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Formulation And Evaluation Of Buccal Film Of Voriconazole Drug For The Treatment Of Oral Thrush

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Abstract
Oral thrush is a fungal infection occurs when the fungus candida albicans grows excessively in the mouth. Voriconazole is an antifungal drug with half life 6 hours having advantages from a tolerability standpoint. Voriconazole has bitter taste thus to improve palatability, the drug was complexed with beta cyclodextrin in ratio (1:3) using kneading method by optimizing the kneading time. Taste evaluation was done by human volunteer. The buccal route was selected to provide rapid onset of action and targeted drug delivery. The formulation was optimized using 3^2 factorial design. The optimized drug-beta cyclodextrin complex was incorporated in FDBF by solvent casting method using HPMC E5 and PVA as polymers and PEG 400 as plasticizer. The prepared films were evaluated for their physicochemical properties including thickness, surface pH, folding endurance, disintegration time, drug content, in vitro dissolution and in vitro antifungal activity. Among all batches, formulation F3 showed the most promising results, with drug content 98.30%, disintegration time 32 second and 97.51 % drug release in 6 minutes with suitable strength and flexibility. It can be concluded that the development of fast dissolving buccal film of voriconazole produce fast onset of action and targeted drug delivery, improve patient compliance and effective management of fungal infection.
Keywords: *Voriconazole, Taste masking, Beta cyclodextrin, HPMC E5, PVA, Fungal infection, Fast dissolving buccal film.*

INTRODUCTION

The buccal delivery of drugs has recently emerged as an effective and safe alternative over other conventional routes of drug administration. Buccal administration easily releases the loaded drug into the buccal cavity for either local or systemic effects.[1] In buccal drug delivery system drug deliver via mucosal membranes in blood stream by placing drug in between gums and the cheeks.[2]

Oral thrush also called oral candidiasis is a condition in which the fungus candida albicans builds up in the mouth. Oral thrush causes white patches or spots, usually on the tongue or inner cheeks. sometimes oral thrush may spread to the roof of the mouth, gum or tonsils or the back to your throat. Voriconazole is a BCS class II drug used to treat various fungal infection like oral candidiasis.[3]

Voriconazole has bitter taste. Taste masking is necessary for formulating fast dissolving buccal film of voriconazole drug. Taste masking of drug is achieved by beta cyclodextrin complexation. The taste masked granules of drug and beta cyclodextrin were prepared by kneading method using molar ratio 1:3 and kneading time 2 hours.[4]

The solvent casting method used for the preparation of fast dissolving buccal film. HPMC E5 and PVA used as polymer, PEG 400 used as plasticizer, sodium saccharin used as sweetener, methanol and water used as solvent and citric acid used as saliva stimulating agent. HPMC E5 is well known for its excellent acceptability and good film forming properties. PVA is synthetic polymer has excellent film forming capacity and dissolve quickly.[5,6]

Fast dissolving buccal films offer several advantages, including rapid on set of action, ease of administration without the need of water, targeted drug delivery, improved patients' compliance, easy to apply and drug is released and absorbed quickly through the buccal mucosa, better absorption compared to oral tablets.[7,8]

MATERIALS AND METHODS

Materials

Voriconazole BP were purchase from Aarti Drugs Limited (Mumbai, India), HPMC E5, PVA, Methanol, Citric acid, PEG 400, Sodium saccharin were received from institute lab.

Methods

FTIR Spectroscopy

Compatibility between Voriconazole and excipients was studied using FTIR spectroscopy (4000 – 650 cm $^{-1,}$ KBr pellet method). Spectra were compared to identify potential interactions. The result shown in fig 1,2 and Table 3,4.

Solubility Studies

Solubility was tested in methanol, water and phosphate buffer pH 6.8 expressed in mg / ml, and interpreted based on pharmacopeial classifications. The result shown in Table 5.

Differential Scanning Calorimetry

The DSC analysis was carried out to determine the melting point of the sample which is critical thermal parameter indicating purity and crystalline nature of the compound. The result shown in fig 3.

Preparation of Voriconazole beta cyclodextrin taste masked granules by kneading method [9]

Beta cyclodextrin was used as inclusion complexing agent. The taste-masked granules of drug and beta cyclodextrin were prepared by kneading method using mortar and pestle. Voriconazole beta cyclodextrin complexation prepared by using molar ratio 1:3 and Water used as solvent. Accurately weighed quantity of beta cyclodextrin was taken in mortar and kneaded with water using pestle for 10 minutes. To the above mixture accurately weighed quantity of voriconazole was mixed and stirred. Kneading time 2 hours, after kneading the mixture was allowed to dry in hot air oven 40 to 50°C until completely dry. Grind the dried mass to get a fine powder using mortar and pestle. Pass the powder through a #80 sieve to get uniform particle size.

