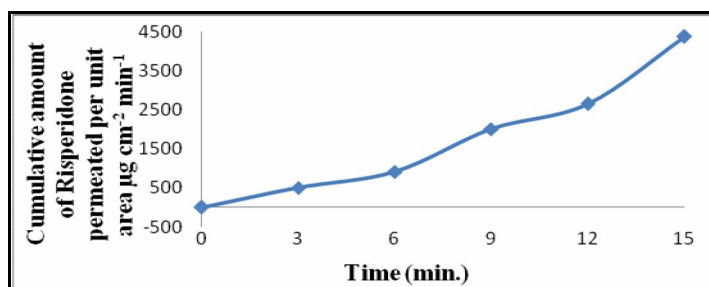


Figure 14: *Ex vivo* permeation of Risperidone through sheep oral mucosa.

3.2.7. Buccal mucosa sensitivity test:

The optimized formulation A2 was subjected for oral mucosa sensitivity test. The sections of control and sample mucosa (treated with final optimized formulation) observed under digital microscope (Motic, B1 Advanced series) (Fig. 15). The histopathological evaluation of sections showed that cellular membrane was intact and there was no damage to the epithelial layer. Cell necrosis was not observed and hence it can be concluded that, formulation is safe for chronic oral administration of Risperidone.

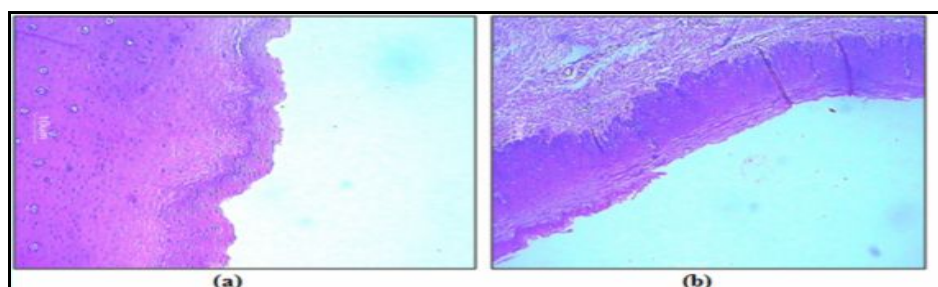


Figure 15: Histopathological evaluation sections of sheep oral mucosa (a) control (b) sample oral mucosa (treated with formulation A2).

3.2.8. Accelerated stability studies:

The results of stability studies performed on batch A2 are shown in Table 6. After the 3 months study, it was found that there was no change in appearance of the films and negligible change in pH. The folding endurance and disintegration time was decreased but not significantly.

Table 6: Evaluation of optimized batch A2 during stability studies at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $75\% \pm 5\text{ RH}$.

Parameters	0 Day	30 Days	60 Days	90 Days
Appearance	No change	No change	No change	No change
Surface pH	6.99	6.97	6.94	6.89
Folding endurance	185	181	177	172
Disintegration time	13	12	10	9

4. Conclusion:

The developed film formulation is a patient-friendly formulation that would be useful for people who have difficulty of swallowing. The results have shown that the HPMC-E5 LV is good film former and shows bioadhesion property. In combination with PG, it has shown promising fast drug release within 10 min. and good folding endurance. Hence a semi-synthetic cellulose derivative which is affordable and abundantly available can be used as a potential drug release modifier and also used to improve flexibility and processability in the mouth dissolving films. Successful formulation of Risperidone mouth dissolving films may prevent first pass metabolism to a large possible extent. From the present study it can be concluded that HPMC-E5 LV based mouth dissolving films of Risperidone can be successfully prepared with considerable good stability and improved bioavailability.

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