ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Application of DoE in polymers screening and optimization of *in situ* topical film-forming solution for spray formulation

Nabil Abdullah*, Amit B Patil

Department of Pharmaceutics sciences, JSS College of Pharmacy, Mysuru JSS Academy of Higher Education and Research, Mysuru, 570015, Karnataka, India

Article History:

Received on: 10 Oct 2020
Revised on: 20 Oct 2020
Accepted on: 03 Nov 2020

Keywords:

DoE,
QbD,
32 Full Factorial Design,
ANOVA,
In Situ Film,
Drying time,
viscosity

ABSTRACT

DoE is a structured and organised method to determine the relationship between the effect of change in the concentration of the independent variables and its impact on the formulation, through establishing a mathematical model. Since the acceptance of the QbD approach by the regulatory authorities across the world, DoE has been widely implemented in the areas of screening and optimisation of the formulations by the pharmaceutical industries. The topical delivery of API still posses' limitations such as insufficient contact time, odd hours of application time, sticking to fabrics, formulation washing off, etc. To address these limitations, the researcher planned to develop an *in situ* polymeric sprays that will form a transparent and flexible film, & will not interfere with the applicant's routine. Polymers such as HPMC, Eudragit RS100, PVP K30, PVP K90, Carbopol, Propylene glycol, Soluplus, and pullulan whereas the plasticisers selected were sorbitol. Voriconazole, a second-generation triazole, was used as a model drug. The article is a technological demonstration, in which the screening of polymers as well as the optimised concentration of the polymeric will be selected through 3^2 factorial design. The aim of the present article is also to establish the relationship between the software response and experimental values. The experiments were designed using 3^2 factorial design which resulted in 9 trial runs. Each run was evaluated for drying time, viscosity, and stickiness. The resultant response surface Later the optimisation, to yield an optimised polymeric solution that can deliver a desired *in situ* films. Based on ANOVA comparison of variability due to treatment, the significance of the regression model was evaluated. Other procedures such as DSC, FRIR, Stickiness, pH, diffusion studies were also performed on the selected formulation.

*Corresponding Author

Name: Nabil Abdullah
Phone:
Email: nabilalbaheli1978@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11iSPL4.4505

Production and Hosted by

IJRPS | www.ijrps.com

INTRODUCTION

Polymeric films form an intact layer with the skin surface and hold the APIs for a longer duration of time by resisting any modification even by rubbing and washing (Mcauley *et al.*, 2015). They are easy to apply and are devoid of any complications systemically observed in dosage and topical semi-solid formulations. Polymeric films are designed so that they produce desired effects, easy to apply with improved patient acceptance (Frederiksen *et al.*, 2016).

In situ polymeric film solution is a novel approach that may produce the unconventional dosage formu-

lae applied on the skin like ointments, creams, gels, spray, and patches. *In situ* film polymeric solution spray is applied in the form of liquid which forms a transparent film *in situ* after quick evaporation of the solvent. Polymeric solutions forming films are widely used in surgery, wound care and protection of skin. In surgery, these are used for sealing incisions without using sutures and act as tissue glue or as disinfectants during pre-operative preparation. Topical polymeric film solutions are also used for treating minor cuts, abrasions or for protecting the ostomy wound from surrounding body fluids, and they may or may not contain antimicrobial substances (Kathe and Kathpalia, 2017).

Polymers are the base for film-forming solutions, and different types of polymers are used for the preparation of these solutions. Polymers can be used alone or in conjunction with other polymers to achieve the desired result. The polymers must have the ability to form a clear transparent film at skin temperature upon application. Film formation using polymeric solutions is a comparatively simple process as the polymer is already in the liquid state. Polymer chains start interpenetrating at a specifying concentration and viscosity when the droplets start vaporising from the substrate surface[9]. The polymeric network formed on the substrate controls the release of the drug constituent by serving as an external reservoir. It reduces the excessive release of drug substance to the skin reservoir (Tran and Tran, 2019).

The research aims to design and characterise antifungal *in situ* film-forming polymeric solution spray containing Voriconazole for topical drug delivery. The work focuses on a wider variety of polymers, on selecting suitable polymers and on characterising the properties of the resulting formulations so the production of this novel *in situ* polymer solution spray as a dosing form can be focused on a broader technical basis.

MATERIALS AND METHODS

Materials

Voriconazole (API) was acquired from yarrow-chem products Mumbai, India. Polymers of various forms used were as Eudragit RS100 (Vikram Thermo India Ltd Mumbai), Polyvinyl pyrrolidine K30, Polyvinyl pyrrolidine K 90, Carbopol, Sorbitol (Lobal Chemie laboratory reagats Mumbai), Hydroxypropyl Methylcellulose (Himedia Laboratories Pvt. Ltd Mumbai), Pullulan (Biodeal Pharmaceuticals Pvt. Ltd Himachal Pradesh), Soluplus (BASF, Mumbai), Propylene glycol (Sisco research laboratories Pvt. Ltd Mumbai) were founded as a pharmaceutical lab. The solvents and other chemicals used were of the pharmaceutical laboratory.

Procedures

Preparation of Voriconazole *in situ* film

Steps associated with the formulation of polymer in situ films, as shown in Figure and Composition of polymeric topical delivery formulations, as shown in Figure 1.

Determination of solubility

Voriconazole saturation solubility was measured in the pH 1.2 HCl, Phosphate pH buffer 6.8, Phosphate pH buffer 6.8, ethanol and distilled water. Each media was prepared, and excess samples were applied to 25 ml of each medium put in the conical 50 ml flask and held for 24 h for shaking on mechanical shake. After 24 h of shaking, 1 ml of aliquot was removed from each sample and filtered through No. 0.45 micron, whattman filter paper. Absorption has been calculated in the 200-400 nm range of visible UV spectrophotometer, and solubility measurements have been carried out (Parthibarajan *et al.*, 2012).

Compatibility Studies of Voriconazole-Excipient

Differential Scanning Colorimetry (DSC)

The pure drug (Voriconazole) and physical mixture with polymer (Eudragite RS100) thermal characteristics were done by differential calorimeter scanning (Shimadzu, japan, DSC-60) mention in the table and figure. Sample with about 5 mg was placed in aluminium pans for each sample on it, and DSC analysis was performed at a flow amount of 20 ml min^{-1}. Dynamic scans were rendered within the temperature range of 10 to 300 ° C in the nitrogen atmosphere at 10 ° C / min. Indium has been used as a standard reference for temperature adjustment (Schroeder *et al.*, 2007).

FTIR Spectral Analysis

The pure drug (Voriconazole), polymer (Eudragite RS100) and their physical mixture of the Fourier – transform (FTIR) spectra were recorded using a visible UV spectrophotometer (FTIR-8400S, Shimadzu, Kyoto, Japan) and mentioned in the table and figure. Disks of each sample (5 mg) were individually mixed with 200 mg of potassium bromide (spectrographic rank) and compressed into the disks using a hydraulic press (4000 cm^{-1} to 400 cm^{-1}) before scanning (Misra *et al.*, 1996).