Method for preparation of voriconazole buccal film [10]

A 3^2 complete factorial design was used to optimize the formulated product. HPMC E5 (X1) and concentration of PVA (X2) were selected as independent variables, whereas disintegration time, folding endurance, drug release were selected as dependent variables. Independent factors were selected at 3 different levels as mentioned in Table 1. For the preparation of fast dissolving buccal film of voriconazole drug solvent casting method was used. The polymers were dissolved in their respective solvents. This polymeric dispersion was stirred on a magnetic stirrer for one hour to obtain a uniform and clear solution. Polyethylene glycol was added as a plasticizer and stirred for 30 minutes. The drug solution was added to the polymeric mixture and sonicated for 15 minutes. Kept aside for a few hours. This solution was poured onto a petri dish and dried 24 to 48 hours. Then the film was carefully removed and cut into suitable size. Table 2 shows the makeup of the formulation batches.

Table 1 Variables in 3^2 factorial designs

Independent Factors	Used Levels		
	-1	0	+1
X1 = HPMC E5	200	250	300
X2 = PVA	100	125	150

Table 2 Formulation batches for Voriconazole buccal film

Sr. No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Voriconazole Betacyclodextrin complex eq. to (50mg) of drug. (1:3)	204	204	204	204	204	204	204	204	204
2	HPMC E5 (mg)	200	200	200	250	250	250	300	300	300

3	PVA (mg)	100	125	150	100	125	150	100	125	150
4	Sodium Saccharin (mg)	2	2	2	2	2	2	2	2	2
5	PEG 400 (ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
6	Methanol (ml)	2	2	2	2	2	2	2	2	2
7	Citric acid (mg)	2	2	2	2	2	2	2	2	2
8	Water (ml)	10	10	10	10	10	10	10	10	10

Evaluation Parameters of Voriconazole Beta Cyclodextrin Complexed Mixture [11]

Carr's Index

Compressibility Index is a commonly used method to evaluate the flowability of a powder. The percentage compressibility of a powder was calculated using bulk density and tapped density. The result shown in Table 6.

Hausner's Ratio

Hausner Ratio is a parameter used to evaluate the flow properties of powders. Hauser Ratio is the ratio of the tapped density to bulk density of powder. The result shown in Table 6.

Angle of Repose

The angle of repose is the maximum angle between the surface of a pile of powder and the horizontal plane. It is commonly used to evaluate powder flow properties. The fixed funnel method was used to estimate the angle of repose. Fix a funnel on a stand at a specific height, fill powder into the funnel and allow it to fall freely to form a conical heap. Measure the height of the pile and radius of the base and calculate angle of repose (θ). The result shown in Table 6.

% Drug Content

The % Drug Content confirms how much amount of drug is actually incorporated in the complex. Accurately weigh a known amount of drug beta cyclodextrin complex and dissolve the weighed complex in a 100 ml of phosphate buffer pH 6.8 stirred continuously in mechanical shaker in order to get complete solubility of drug. The solution is filtered through membrane filter (pore size 0.45 mm) and the absorbance of the sample was determined spectrophotometrically at 256 nm of using phosphate buffer pH 6.8 as a blank using UV spectrophotometer. The result shown in Table 6.

Taste Evaluation

The taste evaluation was carried out with 6 volunteers for each taste masked drug and the unmasked drug was taken as the control which was compared with the taste masked drug. They were allowed to give interpretations as bitter, slight bitter and taste masked. Bitterness scale bitter (+), less bitter (++), non-bitter (+++). The result shown in Table 6.

Evaluation Parameters of Voriconazole Buccal Film [12]

Visual Inspection

Visual inspection of the prepared orally disintegrating film gives information about transparency, color, peeling ability**.**

Surface pH

The pH value of a film is usually determined by putting the prepared film in petri dish and subsequently film is made wet by using distilled water and noting pH by touching the film surface with a pH meter electrode. Determination of surface pH is vital as acidic or basic pH is liable to cause oral mucosal irritation. The result shown in Table 7.

Thickness

As the thickness of a film is directly concern with drug content uniformity so it is necessary to ascertain uniformity in the thickness of the film. It can be measured by calibrated digital vernier calipers at different strategic locations. The result shown in Table 7.

