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FORMULATION AND EVALUATION OF SOLID DISPERSED SUBLINGUAL FILMS OF RILPIVIRINE HYDROCHLORIDE

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ABASTRACT

The results of this study demonstrate that Pullulan can be effectively used as a film-forming polymer, with PEG 400 serving as a plasticizer for the formulation of fast- dissolving sublingual films containing Rilpivirine Hydrochloride. The optimized batch exhibited acceptable mechanical properties, along with an in-vitro disintegration time of 33 seconds. A drug release study was conducted across 9 batches to identify the best polymer and plasticizer combination. Among all batches, T1, which used Pullulan and PEG 400, showed more than 85% drug release within 15 minutes. Based on the trial batch results, a factorial design approach was employed for formulation optimization, with Pullulan and PEG 400 selected as independent factors. Pullulan and PEG 400 were chosen for further formulation optimization using a 32 full factorial design, revealing that increasing the amounts of Pullulan and PEG 400 increased folding endurance and disintegration time, while decreasing drug release. The optimized batch, O1, exhibited acceptable mechanical properties with an in-vitro disintegration time of 28 seconds, indicating suitability for immediate release of Rilpivirine for systemic use due to its maximum drug release. Stability studies of batch O1 was performed and found satisfactory. Hence, O1 batch is optimized batch.

KEYWORDS: Rilpivirine Hydrochloride, Pullulan, PEG 400.

INTRODUCTION

Human Immunodeficiency Virus (HIV) is a life-threatening chronic condition that necessitates lifelong antiretroviral therapy to suppress viral replication and improve patient outcomes. Rilpivirine Hydrochloride, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is used for the management of HIV-1 infection. However, its poor aqueous solubility and low oral bioavailability (32%) limit its therapeutic efficiency. To overcome these limitations, solid dispersion-based sublingual films were developed to enhance solubility, enable rapid onset of action, bypass first-pass metabolism, and improve patient compliance particularly in populations with swallowing difficulties or limited access to water.

A 3^2 full factorial design was employed to study the influence of two formulation variables at three levels each, resulting in nine experimental batches (F1–F9). This design helped evaluate the individual and combined effects of the variables on key parameters such as drug release, disintegration time, and folding endurance of the sublingual films.

MATERIALS AND METHODS

Rilpivirine Hydrochloride is provided as a gift sample Torrent Research Centre, Ahmedabad and exepients were Pullulan, Pectin, PEG 4000, PVA and Propylene Glycol was provided by Balaji Chemicals, Ahmedabad and ACS Chemicals, Ahmedabad.

For Preformulation study, Infrared spectra-photometry is a useful analytical tool to check chemical interactive action in active substance and various ingredients utilized in composition. A sample (1 mg) was mixed and powdered with 10 mg dry powdered of KBr. The mixing of powder was bring in a sample and the spectrums were determined by screening in wavelength range of 400-4000 cm-1 using FTIR spectrophotometer. The drugs IR spectrum was compared with physical mix of drug and polymers to found for such possible active substance-excipients interaction.

Solid dispersions of Rilpivirine Hydrochloride were prepared to enhance solubility using PEG 6000 in 1:1, 1:2, and 1:3 drug-to-polymer ratios. Two methods were employed: (1) physical mixing by triturating drug and PEG 6000, and (2) the melting (fusion) method, where

PEG 6000 was melted at 60°C and the drug was added with stirring. The solidified mass was cooled, pulverized, and sieved to obtain uniform particles.

Evaluation parameters of the prepared Sublingual films, organoleptic properties.

DRUG CONTENT: Drug content determination of the film was carried out by dissolving the film of 4 cm^2 in 100 ml of pH 6.8 phosphate buffer using magnetic stirrer for 1 hour. The drug concentration was then evaluated spectrophotometrically at Amax of 242 nm. The determination was carried out in triplicate for all the formulations and average with standard deviation was recorded.