Film Forming Capacity of Various Polymers

The polymeric placebo films were prepared using the technique of solvent casting. The polymeric placebo films were prepared using various solvents

Table 1: Composition of placebo polymeric film solution with different solvents

Formulation Code	Polymers	Quantity (mg)	Ethanol (ml)	Hydroalcoholic (1:1ml)
F1	Polyvinyl pyrrolidine K30	40	20	20
F2	Polyvinyl pyrrolidine K 90	40	20	20
F3	Eudragit RS100	40	20	20
F4	Hydroxypropyl Methylcellulose	40	20	20
F5	Carbopol	40	20	20
F6	Propylene glycol	40	20	20
F7	Pullulan	40	20	20
F8	Soluplus	40	20	20

Table 2: Composition of the Voriconazole solution spray by DoE %W/V

Code Formulations	Components			
	Voriconazole	Eudragit RS100	Sorbitol	Ethanol purity (96%) upto (ml)
F1	1	20	2	20
F2	1	20	3	
F3	1	20	2	
F4	1	22	3	
F5	1	22	4	
F6	1	22	4	
F7	1	22	4	
F8	1	24	2	
F9	1	24	3	

Table 3: Grading of transparency

SI No.	Transparency	Grade
1	Completely	++
2	Acceptable	+
3	Blurred	-

Table 4: Solubility Profile of Voriconazole

Sr No.	Solvents	Solubility (mg/ml)
01	pH 1.2	1.823
02	pH 6.8	2.612
03	pH 7.4	3.431
04	Ethanol	4.871
05	Distilled Water	0.641

Table 5: DSC data of Voriconazole + Eudragite RS 100

SI. No.	Thermal Analysis	$T_{º(º C)}$	$T_{m\ (º C)}$	$T_{c\ (º C)}$	Melting range
1	Voriconazole	130.95 c	133.67 c	138.67	7.72
2	Voriconazole +Eudragite RS100	129.35	133.63	138.80	7.26

$T_º$ – melt begins, T_m – melting point, T_c– melting completion, DSC data collected at $10_{ºc}$ /min.
Thermographs of DSC of pure Voriconazole show a sharpmelting endotherm at temperature 133.67.

Table 6: Functional groups of *In situ* film-forming polymeric solution

Frequency of drug (cm-1)			Functional group
Voriconazole with Eudragite RS100	Eudragite RS100	Voriconazole	
1678	1650	1670	C=N (Stretch)
1718	1740	1750	C=O (Stretch)
1310	-	1290	C-F (Stretch)
1430	1390	1390	C-N (Stretch)
3390	3450-3550	3100	OH (Stretch)
2850	2970	-	CH2 (Stretch)
1650	-	1590	C=C (Stretch)

Table 7: Placebo polymeric film prepared with ethanol

SI No.	Formulation code	Parameters		
		DT* (min)	Transparency	Stickiness (Yes/No)
1	Polyvinyl pyrrolidine K30	19±0.4	+	Yes
2	Polyvinyl pyrrolidine K 90	17±0.6	+	Yes
3	Eudragit RS100	<1±0.5	+++	No
4	Hydroxypropyl Methylcellulose	21±0.8	+	No
5	Carbopol	29±0.6	-	Yes
6	Propylene glycol	18±0.8	-	Yes
7	Pullulan	Film not formed		
8	Soluplus	Film not formed		

* Average of 6 readings

Table 8: Placebo polymeric film prepared with a hydroalcoholic solution (1:1)

SI No.	Formulation code	Parameters		
		DT* (min)	Transparency	Stickiness (Yes/No)
1	Polyvinyl pyrrolidine K30	21±0.2	-	Yes
2	Polyvinyl pyrrolidine K 90	40±0.6	-	No
3	Eudragit RS100	9±0.5	+	Yes
4	Hydroxypropyl Methylcellulose	34±0.8	+	No
5	Carbopol	42±0.2	-	Yes
6	Propylene glycol	38±0.4	-	Yes
7	Pullulan	29±0.6	-	Yes
8	Soluplus	27±0.4	-	Yes

* Average of 6 readings

Table 9: Various in situ-based variations of VOR with 3^2factorial designs

Code of Formulation	Levels of coded factors		Responses	
	A	B	R1#	R2#
F1	-1	-1	29±0.02	0.12±0.05
F2	0	-1	32±0.02	0.12±0.07
F3	-1	1	33±0.09	0.14±0.08
F4	1	-1	30±0.05	0.13±0.09
F5	1	1	39±0.06	0.13±0.04
F6	-1	0	42±0.04	0.14±0.02
F7	0	0	90±0.05	0.19±0.03
F8	0	1	93±0.07	0.19±0.01
F9	1	0	92±0.03	0.20±0.07
Factors and their coding	-1 0 1			
A: polymers quantity (%)	20 22 24			
B: Plasticizer quantity (%)	2 3 4			

*Mean±SD; n=3

Table 10: ANOVA for Drying time response (DoE)

Source	Sum of Squares	df	Mean Square	Value F	p-value Prob > F	Conclusion
Model	20168.00	4	5042.00	1260.50	< 0.0001	Significant
A-Polymer	16380.50	1	16380.50	4095.13	< 0.0001	Significant
B-Plasticizer	162.00	1	162.00	40.50	< 0.0001	Significant
A2	3601.50	1	3601.50	900.38	< 0.0001	Significant
B2	24.00	1	24.00	6.00	0.0227	Significant
Residual	88.00	22	4.00	-	-	-
Lack of Fit	88.00	4	22.00	-	-	-
Pure Error	0.000	18	0.000	-	-	-
Cor Total	20256	26	-	-	-	-

Table 11: ANOVA for Viscosity response (DoE)

Source	Sum of Squares	df	Mean Square	Value F	p-value Prob > F	Conclusion
Model	0.025	5	4.961.3	760.20	< 0.0001	Significant
A-Poly	0.019	1	0.019	2963.55	< 0.0001	Significant
B-Plasticizer	6.722.4	1	6.722.4	103.01	< 0.0001	Significant
AB	3.333.5	1	3.333.5	5.11	0.0346	Significant
A2	4.446.3	1	4.446.3	681.36	< 0.0001	Significant
B2	3.130.4	1	3.130.4	47.96	< 0.0001	Significant
Residual	1.370.4	21	6.526.6	-	-	-
Lack of Fit	7.037.5	3	2.346.5	6.33	0.0040	Significant
Pure Error	6.667.5	18	3.70.6	-	-	-
Cor Total	0.025	26	-	-	-	-

Table 12: Evaluate the film-forming system according to different standards

Sl. No	Formulation code	Parameters DT* (sec)	Transparency	Stickiness (Yes/No)	Structural features	Flexibility
1	F1	29±0.02	++	No	Smooth/weak	Non-flexibility
2	F2	32±0.02	++	No	Smooth/weak	Non-flexibility
3	F3	33±0.09	++	No	Smooth/weak	Non-flexibility
4	F4	30±0.05	++	No	Smooth/weak	Non-flexibility
5	F5	39±0.06	++	No	Soft/shiny film/ clear	Flexibility
6	F6	42±0.04	++	No	White film residue after drying	Flexibility/ cracking
7	F7	90±0.05	++	No	White film residue after drying & hardness	Flexibility/ cracking
8	F8	93±0.07	+	No	White film residue after drying & hardness	Flexibility/ cracking
9	F9	92±0.03	++	Yes	White film residue after drying & hardness	Flexibility/ cracking

