DESIGN, DEVELOPMENT AND STABILITY STUDIES OF VORICONAZOLE TRANSDERMAL PATCHES BY SOLVENT CASTING METHOD

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Abstract:
The current research objective is to develop and assess transdermal patches containing voriconazole by solvent cast method. Voriconazole is an antifungal drug used that is used to treat a variety of infections of yeast or other fungi. Because they are simple to use and improve patient compliance, transdermal medication delivery systems have begun to acquire popularity and acceptability as novel drug delivery methods. In the current study, polymers such HPMC K 15M, HPMC K 100M, and HPMC K 200M are used to generate Voriconazole transdermal patches. The solvent casting procedure used to make Voriconazole transdermal patches. Tween 80 plasticizer dosage was essential for the separation and patch forming features. The formulations F-5 were determined to be a satisfactory batch and were optimised for the desired qualities. Studies on stability were done on the chosen formulation F5, which was kept at 40°C 2°C / 75% 5% RH for three months. After being stored for 1, 2, and 3 months, samples were tested and assessed.

Key words: Voriconazole, Transdermal patches, stability, solvent casting method and evaluation.

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DOI: - 10.48047/ecb/2023.12.si5a.0585

INTRODUCTION

The transdermal drug delivery system (TDDS) [1] was developed to prolong the drug release, increase its bioavailability, and increase patient compliance. Designing and formulating TDDS of Voriconazole and assessing their extended release in vitro and ex vivo were the goals of the current investigation**.** TDDS are extended release dose forms that can prevent first pass metabolism and provide a stable systemic drug concentration. Even gastrointestinal issues brought on by medicines and poor absorption can be avoided. [2] These therapeutic benefits are a reflection of TDDS a greater marketing potential.[3] Since the majority of medication molecules enter the skin via the intercellular micro route, penetration enhancers play a crucial role in TDDS because they reversibly lower the stratum corneum barrier resistance without harming healthy cells.[4] Voriconazole is a triazole antifungal agent. The major mechanism of action of voriconazole is the suppression of 14 alpha-lanosterol demethylation, which is mediated by fungal cytochrome P-450 and is a crucial stage in the production of fungal ergosterol. Its oral bioavailability is 96%, and its half-life is approximately 1.7 hours. Voriconazole [21-25] may be administered as TDDS Patches in order to decrease associated side effects to skin to increase permeation [5-10]. This increases the drug bioavailability, which reduces side effects and improves patient compliance. In order to increase the efficacy of Voriconazole, the current work presents a systematic method to generate TDDS [11-20] patches by solvent cast method. In the current work, Voriconazole transdermal patches are produced using polymers such HPMC K 15M, HPMC K 100M, and HPMC K 200M. The process of formulating transdermal patches of voriconazole via solvent casting. The separation and patch-forming properties required the precise application of Tween 80 plasticizer.

MATERIALS AND METHODS

Materials

The API Voriconazole is received as gift sample. HPMC K15M, HPMC K100M, HPMC K200M, PVP K30, Tween 80 and Sorbitol are procured from local market.

Formulation of Voriconazole Transdermal patches

Transdermal patches of Voriconazole were prepared by solvent casting method. DCM and Ethanol were taken in 1:1 ratio to dissolve the drug. The ingredients are added one by one and dissolved properly with continuous stirring. The solutions were cast on to glass petri plate of 9 cm diameter and were dried in the oven at 70°C till a peelable film was formed. Then dried films were cut into rectangular shape pieces, with 4.0 cm^2 (2.0 cm × 2.0 cm) total surface area. Desired quantity of Voriconazole was 10 mg (dose of drug) per 4.0 cm^2 films.

Table 1: Formulation of Voriconazole Transdermal patches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Voriconazole	10	10	10	10	10	10	10	10	10
HPMC K15M	40	40	40	-	-	-	-	-	-
HPMC K100M	-	-	-	40	40	40	-	-	-
HPMC K200M	-	-	-	-	-	-	40	40	40
PVP K30	20	40	60	20	40	60	20	40	60
Tween-80	10	10	10	10	10	10	10	10	10
sorbitol	60	40	20	60	40	20	60	40	20