IN-VITRO DISSOLUTION: The dissolution study was carried out using USP Type I (Basket type) dissolution apparatus. The dissolution was carried out in 900 ml of pH 6.8 phosphate buffer maintained at 37 ± 0.5°C at 50 rpm. 10 ml aliquots of samples were taken at various time intervals which were replaced with same volume of fresh pH 6.8 phosphate buffer maintained at 37 ± 0.5°C. Drug amount in the samples was then determined spectrophotometrically at Amax of 242 nm. The results were expressed as mean of three determinations.

TENSILE STRENGTH: Tensile testing was conducted using a texture analyzer equipped with a 5 N load cell. The film was cut into 30 × 20 mm strips. Tensile tests were performed according to ASTM International Test Method for Thin Plastic Sheeting (D 882-02). Each test strip was placed in tensile grips on the texture analyzer. Initial grip separation was 20 mm and crosshead speed were 1 inch/min. The test was considered concluded when the film breaks. Tensile strength, was computed with help of load require to break the film and cross-sectional area to evaluate tensile properties of the films. Tensile strength (TS) Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be calculated by dividing the maximum load by the original cross-sectional area of the specimen and it was expressed in force per unit area (MPa)

Tensile Strength = Force at break (N)/ Cross sectional area (mm^2)

PERCENTAGE ELONGATION: For the determination of percentage elongation of the film formulations, the distance between the tensile grips of the tensile strength testing machine was measured before and after the fracture of the film. Then the percentage elongation of the films was computed with the help of the formula given below: -

$\%E = Dr\text{-}Do/Do \times 100$

EX-VIVO PERMEATION STUDIES: was evaluated using porcine buccal mucosa mounted on a Franz diffusion cell. A pre-moistened sublingual film (2 × 2 cm) was placed in the donor compartment, while the receptor compartment contained phosphate buffer (pH 7.4) at 37 ± 0.2°C. Samples were withdrawn at intervals and analyzed at 242 nm using a UV spectrophotometer to determine % drug permeated.

STABILITY STUDY: Stability study will be carried out at 40°C/75% RH for 1 month. Each piece of the film of optimized formulation was packed in butter paper followed by aluminum foil and plastic tape. After 1 month, the films were evaluated for the physical appearance, surface pH, drug content and in vitro drug release.

Dose Calculation for Petridish:
Diameter of the Petridish = 9.3 cm
Radius = Diameter /2 = 9.3/2 = 4.65 cm.

Area of Petridish = πr^2 = 3.14 X 4.65 X 4.65= 67.89 cm^2

Dose is 25 mg and film dimension are 2 cm X 2 cm = 4 cm^2
4 cm^2 contain = 25 mg of Rilpivirine Hydrochloride
Therefore, 67.89 cm^2 contain (?) = 424.3 mg~ 424.3 mg Rilpivirine Hydrochloride.

Optimized Solid Dispersion ration is 1:2. Hence, 1272.9-1273 mg of SD require.

Application of Factorial design: Independent and different level for 3^2 factorial design

Independent variables	Levels		
	Low	Medium	High
	-1	0	+1
Pullulan (X_1) mg	400	500	600
PEG 400 (X_2) ml	0.4	0.5	0.6

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rilpivirine Hydrochloride + PEG 6000 (SD)	1272	1272	1272	1272	1272	1272	1272	1272	1272
Pullulan (mg)	400	400	400	500	500	500	600	600	600
PEG 400(ml)	0.4	0.5	0.6	0.4	0.5	0.6	0.4	0.5	0.6
Aspartame (mg)	30	30	30	30	30	30	30	30	30
Citric acid (mg)	50	50	50	50	50	50	50	50	50
Water (ml)	20	20	20	20	20	20	20	20	20

Formulation table for factorial batches:

RESULT AND DISCUSSION

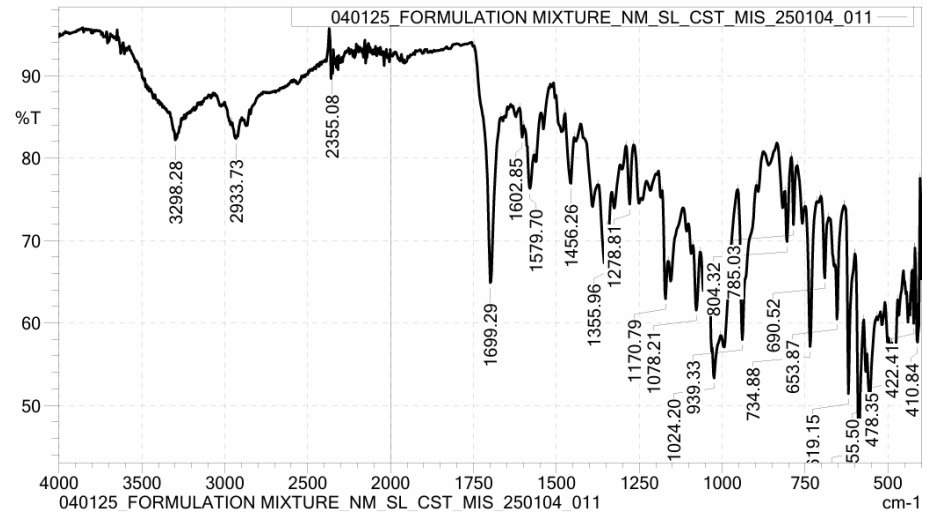
Preformulation Study Results: Melting point determination: The melting point of Rilpivirine Hydrochloride was checked using capillary system and it was found to be 242°C which complies with the reported value.

UV Spectrum of Rilpivirine Hydrochloride in 6.8 Phosphate Buffer: UV spectrum of Rilpivirine Hydrochloride in 6.8 phosphate buffer showed that the drug had a Amax of 242 nm that was similar as reported.

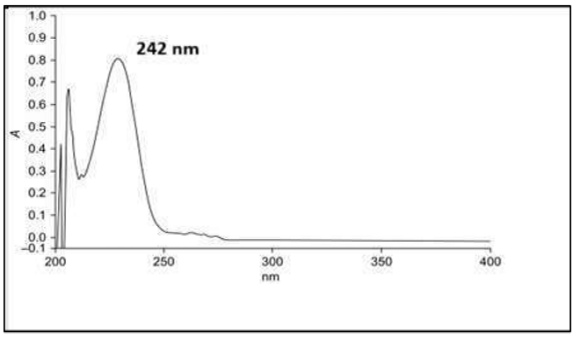
Standard curve of Rilpivirine Hydrochloride: The standard calibration data is shown in below table. The standard plot of Rilpivirine Hydrochloride in 6.8 phosphate is shown in below figure. The correlation coefficient obtained was 0.9965 and equation of regression line was y = 0.0765x-0.0115.

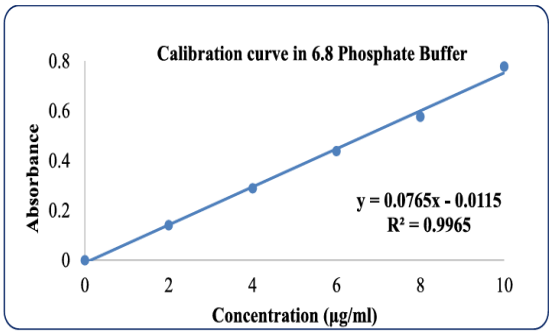
Concentration (µg/ml)	Absorbance ± SD
0	0
2	0.141 ± 0.002
4	0.289 ± 0.003
6	0.439 ± 0.002
8	0.577 ± 0.001
10	0.779 ± 0.003