*Average of 6 readings

Table 13: pH test for the formulation

No	Code of formulation	pH*
1	F1	6.05 ±0.2
2	F2	7.01 ±0.5
3	F3	7.04 ±0.3
4	F4	7.09 ±0.1
5	F5	7.11 ±0.4
6	F6	6.98 ±0.3
7	F7	7.02 ±0.2
8	F8	6.93 ±0.2
9	F9	7.13 ±0.3

*Mean±SD; n=3

Table 14: Thickness measured for the formulation

No.	Code of formulation	Thickness
1	F1	0.01 ±0.2
2	F2	0.01 ±0.5
3	F3	0.02 ±0.3
4	F4	0.02 ±0.1
5	F5	0.08 ±0.4
6	F6	0.08 ±0.3
7	F7	0.09 ±0.2
8	F8	0.12 ±0.2
9	F9	0.14 ±0.3

*Mean±SD; n=3

Table 15: WVP of polymeric films

Formulation Code	WVP (g-mm/kpa-m^2) 8^{th} hours	24^{th} hours
F1	0.0025±0.3	0.011±0.4
F2	0.0025±0.2	0.12±0.3
F3	0.0045±0.1	0.15±0.4
F4	0.005±0.2	0.016±0.1
F5	0.0057±0.2	0.0183±0.2
F6	0.0052±0.3	0.019±0.2
F7	0.0075±0.1	0.023±0.4
F8	0.0083±0.3	0.027±0.2
F9	0.0112±0.3	0.33±0.3

* Mean of 6 reading±S.D

Table 16: Moisture content Analysis %

Formulation Cod	Moisture Content
F1	1±0.11
F2	1±0.12
F3	1±0.10
F4	1.5±0.12
F5	1.5±0.12
F6	2±0.13
F7	2±0.12
F8	2.05±0.14
F9	2.5±0.11

* Mean of 6 reading ±S.D

Table 17: Viscosity Analysis %

Formulation Cod	Moisture Content
F1	0.12±0.05
F2	0.12±0.07
F3	0.14±0.08
F4	0.13±0.09
F5	0.15±0.04
F6	0.14±0.02
F7	0.19±0.03
F8	0.19±0.01
F9	0.20±0.07

Table 18: Mechanical properties of apolymeric film formed

Formulation cod	Width (mm)	Area of cross-section (cm^2)	Thickness (mm)	Max force (Kg)	Tensile strength Kg/cm^2	Elongation %
F5	20±0.03	0.04±0.08	0.08±0.01	1.08±0.05	3±0.04	5.71±0.03

Mean value (±SD)

Table 19: Absorbance Values of *In vitro* release study

No.	Time (hours)	Absorbance	%CDR
1	0	0	0
2	15	0.152±0.05	5.14
3	30	0.197±0.02	39.3
4	60	0.243±0.01	38.9
5	120	0.287±0.05	45.3
6	180	0.361±0.09	55.97
7	240	0.433±0.02	66.42
8	300	0.519±0.04	78.99
9	360	0.623±0.04	93.99
10	420	0.673±0.05	101.30

Mean value (±SD) n=3

such as ethanol, and hydroalcoholic solution. The purpose of the experiment was to research the impact of solvent on the film-forming capacity of the polymers without plasticisers. Solvent effects and film quality were studied in terms of transparency, film stickiness, and drying time. The different types of polymers like as Eudragit RS100, Polyvinyl pyrrolidine K30, Polyvinyl pyrrolidine K 90, Hydroxypropyl Methylcellulose, Carbopol, Pullulan, Soluplus, Propylene glycol, were investigated for their film-forming ability given in Table 1.

DoE for optimising formulation

For the optimisation of the formulated polymeric film, a full 3^2 design factory was used. The concentration of polymer (X1 Eudragit RS100) and plasticiser (X2 sorbitol) was chosen as independent variables according to the literature review, and it is shown in Table 2, Viscosity (Y1) and dry time (DT %) (Y2) were chosen as dependent variables, and API was a constant value. A statistical model is concerned with compositional response (degradation) Equation (1).

$$Y = b_\circ + b_1X^1 + b_2X_2 + b_3X^2 + b_4X^2$$

It is proved that Y is the interaction response, whereas b0 is the arithmetic uncaring overreaction of the nine trails. The above interaction in the equation Y is the measurable result of preparation ingredient or different autonomous changes X and Y; b0 is the average arithmetic interaction; b1, b2 and b3 are the correlated coefficients for the elements

Table 20: Storage stability data of the optimised formulation batch F5

No	Parameters	Room temperature (30±2°C)		
		2 months	3 months	6 months
1	DT* (sec)	44±0.03	47±0.03	48±0.03
2	Transparency	++	++	++
3	Stickiness (Yes/No)	No	No	No
4	Viscosity (cps)	15.1±0.3	15.4±0.3	15.21±0.3
5	The volume of solution delivered by actuation (ml)	0.289±0.021	0.291±0.022	0.292±0.021
6	Density (gm/ml)	0.691±0.01	0.686±0.03	0.685±0.02
7	Spray angle	81.63±0.07	81.12±0.04	80.72±0.04
8	Spray pattern	Transparent, clear, spherical and uniform	Transparent, clear, spherical and uniform	Transparent, clear, spherical and uniform
9	Folding Endurance	Satisfactory	Satisfactory	Satisfactory
10	Thickness	0.08±0.01	0.08.7±0.06	0.08.7±0.10
11	Tensile strength (Kg/cm2)	3±0.02	2.7±0.05	2.7±0.04
12	Elongation at break %	5.71±0.02	5.41±0.07	5.53±0.03
13	Water Vapor Permeability (g-mm/kpa-m2)	0.0025±0.2	0.0024±0.3	0.0024±0.4
14	Surface pH study	6.3±0.02	6.4±0.01	6.4±0.03
15	Moisture content (%)	1±0.12	1.1±0.11	1.1±0.14
16	CDR (%)	101.30	100.47	100.50

* Mean of 6 reading ±S.D

X and Y. Factorial design details are provided in the table. Variables representing each factor, with corresponding qualitative levels for each excipient, were included. DESIGN EXPERT® (version 10) software brought optimised formulation. In the standard container, the optimised formulation was filled in. Analyses for DSC, FTIR, water vapour permeability (VWP), moisture content, moister absorption, mechanical properties (folding capacity, thickness, elongation percentage, tensile strength), spray angle, spray pattern and *In-vitro* release studies were the optimisation formulation (Osmani *et al.*, 2016).

Characterisation of Voriconazole polymeric film formulations

Typical control tests in topical film polymeric solutions are designed to optimise and improve the delivery system and formula proficiency.

Drying time (DT)

The solution was sprayed on the skin surface, allowing drying and recording the time. In a normal environment, solution drying can be done, and the film is formed.