Evaluation of Trans dermal patches

1. **Thickness:** The thickness of patches was measured at three different places using a micrometer and mean values were calculated.
2. **Weight variation:** The patches were subjected to mass variation by individually weighing randomly selected patches. Such determinations were carried out for each formulation.
3. **Drug content:** Patches of specified area (1 cm2) were dissolved in 5 mL of dichloromethane and the volume was made up to 10 mL with phosphate buffer pH 7.4; dichloromethane was evaporated using a rotary vacuum evaporator at 45 °C. A blank was prepared using a drug-free patch treated similarly. The solutions were filtered through a 0.45 μm membrane, diluted suitably and absorbance was read at 274 nm in a double beam UV-Vis spectrophotometer.
4. **Folding endurance:** This was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.
5. **Tensile strength:** In order to determine the elongation as a tensile strength, the polymeric

patch was pulled by means of a pulley system; weights were gradually added to the pan to increase the pulling force till the patch was broken. The elongation i.e. the distance traveled by the pointer before break of the patch was noted with the help of magnifying glass on the graph paper, the tensile strength was calculated as kg cm-2.

6. **In-vitro skin permeation studies:** *In-vitro* skin permeation studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 22.5 mL. The excised rat abdominal skin (Wistar albino) was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were placed over the skin and covered with paraffin film. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 32 ± 0.5 °C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer pH 7.4 at each sample withdrawal. The cumulative percentages of drug permeated per square centimeter of patches were plotted against time.

Stability Studies

In designing a dosage form it is necessary to know the inherent stability of the drug substance, to have an idea of what excipients to use, as well as how best to put them together with the drug and to know that no toxic substance are formed. Limits of acceptability and therefore compromises must be reasonably defined. Because the measurements of these aspects of stability as well as determination of shelf life or expiration date for the final dosage form require long term stability studies for confirmation, they can be expensive and time consuming. Consequently it is necessary to define those study designs and conditions that show the greatest probability of success. The objective therefore of a stability study is to identify and help avoid or control situations where the stability of the active ingredient may be compromised.

Table 2: Stability Storage Conditions

Stability Storage Category	Testing schedule for Physical and Chemical attributes
LONG TERM 25°C ± 2°C / 60% ± 5% RH	3, 6, 9, 12, 18, 24 and annually till expiry and 6 Months hence after.
ACCELERATED 40°C ± 2°C / 75% ± 5% RH	1, 2, 3 & 6 Months
INTERMEDIATE 30°C ± 2°C / 60% ± 5% RH	3, 6, 9 & 12 Months
ZONE IV 30°C ± 2°C / 70% ± 5% RH	3, 6, 9, 12, 18, 24 and annually till expiry and 6 Months hence after.

RESULTS

Compatibility study by FTIR:

The compatibility of the drug with polymer was evaluated by performing FTIR analysis of standard drug and best formulation.