Folding Endurance

Folding endurance is another procedure to estimate the mechanical properties of a film. It is measured by repeatedly folding a film at the same point until it breaks. Folding endurance value is number of times the film is folded without breaking. Higher folding endurance value depicts the more mechanical strength of a film. A direct relation exists between mechanical strength and folding endurance of films. As

mechanical strength is governed by plasticizer concentration so it is clearly evident that plasticizer concentration also indirectly affects folding endurance value. The result shown in Table 7.

Drug Content Uniformity

Film of dimension 2×2 cm^2 was added in 100 ml of phosphate buffer pH 6.8, stirred continuously in mechanical shaker in order to get complete solubility of drug. The solution is filtered through membrane filter (pore size 0.45 mm) and the absorbance of the sample was determined spectrophotometrically at 256 nm of using phosphate buffer pH 6.8 as a blank using UV spectrophotometer. The result shown in Table 7.

Disintegration Time

The disintegration time was determined by petri dish method. A film is placed onto 10 ml distilled water taken in petri dish. Time taken by the film to dissolve completely is considered as the disintegrating time. The result shown in Table 7.

In Vitro Dissolution Study

The dissolution paddle apparatus was used to determine in vitro dissolution studies. A Phosphate Buffer pH 6.8 (used as dissolution media) was used for dissolution purposes. Film strips having a dimension of 2 × 2 cm2 were cut and dipped into a dissolution vessel. Vessel was already filled with 250 mL of dissolution media. The media temperature was set at 37 ± 0.5 °C and paddles were rotated at 50 rpm. Samples were withdrawn after 2, 4, 6, 8, 10, 14, min. A sample size of 5 mL was withdrawn each time, which was replaced with the same amount of buffer maintained at the same temperature (mentioned above 37 ± 0.5 °C). At the end of the test, the absorbance of the samples was analyzed at 256 nm using a UV-Vis spectrophotometer. The result shown in Fig 4.

In Vitro Antifungal Study

In vitro antifungal activity was evaluated by agar diffusion method against candida albicans. A swab of pure bacterial culture is evenly spread over Mueller-Hinton agar. Using cork borer boor the wells on media, the100µl of samples were pour on the media plate. This petri plate is kept for incubation for 18-24 hours at 37°C along with other optimal conditions for bacterial growth. After the incubation period, a clear area (zone of inhibition) around the antifungal product sample is observed and measured. The result shown in Fig 5 and Table 8.

Stability Study

Stability of product may be defined as the capability of a particular formulation in a specific container / closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specification. The optimized formulation packed in aluminium foil at foil at 40±2° C/75±5% RH for 45days in stability chamber. The samples were withdrawn initially, after 15 days, 30 days and 45 days and analysed. The result shown in Table 9.