Morphological characterisation of the films

The outer surface of the dried films was evaluated for its stickiness/ smoothness by pressing and absorptive rubbing cotton wool under low manual pressure on the dry film, after pressing and rubbing of cotton wool, if the fibres from the cotton wool stick to the outer surface of the film then it was termed as sticky. If no fibres were found, the outer surface was said to be smooth (Saudagar, 2014).

Determination of Transparency

The transparency of the dried films forming was established by visual inspection and graded according to Table 3. The films were also inspected for any bubble entrapment a deformation.

pH

Digital pH meters were used to determine the pH of the polymeric spray solution. The phosphate buffer pH meter of 7.4 has been calibrated. The pH electrode was dipped to reach a pH of 20 ml of polymeric solution spray in a little beaker of glass. The pH was determined three times in every formula, and aver-

age values were estimated (Padula *et al.*, 2019).

Uniform Thickness of Films

The film-forming thickness was measured using a 0.01 mm precision handheld micrometre (Dial Gauge thickness 7301, Mitutoyo, Kanagawa, Japan).

The thickness of the film samples was measured at 4 to 6 random points, and the mean value was used (Gohel and Nagori, 2009).

Viscosity

The solutions were measured with Brookfield viscometer (Brookfield engineering laboratories, Inc., USA.) at a viscosity of $25 \pm 1^{\circ}$C. The spindle ULA S00 was rotated at 10 rpm, and 20 ml of the sample was taken in ULA cylinder. The torque readings were still higher than 10%. Three measurements were taken, and the average was determined.

AL= (W_t – W_o) Dn.

AL- the quantity of the sample given at each distribution, Wt- after distribution of formula weight, Wo- initial formulation weight before distribution, and Dn- density.

Quantity of solution given for each actuation

Amount of solution supplied with every operation. Using the volume of the polymeric film solution provided at each actuation was calculated (Pawar *et al.*, 2017).

A_L = (W_t – W_o) $D_{n.}$

Where, A_L- The quantity of solution given at every actuation, Wt- Weight after-action formulation, Wo- initial formulation weight before a performance, and Dn- formula's density.

Density

The dried and emptied Pycnometer was weighed and filled with the sample. The air bubble was permitted to rise to the top before inserting the stopper. The right value of the density was calculated by dividing the final liquid weight in Pycnometer (Ranade *et al.*, 2017).

The angle of the spray

The spray of solutions was stimulated flatly onto a white paper attached at 10 cm from the nozzle. A circle is formed on the paper, the radius of which is noted down. Radius from different directions was registered three times. The angle of spray (θ) was calculated by

$$Eq = \tan^{-1}(1/r)$$

Where 1- the distance between the paper and the nozzle, r- Median circular radius.

The pattern of the spray

For the study, the method used to impinge spraying on a piece of paper. 10 mg Methylene blue was dissolved in the polymeric film solution to facilitate visualization (Mustapha *et al.*, 2016).

Folding Endurance

Folding stamina was specific by repeated film folding at the same location until the film breaks. That indicates the film's brittleness. It is measured as the amount of folding endurance as the number of times when the film is plied without breaking. In the paper test, the folding endurance is the logarithm (to the base of ten) of the number of double folding parts necessary for breaking the test part under standardised conditions (for Testing and Materials, 2002).

$$F = \log_{10} d$$

Where F is the folding endurance; d the number of double folds.

Tensile strength

The tensile strength was a film strength measurement and is calculated by dividing the maximum force required to break the films by the film cross-sectional area. To determine the peak load and tensile strength of the film, a universal test machine (International Equipment's, Mumbai) was used (Anter *et al.*, 2018). The result is expressed in megapascals (MPa) and registered to a significant character.

$$Tensile \quad strength = \frac{(load\ at\ break)}{(original\ width)(original\ thickness)}$$

Elongation at break %

The per cent elongation was determined by dividing the elongation by the initial gauge length at the moment of the rupture and multiplying by 100. When using gauge marks or extensometers to define a particular section of the test. Tensile testing was used to determine the film peak charge, elongation at peak load. The tested film was determined as follows (Kaur *et al.*, 2013).

$$Eb = \frac{L - L_0}{L_0} \times 100$$

Where L is the film's final length and where L_0 its original length.

Water Vapor Permeability

The permeability of the film samples to water vapour was calculated gravimetrically by the process. In WVP tests, films were chosen based on a lack of physical defects like cracks, bubbles and pinholes. Horizontally placed rectangular film samples (5 mm / 5 mm) on the WVP weighed in 10 ml beakers and

filled with distilled water up to 1 cm below the picture. The beakers were set at 25°C and 50 per percentage RH in the regulated humidity chamber with 1 m / min air current circulation. For a period of 8 and 24 hours, the cup was weighed every hour. The transmission rate of the water vapour (WVTR) was estimated from the slopes of the cup's steady-state portion of weight loss versus the time curve (Abdellatif and Tawfeek, 2016).

$$WVPR = \frac{W}{A*t}(g/cm^2 * 24\ h)$$

Where WVTR is the calculated rate of water vapour transmission (g / m^2s) through with a film, A was film surface area, and t was the time (h).

Moisture content

The polymeric films (2 cm^2) were held for three days in a desiccator that contained activated silica and weighed (W_i) at room temp. The films were weighed periodically until we obtained a constant weight (W_f). The calculation of the (per cent) moisture content was based on the following equation (Maghraby *et al.*, 2008).

$$Moisture\ content\ (\%) = \frac{W_i - W_f}{W_i} \times 100$$

Where W_i is the film's initial mass and W_f is the film's final weight.

In-vitro release review of cellophane membrane

The modified Franz diffusion cell was used as a cellophane membrane for the permeation test. The cellophane membrane was immersed overnight in distilled water. Then it was soaked 24h before usage in pH 7.4 stock solution. The cellophane membrane was between the donor cell and the recipient cell. The spray of a polymeric solution was moved to the donor cell. The entire membrane surface was in contact with a receptor compartment containing 20 ml of pH 7.4 buffer of phosphate[19]. The cell was agitated at 50 rpm on a magnetic stirrer and kept at 37±1 ° C. Every time 1 ml was withdrawn at intervals of 15, 30, 60, 120, 180, 240, 300, 360, and 420 min and replaced with the same fresh buffer of phosphate pH 7.4.

Stability Studies

Optimised formulation (batch F5) was kept away from the light for six months at 30 ± 3 2C. And checked every tow month, Various measures including viscosity, the volume of solution delivered for every actuation, pH, angle of spray, the pattern of spray and in vitro experiments of drug release were subjected to the formulation. The study procedure used was identical to that mentioned previous section (Deekshitha *et al.*, 2020).