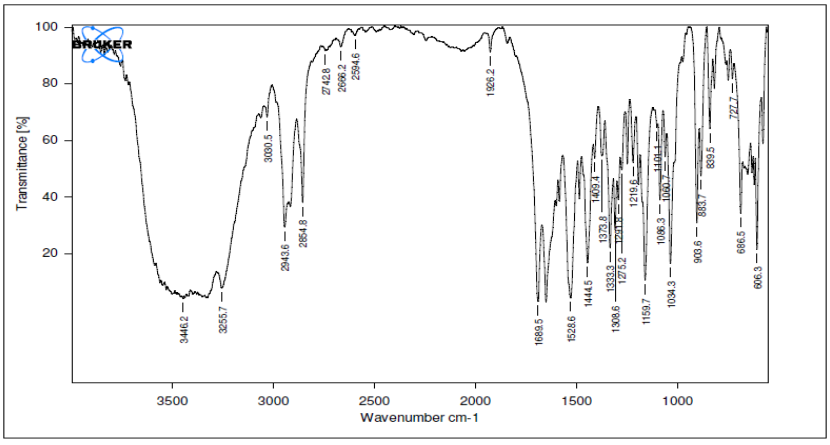

Figure 1: FTIR graph of Voriconazole pure drug

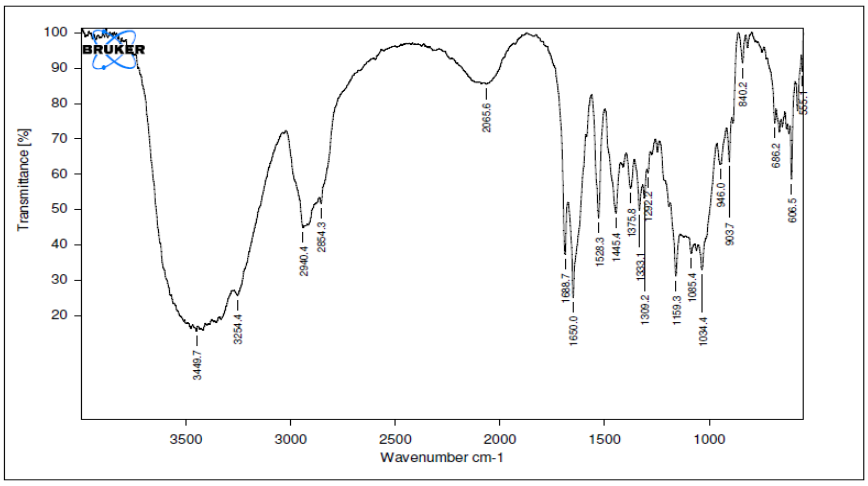

Figure 2: FTIR graph of Voriconazole best formulation

Table 3: Evaluation parameters of Voriconazole Transdermal patches

Formulation code	Thickness	Weight variation	Drug content	Folding endurance	Tensil strength
F1	162	Pass	98.23	201	2.74
F2	158	Pass	99.14	199	2.96
F3	153	Pass	99.67	212	3.12
F4	160	Pass	98.83	219	3.04
F5	157	Pass	99.37	210	2.83
F6	152	Pass	99.95	206	2.92
F7	147	Pass	99.67	218	3.15
F8	138	Pass	99.82	237	2.86
F9	156	Pass	99.37	204	2.46

Table 4: In-vitro drug release data for Transdermal patches

Time (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	**0**	0	0	0	0
1	32	28	25	20	**16**	5	12	5	0
2	46	39	34	38	**24**	8	20	11	3
3	58	52	50	59	**36**	15	28	19	9
4	64	59	55	67	**53**	20	42	31	17
6	85	78	69	78	**64**	29	56	42	28
8	96	89	81	84	**78**	48	62	55	43
10	100	95	89	99	**86**	56	75	67	51
12	100	100	**96**	100	**98**	74	81	73	63