RESULT AND DISCUSSION

FTIR Spectroscopy

Figure 1. FTIR of Voriconazole

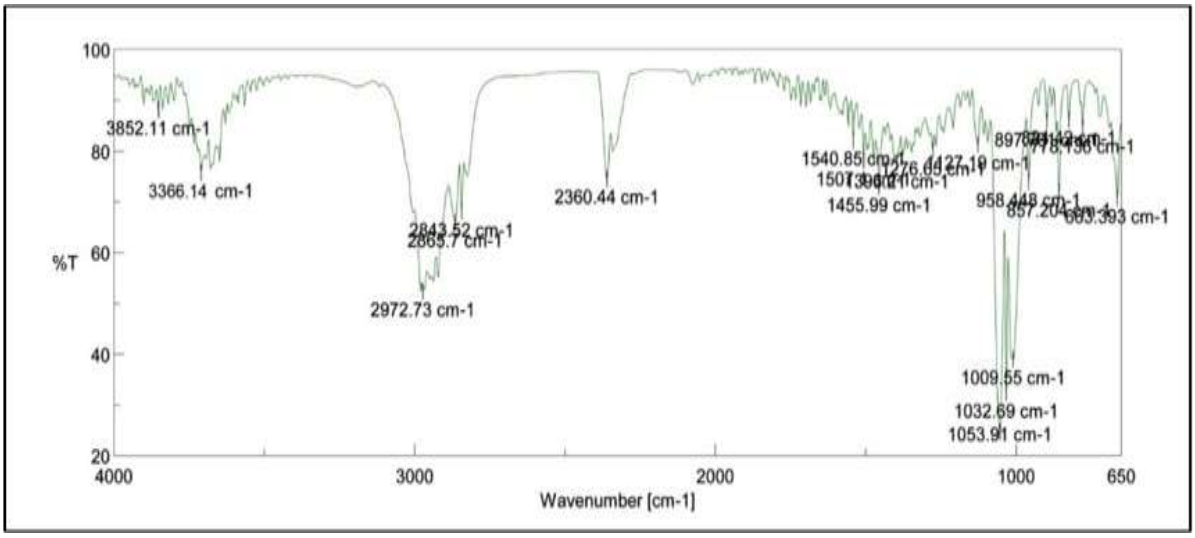


Table 3 Interpretation of FTIR Spectrum of Voriconazole

Sr. No.	Functional Group	Standard Value	Obtained Value
1	O - H	3000 - 3700	3366.14
2	C - O	900 - 1300	958.448
3	C - H	2700 - 3300	2972.73
4	C = C	1450 - 1600	1455.99
5	C - F	1000- 1400	1032.69

Based on the FTIR interpretation table, the chemical structure and the FTIR spectrum of Voriconazole (Fig1 and Table 1) the presence of characteristic peaks confirms that the sample is pure.

Figure 2 . FTIR Compatibility study of Voriconazole with excipients

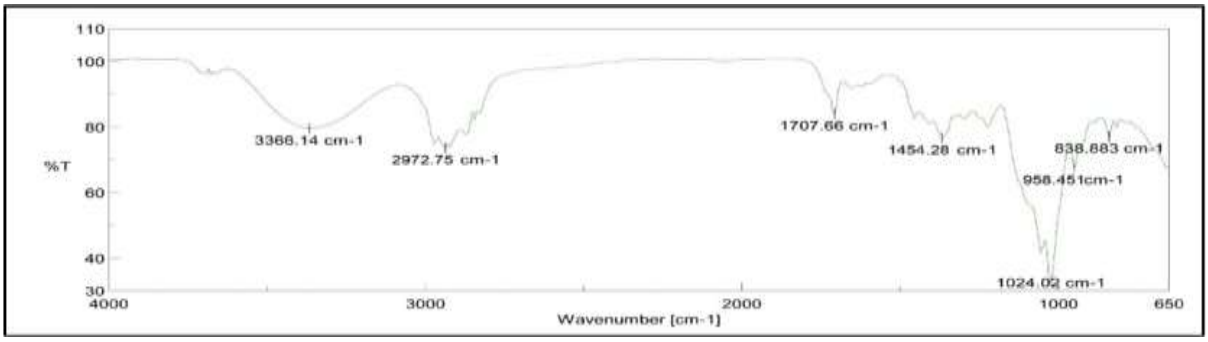


Table 4. FTIR Spectra of Voriconazole + Excipients

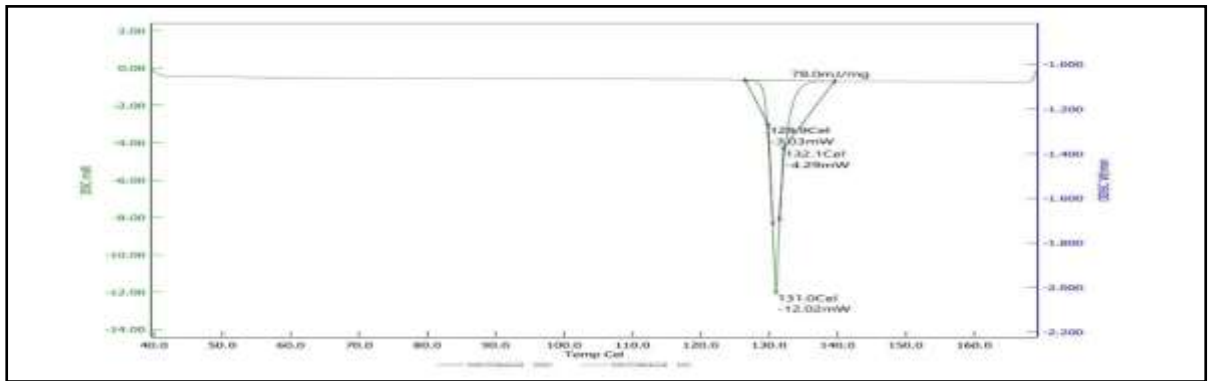
Sr. No.	Functional Group	Standard Value	Voriconazole	Voriconazole + Excipients	Compatible or not
1	O - H	3000 - 3700	3366.14	3366.14	Compatible
2	C - O	900 - 1300	958.448	958.451	Compatible
3	C - H	2700 -3300	2972.73	2972.75	Compatible
4	C = C	1450 - 1600	1455.99	1454.28	Compatible
5	C - F	1000 - 1400	1032.69	1024.02	Compatible

The IR spectra obtained for the physical mixture showed no significant differences, including no interaction between voriconazole and excipients. These findings suggest that the above-mentioned excipients are compatible with the drug.