RESULTS AND DISCUSSION

Determination of solubility

The results of Voriconazole's qualitative solubility in various solvents are shown in Table 4 and Figure 2 below,

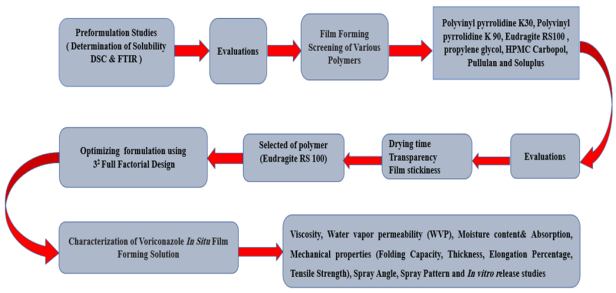

Figure 1: Scheme of (VOR) in situ polymeric film

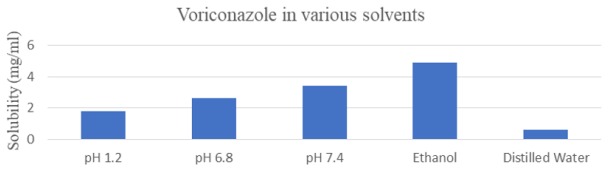

Figure 2: Histogram representing the solubility of API in different solvents

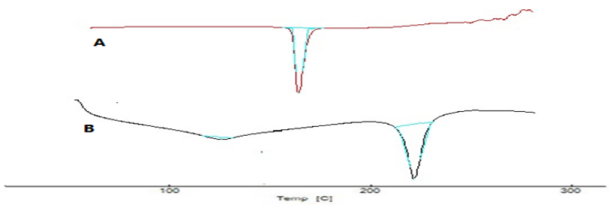

Figure 3: Thermographs of DSC: (A) Voriconazole pure (B) their physical combination (Voriconazole with Eudragite RS 100)

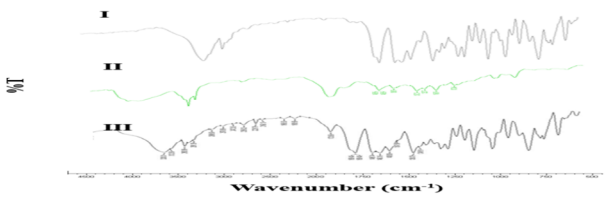

Figure 4: FT-IR Spectral of (I) Pure of Voriconazole, (II) Eudragite RS 100, (III) Physical mixture of (Voriconazole + Eudragite RS 100).

Compatibility Tests of Voriconazole-Excipient

Differential Scanning Colorimetry Studies (DSC)

Table 5 and Figure 3 show the respective voriconazole DSC thermograms and their physical mixture (Voriconazole with Eudragite RS 100).

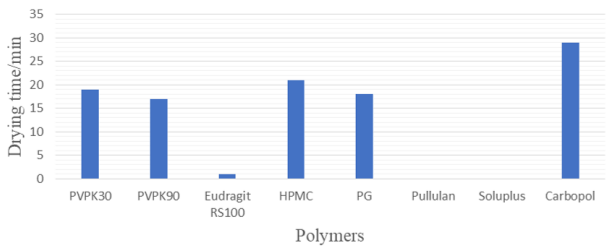

Figure 5: Drying time of Ethanol polymeric film

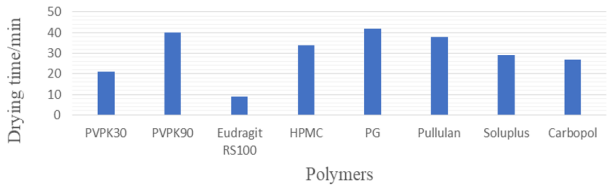

Figure 6: Drying time of the hydroalcoholic polymeric film

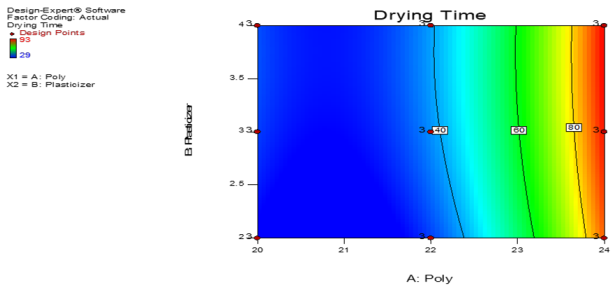

Figure 7: Response surface plots of R1 Drying time (sec) of VOR based in situ polymeric film.

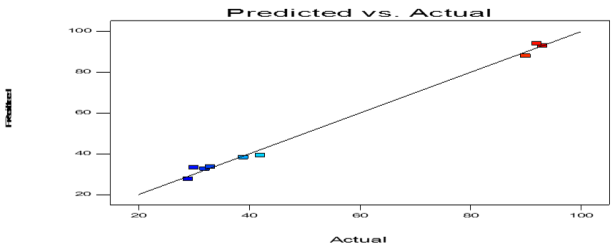

Figure 8: The linear difference between occurrence and estimated drying time value (Y_1).

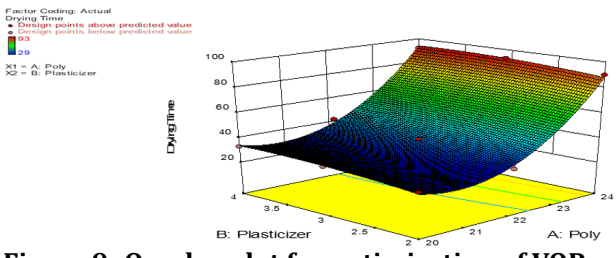

Figure 9: Overlay plot for optimisation of VOR based in situ polymeric films.

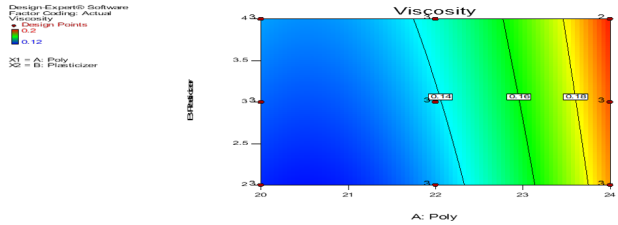

Figure 10: Response surface plots of R2 viscosity (cps) of VOR based in situ polymeric film

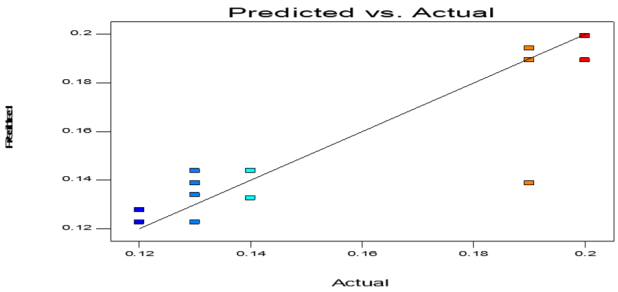

Figure 11: The linear difference between occurrence and estimated viscosity value (Y_2).