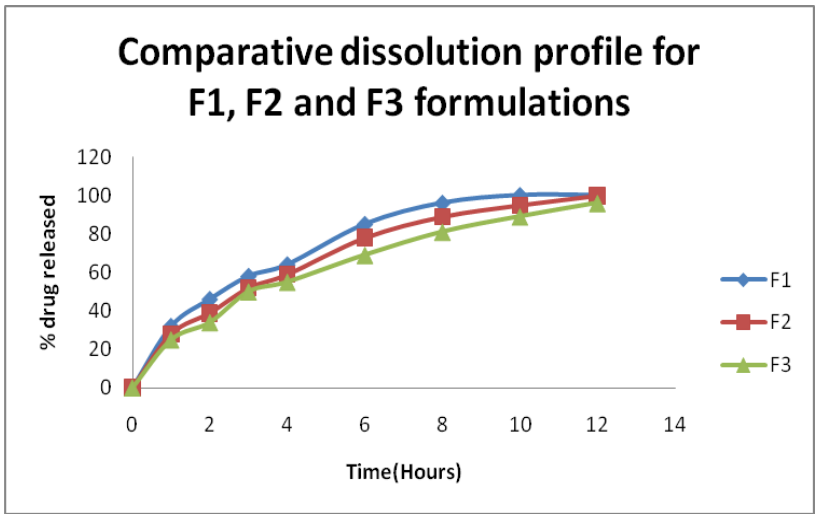

Figure 3: Comparative Dissolution profile for F1, F2 and F3 formulations

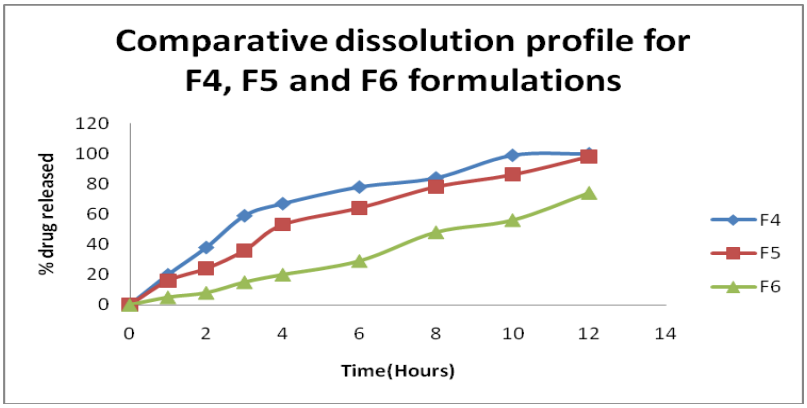

Figure 4: Comparative Dissolution profile for F4, F5 and F6 formulations

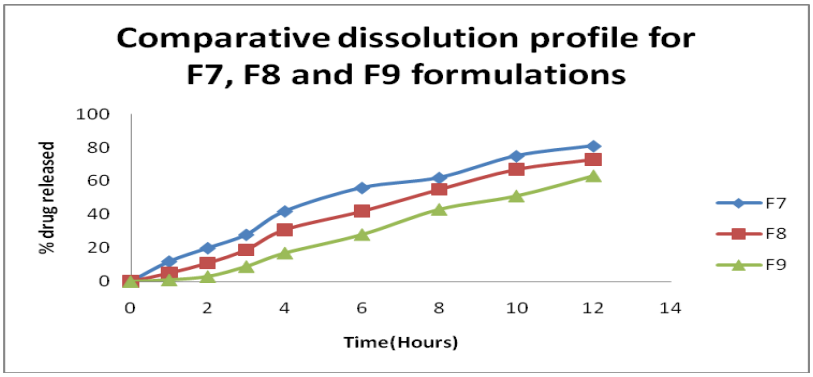

Figure 5: Comparative Dissolution profile for F7, F8 and F9 formulations

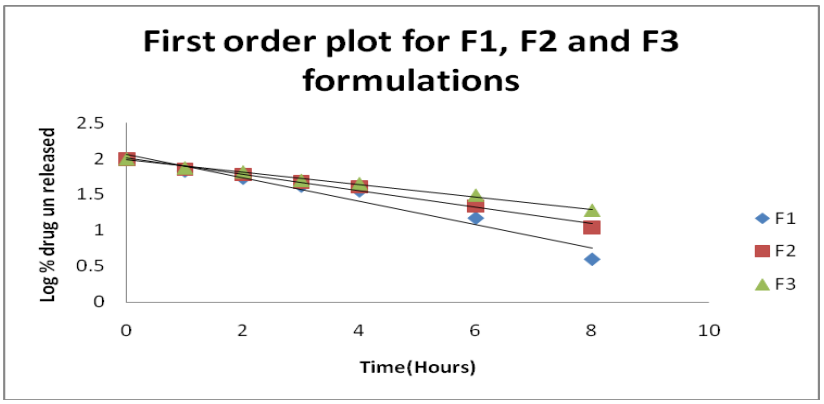

Figure 6: First order plot for F1, F2 and F3 formulations

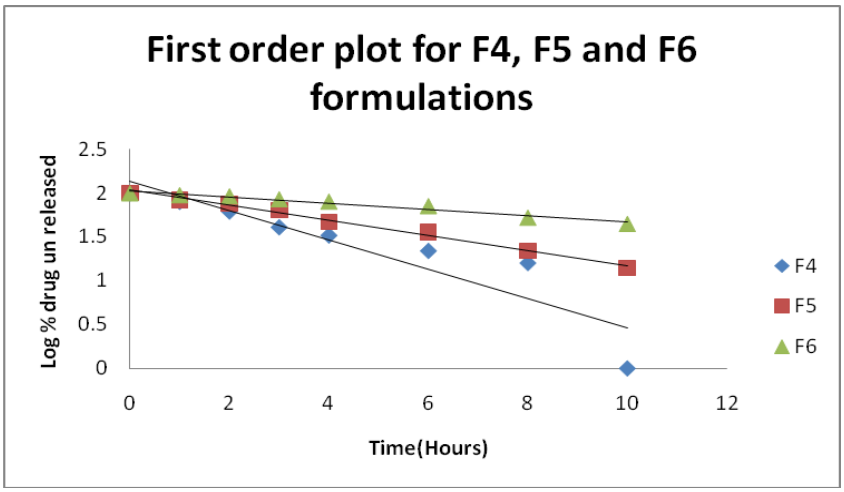

Figure 7: First order plot for F4, F5 and F6 formulations

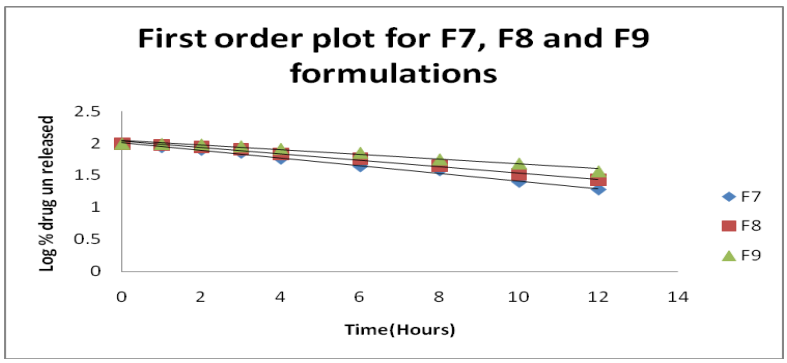

Figure 8: First order plot for F7, F8 and F9 formulations

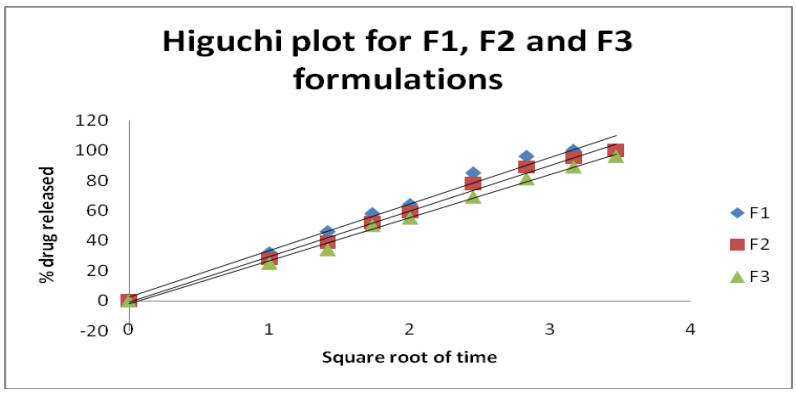

Figure 9: Higuchi plot for F1, F2 and F3 formulations

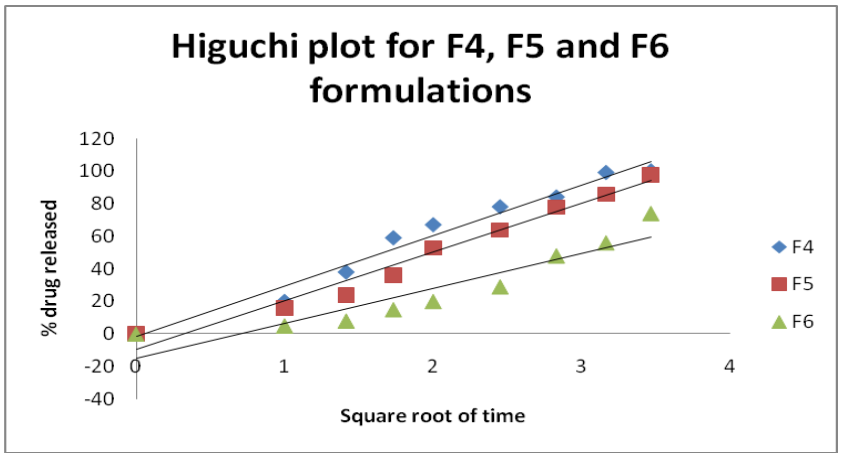