FTIR Study for Drug and Exepient Compatibility



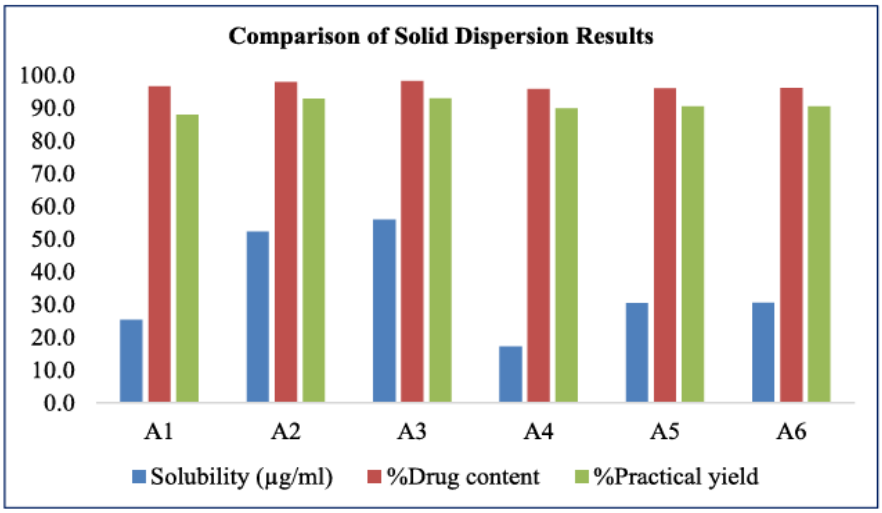
Calibration curve in 6.8 phosphate buffer:





Evaluation of solid dispersion:

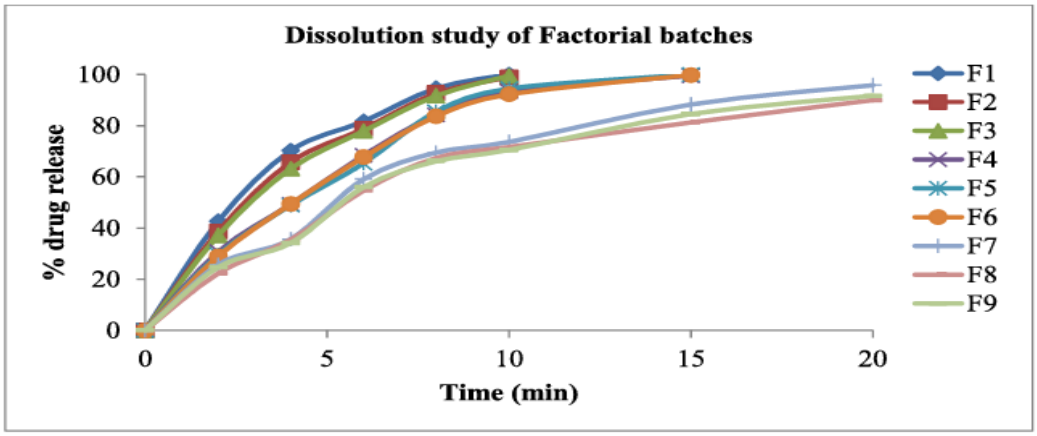
Sr. No.	Formulation Code	Solubility (µg/ml)	%Drug Content	%Practical yield
1	A1	25.30±1.95	96.60±0.96	87.88±1.36
2	**A2**	**52.30±1.37**	**97.89±1.35**	**92.90±0.98**
3	A3	55.95±1.90	98.25±1.55	93.00±1.02
4	A4	17.25±1.87	95.85±0.90	89.88±1.34
5	A5	30.52±1.90	96.00±1.50	90.55±1.05
6	A6	30.60±1.95	96.10±1.54	90.57±1.00



Dissolution profile for factorial batches F1-F9:

% Cumulative drug release

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
2.0	42.65 ± 0.11	38.68 ± 0.38	37.14 ± 0.47	30.72 ± 0.15	29.64 ± 0.97	28.99 ± 0.31	25.68 ± 0.78	22.33 ± 0.29	24.75 ± 0.34
4.0	70.23 ± 0.27	65.70 ± 0.29	63.15 ± 0.54	49.23 ± 0.28	48.90 ± 0.84	49.34 ± 0.37	35.69 ± 0.92	35.42 ± 0.51	34.10 ± 0.47
6.0	81.65 ± 0.35	78.69 ± 0.51	77.84 ± 0.39	68.34 ± 0.71	65.27 ± 0.75	67.68 ± 0.71	59.08 ± 0.53	54.65 ± 0.76	55.92 ± 034
8.0	94.61 ± 0.43	92.69 ± 0.46	91.68 ± 0.92	84.25 ± 0.32	85.42 ± 0.63	83.67 ± 0.35	69.51 ± 0.97	67.42 ± 0.34	66.12 ± 0.58
10.0	99.99 ± 0.57	98.88 ± 0.47	99.46 ± 0.88	93.33 ± 0.52	94.45 ± 0.55	92.23 ± 0.43	73.65 ± 0.39	71.61 ± 0.46	70.46 ± 0.94
15.0	-	-	-	99.54 ± 0.25	99.96 ± 0.41	99.83 ± 0.57	88.24 ± 0.17	81.24 ± 0.21	84.51 ± 0.86
20.0	-	-	-	-	-	-	95.81 ± 0.59	89.91 ± 0.47	91.67 ± 0.63

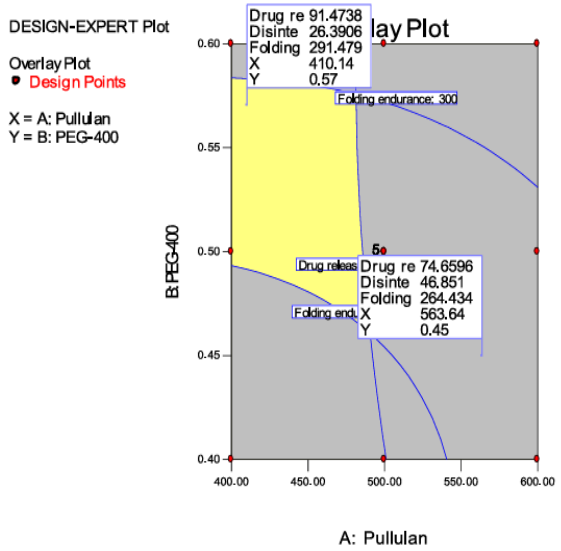


3^2 Full Factorial Design Layout:

Batch	Independent variable		Dependent Variables		
	X_1 Pullulan (mg)	X_2 PEG 400 (ml)	Y_1 (% Drug Release at 8 min)	Y_2 Disintegration Time (sec)	Y_3 (Folding Endurance)
F1	400.0	0.4	94.6	18.0	220.0
F2	400.0	0.5	92.7	24.0	255.0

F3	400.0	0.6	91.7	25.0	310.0
F4	500.0	0.4	84.6	32.0	239.0
F5	500.0	0.5	85.4	38.0	265.0
F6	500.0	0.6	83.7	40.0	318.0
F7	600.0	0.4	69.5	49.0	270.0
F8	600.0	0.5	67.4	59.0	287.0
F9	600.0	0.6	66.1	60.0	335.0