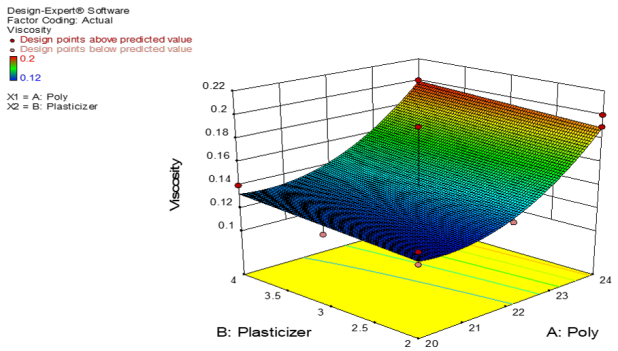

Figure 12: Overlay plot viscosity on VOR dependent in situ polymeric film optimisation

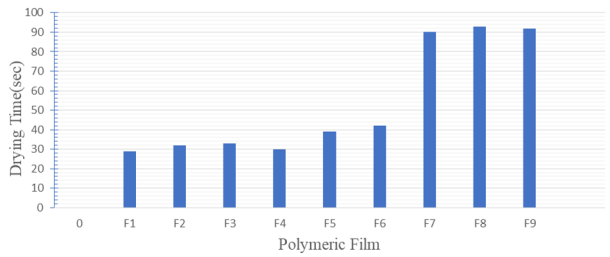

Figure 13: Drying Time of Polymeric Film Formulations

Voriconazole thermogram exhibited a broad endothermic peak at 138.07 °C related to the evolution of the sample's moisture. The prominent melting peak at 182.91 °C manifested the natural crystalline state of polymer (Eudragite RS 100). The characteristic endothermic peaks of both drug and polymer were observed at their authentic locations in the case of a physical mixture, and there was

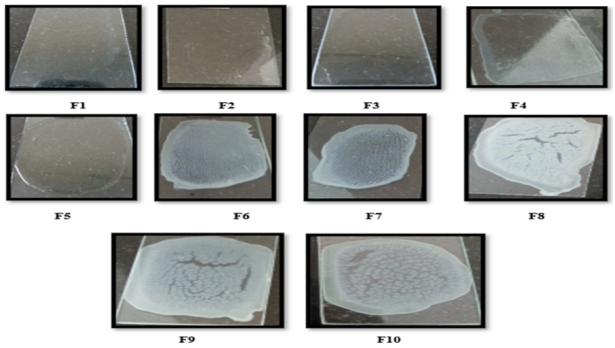

Figure 14: Drying Time In Situ Polymeric Film Forming Formulations

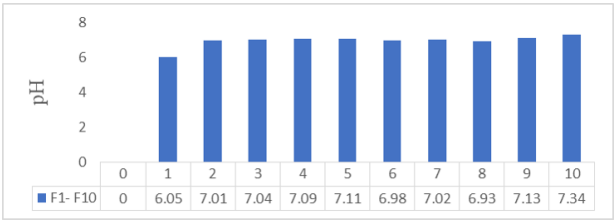

Figure 15: Measured pH for polymeric solution

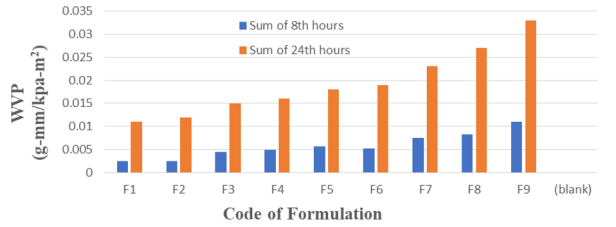

Figure 16: WVP of polymeric films

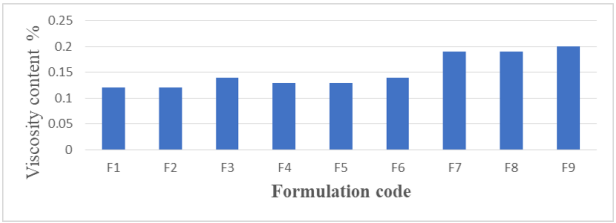

Figure 17: Moisture content %

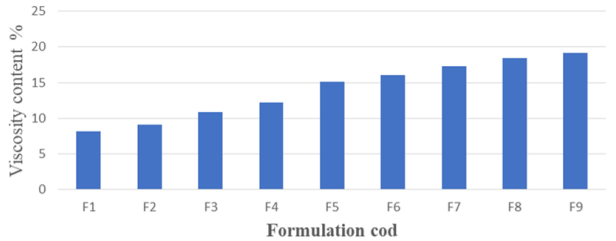

Figure 18: Viscosity content %

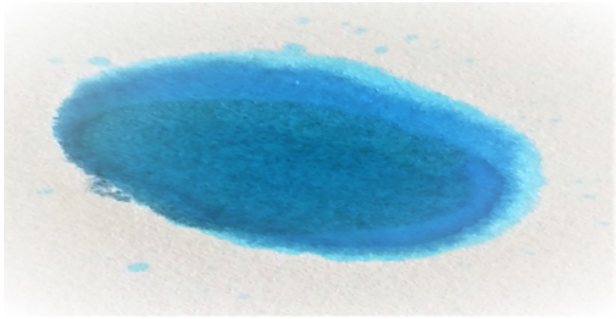

Figure 19: Spray pattern (F5)

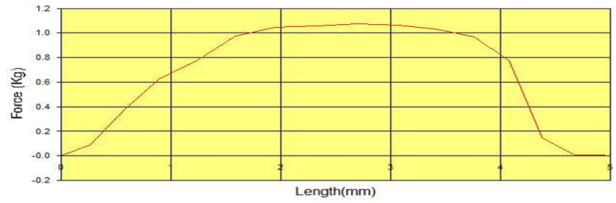

Figure 20: Mechanical Properties for the film formed F5

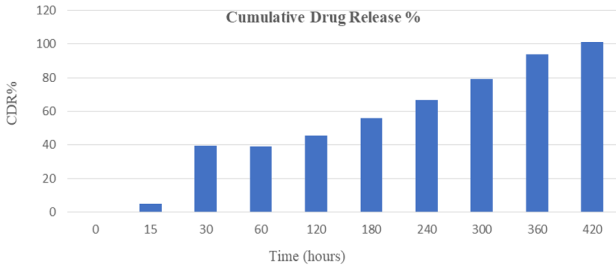

Figure 21: Cumulative Drug Release CDR%

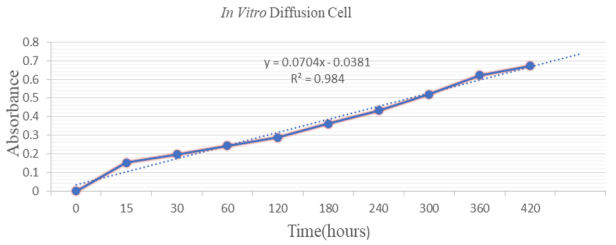

Figure 22: In vitro diffusion cell using cellophane membrane

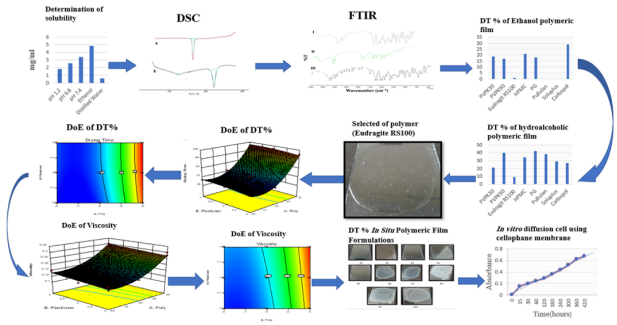

Figure 23: Scheme result of (VOR) in situ polymeric film

almost no interaction between Voriconazole and polymer.