Figure 10: Higuchi plot for F4, F5 and F6 formulations

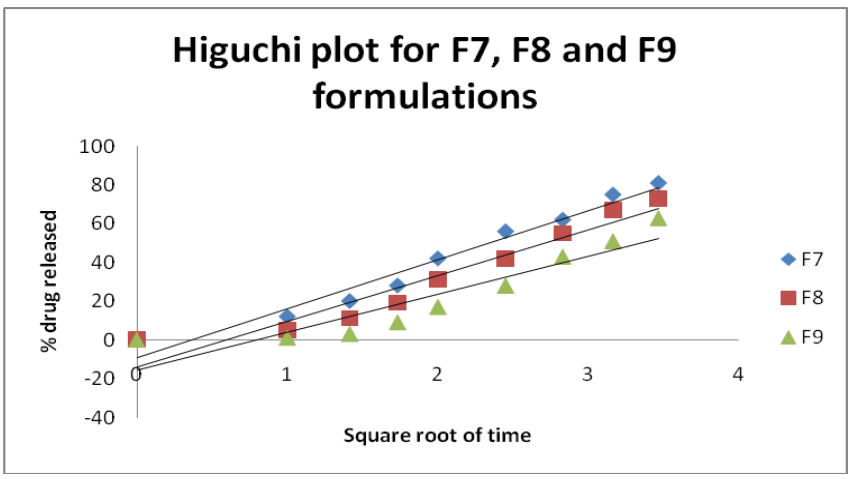

Figure 11: Higuchi plot for F7, F8 and F9 formulations

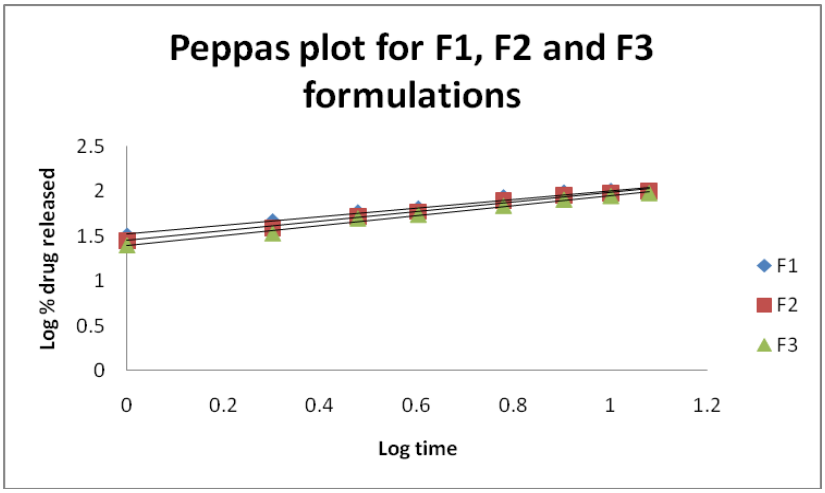

Figure 12: Peppas plot for F1, F2 and F3 formulations

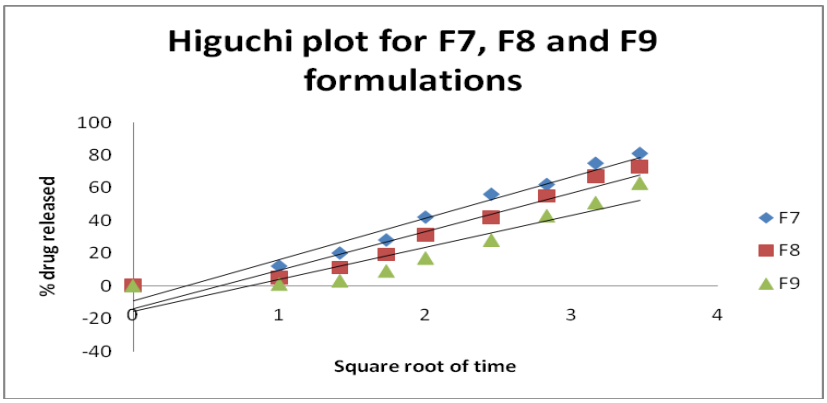

Figure 13: Higuchi plot for F7, F8 and F9 formulations

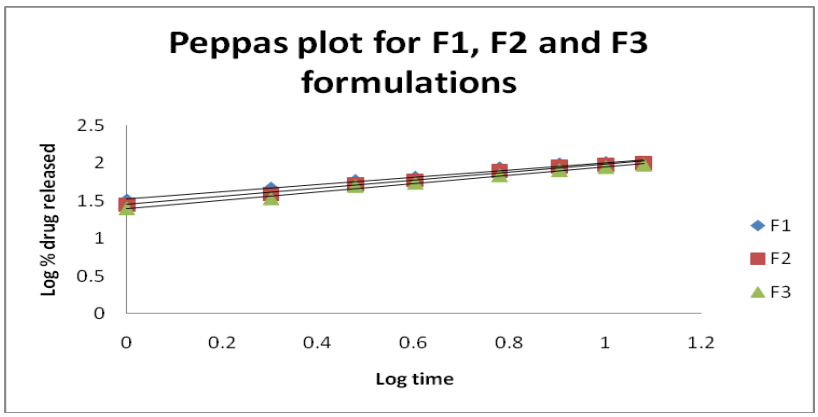

Figure 14: Peppas plot for F1, F2 and F3 formulations

Table 5: R^2 and 'n' result table

Formulation code	R^2 Values				N Value
	Zero order	First order	Higuchi	Peppas	
F1	0.852	0.951	0.98	0.982	0.483
F2	0.9	0.986	0.992	0.991	0.535
F3	0.918	0.992	0.995	0.99	0.556
F4	0.869	0.84	0.973	0.94	0.624
F5	0.96	0.991	0.971	0.984	0.753
F6	0.988	0.964	0.867	0.989	1.113