Table 5. Solubility study of Voriconazole in the different solvents

Sr. No.	Media	Solubility (mg/ml)	Interference
1	Methanol	9.2	Freely soluble
2	Water	0.9	Slightly soluble
3	Phosphate buffer 6.8	1.2	Soluble

Figure 3. Differential Scanning Calorimetry



Evaluation of Voriconazole Beta cyclodextrin Complexed Mixture

The % drug content, taste evaluation, carr's index, hausner's ratio, angle of repose displayed in Table 6. The % drug content is 98%, taste is non bitter, carr's index found in range 14.17±0.32 this indicates good flow properties, hausner's ratio found in range 1.10± 0.13 this indicates excellent flow properties and angle of repose found in range 27.49±0.36 this also indicates excellent flow properties.

Table 6. Evaluation of Voriconazole Beta cyclodextrin Complexed Mixture

Sr.No.	Drug: Beta cyclodextrin molar ratio	% Drug content	Taste Evaluation	Carr's Index (%)	Hausner's Ratio	Angle of Repose
1.	1:3	98%	(+++)	14.17±0.32	1.10± 0.13	27.49±0.36

Evaluation of Voriconazole Buccal Film

Visual Inspection

Visual inspection of a prepared Fast dissolving buccal film gives information about transparency, surface texture and peeling ability. The prepared films were transparent, smooth in texture and peel easily.

Surface pH, Thickness, Folding Endurance, Drug Content, Disintegration Time

The surface pH, Thickness, Folding endurance, Drug content, Disintegration time of the designed batches (F1 to F9) are displayed in Table 7. The prepared batches (F1 to F9) had surface pH values between 6.6 – 6.8, which is close to the neutral pH, which indicated that films may have less potential to irritate the mucosa and hence, more acceptable by the patients. The thickness varies from 0.052± 0.002 to 0.078 ± 0.001 mm. Folding endurance was observed in the range of 150 to 170, this data revealed that the films had good mechanical strength along with flexibility. The percentage drug content of all formulations was found to be between 95.32 ± 0.02 to 98.30 ± 0.01. The disintegration time of all formulation was found in the range 32 to 47 sec.

Table 7. Evaluation of Voriconazole Buccal Film

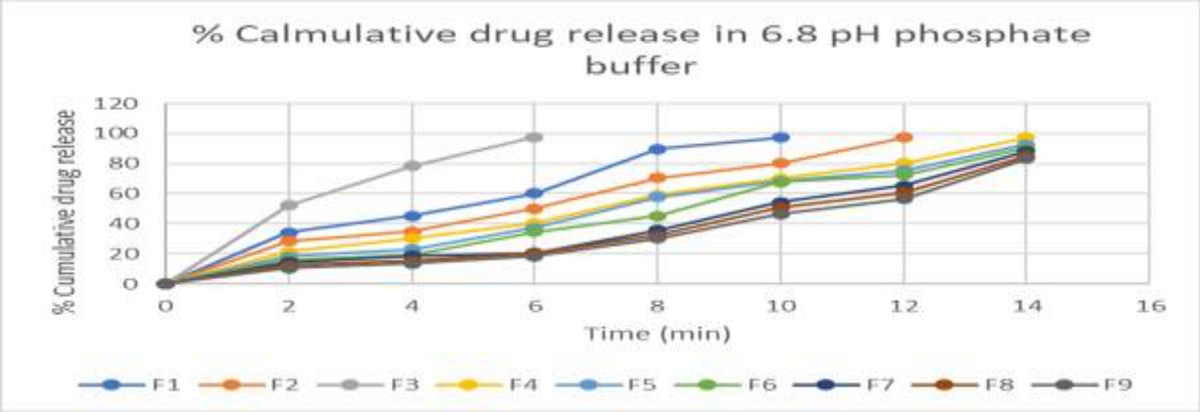
Formulation Code	Surface pH	Thickness	Folding Endurance	Drug Content	Disintegration Time
F1	6.7 ± 0.02	0.052± 0.002	158	95.32±1.05	35±0.01
F2	6.7 ± 0.05	0.055 ±0.003	160	96.73 ±1.04	34±0.02
F3	6.8 ± 0.01	0.059 ±0.001	170	98.30±2.01	32±0.01
F4	6.6 ± 0.02	0.059 ±0.004	159	96.45 ± 1.5	37±0.03
F5	6.7 ± 0.04	0.064± 0.004	157	96.70 ± 0.80	39±0.02