FTIR Spectral Analysis

FT-IR spectra of Voriconazole, polymer (Eudragite RS 100) and its physical mixture (Voriconazole + Eudragite RS 100), The range of OH Voriconazole FTIR generally exhibited stretching at 3200.09–3046.04 cm^{-1}, C-N extending at 1510.28–1451.28 cm^{-1}, and C-F at 1587.44–1451.28 cm^{-1}, shown in Figure 4, respectively. The Eudragite RS-100 FTIR spectrum showed a peak of 2953.9 cm–1 due to the presence of O – H (carboxylic acid), 1450.7 cm–1 due to the -CH2 bend, and 1731.2 cm–1 due to the presence of C = O (ester). The spectrum of the physical mixture of the drug (Voriconazole) and polymer (Eudragite RS 100) was identical, in a physical mixture of Voriconazole and polymer, no presence or disappearance of voriconazole peaks of the same characteristics as the ones listed in Table 6 and verified by the lack of chemical interactions between Voriconazole and polymer.

Characterisation of placebo film-forming polymers

Characterisation of placebo polymeric film-forming solution with absolute ethanol it's given in Table 7 and Figure 5.

Characterisation of placebo polymeric film of a film-forming solution with a hydroalcoholic solution it's given in Table 8, Figure 6.

DoE for optimising formulation

A 3^2-level factorial, for optimisation of the formulation, complete factor design was used. The rates of the autonomous variables were based on the preliminary results of the batch. The low, medium and high rates were 20%, 22% and 24% respectively for Eudragite RS100. Plasticiser was used at low (2%), medium (3%) and high (4%) rates, respectively. Variable effect independently on Y1 (cps) viscosity and time of drying Y2 (seconds). The equation ANOVA indicated the model F values 760,20, P-value < 0,0001; showing the model to be significant. ANOVA for drying time and viscosity conclusion mentioned in Tables 9, 10 and 11. The reduced model was confounding, but the most important parameters influencing the response were screened (Eq. 1).

$$2644 - 254.42\ X_1 + 15\ X_2 + 6.12\ X^1 - 2\ X^2$$

The correlation coefficient was respectively 0.995 and 0.993 in the complete model and reduced form. Increased Eudragit RS 100 concentration increased drying time requires optimised formulation (Y1) development mention in Figures 7, 8 and 9. The polynomial equation above shows a strong match of response variables at various levels.

For both the full model and reduction model the correlation coefficient value was 0.859 and 0.810 respectively. Y2 (Viscosity) was affected as a major factor by the increased concentration of polymers (Eq. 2). $2.44 - 0.23\ X_1 + 0.00 + X_2 + 0.01 + X^1 - 2\ X^2$ note in Figures 10, 11 and 12.

Characterisation parameters related to polymeric film formulations

Forms of evaluation films for all formulations such as drying time, transparency, stickiness, flexibility and structural characteristics. After analysing all the formulations, in terms of the film-shaped and unregulated from the negatives and defects present in some of the formulas are shown in Table 12 and in Figures 13 and 14 the best suitable.

pH

pH measurements were made using a pH meter. For measuring pH, 20ml Spray for the solution was used. Results are shown in Table 13 and Figure 15.

Thickness

The thickness of all formulations was between 0.01±0.03 to 0.08±0.02 their mention in Table 14.

Water Vapor Permeability (WVP)

The results of studies on the transmission rate of water vapour (WVTR) are shown in Table 15. And then in Figure 16. Also, plasticiser addition was found to affect the permeability of polymer film as the experimental humidity conditions affected the WVTR, 25 per cent humidity conditions, and 50 per cent throughout the study were employed.

All polymeric films showed low WVTR indicative of its hydrophobic character. A decrease in WVP is considered advantageous for application to skin targets.

Moisture content

Studies of the moisture content gave an insight concerning the stability of the film. The moisture content (percentage) of polymer films was low (1± 0.113 per cent, 1± 0.113 per cent, 1± 0.113 per cent, 1.5± 113 per cent, 1.5± 0.113 per cent, 2. ± 113 per cent, 2±11 per cent, 2.05± 12 per cent, 2.5± 10 per cent) respectively, which may help preserve stability and prevent dryness and fragility during long-term storage, especially under dry co-storage, noted in Table 16 and Figure 17.

Viscosity

Formulations viscosity containing Eudragite RS100 as a polymer and glycerol as a plasticiser, formulations viscosity results were noted in Table 17 and

Figure 18 and sufficient spray capability is demonstrated.

Characterisation of Optimisation in situ film-forming solution spray formulation

Quantity of solution given for each actuation

According to the equation given in the evaluation, the result will be as follows.

For each actuation, the quantity of solution was 0.289±0.021 ml.

$$20ml = \frac{2.55-2.75}{0.691} = 0.289\ ml$$

Density

A pycnometer determined density, and the density value was estimated by measuring the resulting liquid weight into a pycnometer by amount.

$$31.07 - 44.9 = 13.83$$
$$= \frac{13.83}{20} = 0.691(gm/ml)$$

Density spray solution was 0.691(gm/ml).

Spray angle

Spray angle was evaluated from local container spray and equation calculated by =$\tan^{-1}$ (1/ r).

Where 1- the distance between the paper and the nozzle, r- Median circular radius. Average radius circle = 2.2 cm and distance of paper from nozzle was 15cm so,

$$\tan^{-1} = \frac{15}{2.2} = 6.8\ cm$$
$$\tan^{-1} = 81.63$$

spray angle was 81.63^0±0.07

Spray pattern

It was observed that the formulation of the spray pattern was transparent, clear, spherical and uniform. After application of a clear transparent film, the drying time was 43 sec.

The optimised formulation showed good sprayed properties. Figure 19 depicts an illustration of the films formed after drying (with the inclusion of methylene blue to improve visibility).

Folding Endurance

The values of folding endurance of formulation developed by the polymeric film were found in 80 folds which are considered adequate, elastic and reveal good film quality.

Tensile strength

Tensile strength was determined to define polymer film for its abrasion resistance and durability, the formula determined the tensile strength.

$$Tensile\ strength = \frac{(1.08\ Kg)}{(2\ mm)(0.18mm)} = 3\ Kg/cm^2$$

The result mention in Table 18.

Elongation at break %

Due to their abrasion resistance and durability, elongation at break was determined to characterise polymer film, noticed in Figure 20.

$$Elongation\ at\ break = \frac{74-70}{70} \times 100 = 5.71\ \%$$

In vitro release study using cellophane membrane

Studies of the release of the drug were performed *in vitro* using a cellophane membrane in Franz diffusion cell. It includes a donor cell and a receiver compartment. The receptor compartment was filled in as a diffusion medium with 20ml of phosphate buffer pH 7.5 solution. In the receptor compartment, the prepared polymer solution was a spray, Magnetic beads used to stir the liquid constantly with 50 rpm, and 37±1 °C held its temperature. 2ml receptor fluid sample was withdrawn at fixed intervals, and the same amount of 2ml phosphate buffer solution was replaced with the samples measuring their absorbance at 256 nm. The total volume of drug release transported in a formulation containing 22% of Eudragite RS 100 and 1% of Voriconazole was 101±0.07 per cent by measured from the slope of the linear portion of the curve found in Table 19 and Figures 21 and 22.