F5	0.963	0.992	0.966	0.987	0.793
F6	0.987	0.99	0.926	0.986	1.103
F7	0.987	0.969	0.858	0.979	1.709

Stability Studies

Selected formulation F5 was stored at 40°C ± 2°C / 75% ± 5% RH or a period of 3 months. Samples were analyzed after storage for 1, 2 and 3 month and evaluated.

Table 5: *In-vitro* release profile of F5 during Stability studies (40°C ± 2°C / 75% ± 5% RH)

Time (Hrs)	Initial	Month 1	Month 2	Month 3
0	0	0	0	0
1	16	15	16	14
2	24	22	25	24
3	36	35	36	33
4	53	53	51	51
6	64	62	63	62
8	78	77	76	75
10	86	84	85	84
12	98	97	97	98

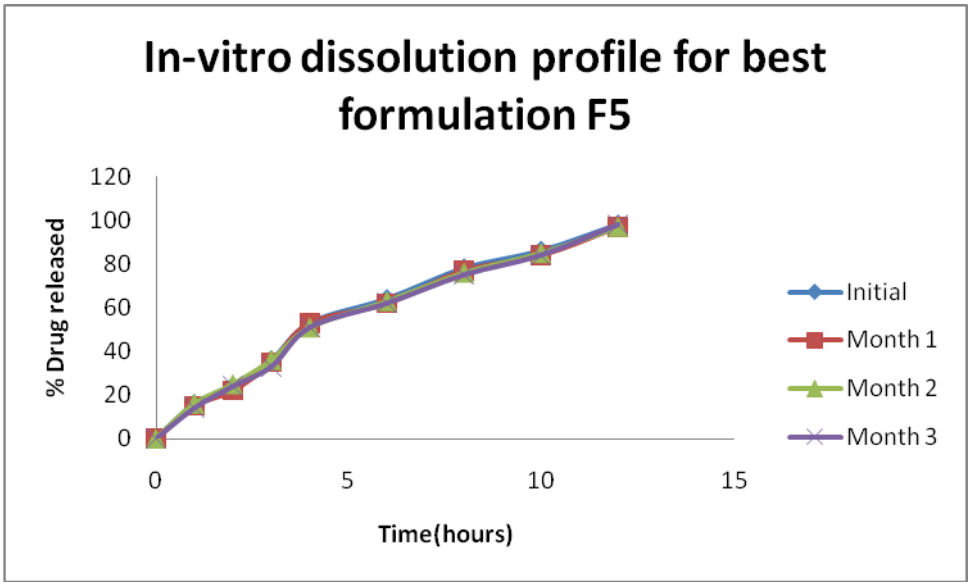

Fig. 15: *In-vitro* release profile of F9 during Stability studies (40°C ± 2°C / 75% ± 5% RH)

CONCLUSION

The investigators found that solvent casting was used for generating the transdermal patches of Voriconazole. The solutions were poured onto a 9 cm diameter glass petri plate and dried in an oven at 70°C until a peelable layer developed. The dried films were then cut into rectangular pieces with a total surface area of 4.0 cm2 (2.0 cm 2.0 cm). The desired dosage of Voriconazole was 10 mg per 4.0 cm2 films. The preparation of Voriconazole transdermal patches using HPMC K15M, HPMC K100M, and HPMC K200M was successful. Tween 80 plasticizer dosage was essential for the separation and patch forming features. Tween 80 was chosen as a plasticizer and solubility booster during the shelf life period. It was determined that formulation F-5 was a successful batch that had been optimised for the desired attributes.

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