F6	6.7 ± 0.01	0.068± 0.003	155	97.32 ± 1.02	41±0.05
F7	6.7 ± 0.05	0.072 ±0.002	153	95.22 ± 0.70	43±0.05
F8	6.6± 0.01	0.075 ±0.002	151	95.67 ±1.05	45± 0.02
F9	6.7 ± 0.02	0.078 ±0.001	150	96.20 ±0.80	47± 0.02

In Vitro Dissolution Study

For 14 minutes, in vitro dissolution test was performed on each of the generated voriconazole buccal films formulation. The graphical depictions of the percentage cumulative medication release for the same are shown in figure 4. The investigation verified that formulation polymer concentration had a major impact on drug release behaviour. The F3 batch shows highest drug release in 6 min compared to all other formulations.

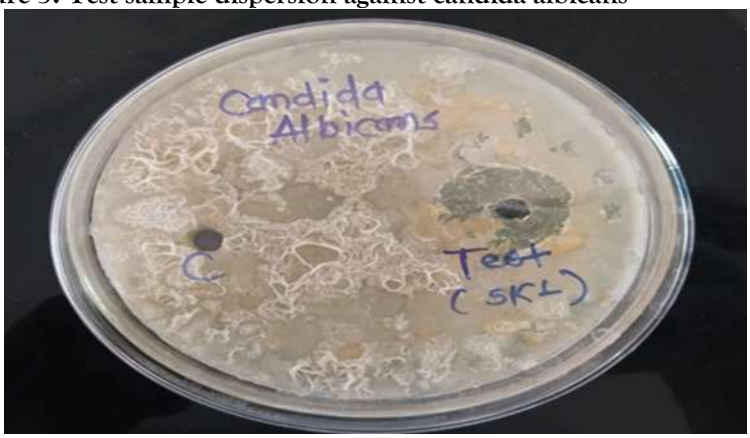
Figure 4 . In Vitro Drug Release



In Vitro Antifungal Study

The the film is considered effective, with good antifungal activity against the microorganism / fungi. This indicates that it can be used to treat infection caused by microorganism / fungi. The results indicate test sample Voriconazole buccal film (SK1) has antifungal activity. C means Control and SK1 means Test formulation of voriconazole buccal film.

Figure 5. Test sample dispersion against candida albicans



The voriconazole buccal film produced an 18.34 mm zone of inhibition, which show good antifungal activity (>15 mm).

Table 8. In Vitro Antifungal Study

Sr. No.	Sample Name	Zone of inhibition in mm

1	Control	NA
2	Voriconazole Buccal Film (SK1)	18.34 mm

Stability Study

The optimized formulation was selected for stability study (F3). The results obtained were show in Table 9 From the result it was concluded that formulation F3 is stable and retained their original properties with minor differences.

Table 9. Stability studies of optimized formulation (F3)

Parameters	**Initials**	**After 15 days stability study**	**After 30 days stability study**	**After 45 days stability study**
Appearance	Good	Good	Good	Good
Folding Endurance	170	167	165	164
Surface pH	6.8 ± 0.01	6.8 ± 0.03	6.8± 0.05	6.7 ± 0.01
Drug Content (%)	98.30±2.01	98.17 ± 1.05	97.24 ± 0.80	96.75 ± 0.40
% Drug Release	97.51	96.24	95.34	95.25

CONCLUSION

From the present investigation it can be concluded that the drug Voriconazole could be successfully incorporated in the fast-dissolving buccal film with the help of HPMC E5 and PVA as film former and PEG 400 as plasticizer. Solvent casting is one of the simplest and cost-effective method use for the preparation of fast dissolving buccal film of voriconazole drug. Voriconazole is selected as modern drug candidate to provide treatment for oral thrush. The F3 batch showed satisfactory result compared to other batches. The disintegration time is 32 sec and 97.51 % of drug release in 6 min concluded as best formulation. The fast dissolving buccal film of voriconazole drug provide target drug delivery and produce onset of action.

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