Stability Studies

Optimised formulation F5 batch short-term stability test was conducted at 30±2 ° C at room temperature for six months. Table 20 Shows that pH, viscosity, performance volume, spray angle, spray pattern, folding endurance, thickness, tensile strength, break per cent elongation, density, and *in vitro* release study the physical appearance of optimised formulation batch F5 remained unchanged through the study reference.

Discussion

The polymeric film-forming solution was prepared by dissolving selected polymers in different solvents such as ethanol, hydroalcoholic solution (1:1) and distilled water. The films formed upon drying were subjected to various preliminary evaluation like drying time, transparency and stickiness. The films prepared using absolute ethanol solvent with plasticiser showed satisfactory results when considering the drying time and visual observation. The polymeric film solution prepared using sorbitol as a plasticiser, which was selected based on the exhaustive literature search performed. It can be concluded that, the polymeric solution that was prepared using as a solvent was considered to be unfit for the incorporation of the API because the film took a long time for drying and one of the formulations did not form a film.

The polymeric film formed using ethanol as solvent F5 showed the best drying time and was considered as optimiser formulation.

Formed films were prepared and evaluated. The drug used in these film formulations was Voriconazole. Out of 9^{th} formulations, 5^{th} formulation is best and gives aspired results from the evaluation conducted Figure 23 .

CONCLUSIONS

This study concludes that Voriconazole can form a topical in situ film-forming development by using a mixture of Eudragite RS100 and Sorbitol as plasticiser using the response surface method, and mentioned below results work. The impact of formulating variables on product properties can be easily predicted by using a 3^2-level factorial experimental design and quadratic mathematical equations developed. Based on the specifications of the product, such as Drying time (DT %), Transparency, Stickiness, Structural features of the film formed, Viscosity, Spray angle, Spray pattern, Mechanical properties of the polymeric film formed and *in vitro* using a cellophane membrane, the best batch of topical Voriconazole in situ film-forming would be 22% Eudragite RS100 and 4% Sorbitol. It can be concluded.

ACKNOWLEDGEMENT

The authors express a deep sense of gratitude towards the JSS Academy of Higher Education and Research, Mysuru, 570015, Karnataka, India. For the provision of obligatory facilities to carry out present research work.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

Funding Support

The authors declare that they have no funding support for this study.

REFERENCES

Abdellatif, A. A. H., Tawfeek, H. M. 2016. Transfersomal Nanoparticles for Enhanced Transdermal Delivery of Clindamycin. *AAPS PharmSciTech*, 17(5):1067–1074.

Anter, H., Hashim, I. A., Awadin, W., Meshali, M. 2018. Novel anti-inflammatory film as a delivery system for the external medication with bioactive phytochemical “Apocynin”. *Drug Design, Development and Therapy*, Volume 12:2981–3001.

Deekshitha, H. M., Saraf, N. S., Kulkarni, P. K., Akhila, A. R., Jayaprakash, J. S. 2020. Formulation and evaluation of antifungal agent in a hydrogel containing nanoparticle of low molecular weight chitosan. *International Journal of Research in Pharmaceutical Sciences*, 11(1):247–259.

for Testing, A. S., Materials 2002. *D 882-02 Standard Test Method for Tensile Properties of Thin Plastic Sheeting, ASTM International, 100 Barr Harbor Drive, PO Box C700*, volume 100. West Conshohocken, USA.

Frederiksen, K., Guy, R. H., Petersson, K. 2016. The potential of polymeric film-forming systems as sustained delivery platforms for topical drugs. *Expert Opinion on Drug Delivery*, 13(3):349–360.

Gohel, M. C., Nagori, S. A. 2009. Fabrication of Modified Transport Fluconazole Transdermal Spray Containing Ethyl Cellulose and Eudragit® RS100 as Film Formers. *AAPS PharmSciTech*, 10(2):684–691.

Kathe, K., Kathpalia, H. 2017. Film forming systems for topical and transdermal drug delivery. *Asian Journal of Pharmaceutical Sciences*, 12(6):487–497.

Kaur, S., Kaur, N., Sharma, A. K., Kanwar, K. 2013. Development of modified transdermal spray formulation of psoralen extract. *Der Pharmacia Lettre*, 5(2):85–94.

Maghraby, G. M. E., Barry, B. W., Williams, A. C. 2008. Liposomes and skin: From drug delivery to model membranes. *European Journal of Pharmaceutical Sciences*, 34(4-5):203–222.

Mcauley, W. J., Caserta, F., Hoboken, N. J., Donnelly, R. F., Singh, T. 2015. *Film-forming and heated systems. In: Novel delivery systems for Transdermal and Intradermal drug delivery, Donnelly RF, Singh TRR*. John Wiley & Sons, United States.

Misra, A., Raghuvanshi, R. S., Ganga, S., Diwan, M., Talwar, G. P., Singh, O. 1996. Formulation of a transdermal system for biphasic delivery of testosterone. *Journal of Controlled Release*, 39(1):1–7.

Mustapha, N., Khairuddin, N., Muhamad, I. I., Hashim, S., Siddique, M. B. M. 2016. Characterisation of HEC/PANI film as a potential electroactive packaging with a pH sensor. *Sains Malaysiana*, 45(7):1169–1176.

Osmani, R. A. M., Kulkarni, P. K., Shanmuganathan, S., Hani, U., Srivastava, A., Prerana, M., Bhosale, R. R. 2016. A 3 2 full factorial design for development and characterisation of a nanosponge-based intravaginal in situ gelling system for vulvovaginal candidiasis. *RSC advances*, 6(23):18737–18750.

Padula, C., Nicoli, S., Pescina, S., Santi, P. 2019. Thin

polymeric films for the topical delivery of propranolol. *Colloids and Surfaces B: Biointerfaces*, 174:582–586.

Parthibarajan, R., Gowrishankar, N., Rajitha, M., Vinaykumar, A., Himavanthu, M., Ramesh, K., Vijaya, K. 2012. Formulation and evaluation of Voriconazole floating tablets. *Asian Journal of Pharmaceutical and Clinical Research*, 5(3):180–184.

Pawar, I. N., Rajput, R. R., Vaghani, S. S., Katara, B. V. 2017. Formulation and Evaluation of Topical Spray Containing Anti Acne Agent. *Asian Journal of Pharmaceutical Technology and Innovation*, 5(24):14–28.

Ranade, S., Bajaj, A., Londhe, V., Babul, N., Kao, D. 2017. Fabrication of topical metered dose film forming sprays for pain management. *European Journal of Pharmaceutical Sciences*, 100:132–141.

Saudagar, R. B. 2014. Formulation, development and evaluation of film-forming gel for prolonged dermal delivery of terbinafine hydrochloride. *Int J Pharm Sci Res*, 5(9):537–54.

Schroeder, I. Z., Franke, P., Schaefer, U. F., Lehr, C.-M. 2007. Development and characterization of film forming polymeric solutions for skin drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics*, 65(1):111–121.

Tran, T. T. D., Tran, P. H. L. 2019. Controlled Release Film Forming Systems in Drug Delivery: The Potential for Efficient Drug Delivery. *Pharmaceutics*, 11(6):290–290.