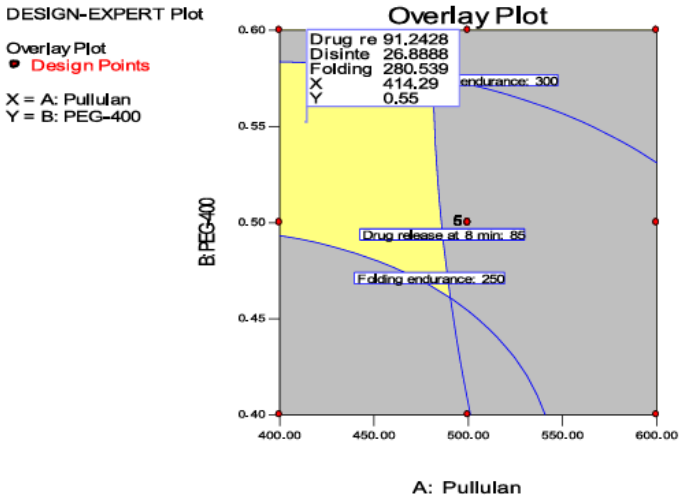
Validation of optimized batch:



Check point batch:

Batch	F10	F11
Pullulan (mg)	410.1	563.6
PEG 400 (ml)	0.570	0.450
Predicted % Drug release at 8 min	91.4	74.6
Observed % Drug release at 8 min	93.9	76.2
% Bias	2.6	2.1
Predicted Disintegration time (sec)	26	46
Observed Disintegration time (sec)	26	48
%Bias	1.00	2.46
Predicted Folding Endurance	291	264
Observed Folding Endurance	285	262
% Bias	2.2	0.9

Overlay plot of optimized batch:



Formulation table for optimized batch O1

Ingredients (mg)	O1
Rilpivirine Hydrochloride+ PEG 6000 (SD) (mg)	1272.000
Pullulan (mg)	414.290
PEG 400 (ml)	0.550
Aspartame (mg)	30.0
Citric acid (mg)	50.0
Water (ml)	10.0

Results of evaluation of optimized batch O1

Evaluation Parameters	Results
Surface of film	Smooth film
Transparency of film	Transparent film
Stickiness of film	Non-Sticky film
Weight variation (mg) Test	41.3±2.2
Thickness (mm) Test	0.14±0.02
Surface pH Test	6.9±0.1
Drug Content (%)Test	99.2±1.6
Folding Endurance Test	280±4
Disintegrating time(sec) Test	28±5
Tensile Strength (kg/cm²) Test	0.452±0.05
% Elongation Test	19.23±0.02
% Drug Release study:-	
Time (min)	% Drug Release
0.0	0.00
2.0	33.8±2.1
4.0	59.5±3.5
6.0	72.4±2.6
8.0	91.7±2.3
10.0	95.5±1.5
15.0	99.9±0.4

Result of stability study of batch O1:

Evaluation Parameters of Batch O1	Initial Results	After 1 month
Surface of film	Smooth film	Smooth film
Transparency of film	Transparent film	Transparent film
Stickiness of film	Non-Sticky film	Non-Sticky film
Surface pH Test	6.9±0.1	6.8±0.1
Drug Content (%)Test	99.2±1.6	99.0±1.5
% Drug Release in 15 mins	99.9±0.4	99.1±1.3

CONCLUSION

The results of this study demonstrate that Pullulan can be effectively used as a film-forming polymer, with PEG 400 serving as a plasticizer for the formulation of fast-dissolving sublingual films containing Rilpivirine Hydrochloride. The optimized batch exhibited acceptable mechanical properties, along with an in-vitro disintegration time of 33 seconds. A drug release study was conducted across 9 batches to identify the best polymer and plasticizer combination. Among all batches, T1, which used Pullulan and PEG 400, showed more than 85% drug release within 15 minutes. Based on the trial batch results, a factorial design approach was employed for formulation optimization, with Pullulan and PEG 400 selected as independent factors. Pullulan and PEG 400 were chosen for further formulation optimization using a 32 full factorial design, revealing that increasing the amounts of Pullulan and PEG 400 increased folding endurance and disintegration time, while decreasing drug release. The optimized batch, O1, exhibited acceptable mechanical properties with an in-vitro disintegration time of 28 seconds, indicating suitability for immediate release of Rilpivirine for systemic use due to its maximum drug release. Stability studies of batch O1 was performed and found satisfactory. Hence, O1 batch is optimized batch.