



## FORMULATION AND EVALUATION OF VORICONAZOLE PATCHES FOR BUCCAL DRUG DELIVERY SYSTEM

T. Mangilal<sup>1\*</sup>, K. Soundarya<sup>1</sup>, M. Nagaganesh<sup>1</sup> and M. Ravikumar<sup>1</sup>

Geethanjali College of Pharmacy, Cheeryal (V), Keesara (M), 501301, Medchal (Dist), Telangana, India.

\*Corresponding Author: Dr. T. Mangilal

Professor, Geethanjali College of Pharmacy, Cheeryal (V), Keesara (M), 501301, Medchal (Dist), Telangana, India.

Article Received on 11/05/2017

Article Revised on 01/06/2017

Article Accepted on 21/06/2017

### ABSTRACT

Voriconazole is a triazole antifungal drug that generally used to treat serious, invasive fungal infections. These are generally seen in patients who are immune compromised, and include invasive candidacies, invasive aspergillosis, and certain emerging fungal infections. In the present study buccal drug delivery of Voriconazole was developed to overcome the first pass metabolism and to reduce the frequency of dosing compared to oral route. Matrix type of buccal patches was developed by using polymers HPMCK4M and HPMCK100M. Buccal patches were prepared by employing solvent casting method. Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions. The formulations were prepared with the varying concentrations of polymers ranging from F1-F6, and all the formulations were evaluated for various parameters like Physical appearances, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and Swelling study and all the results were found to be within the pharmacopeial limits, *invitro* drug release studies done by using dialysis membrane. Among all the 6 formulations F6 formulation which contain HPMC K100M 500mg had shown 94.7% cumulative drug release within 12 hours. For F6 formulation release kinetics were plotted and the Regression coefficient value was found to be high for Korsmeyer-peppas release model i.e., 0.989.

**KEYWORDS:** Voriconazole, HPMCK4M, HPMCK100M, Buccal Patches and Buccal Drug Delivery.

### INTRODUCTION

There are several routes of drug administration for delivering the drug. Among them in recent years, many investigations are done in the field for delivering the drug locally to the tissues in the oral cavity, especially for treating bacterial and fungal infections, and periodontal treatments. Bioadhesive drug delivery plays an important role in delivering drug locally in the oral cavity as it retains the drug at the site of action. Adhesive material may be natural or synthetic. Surface of adhesion can be either epithelial tissue or mucous coat of the tissue. If adhesion is to a mucous coat, then it is referred as mucoadhesion. Over the decades mucoadhesion has become popular for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining the formulation in intimate contact with the absorption site (e.g. buccal cavity).<sup>[1]</sup>

Mucoadhesive polymers have greater application in buccal drug delivery system. Recently, many mucoadhesive forms have been developed like patches, films, disks, strips, ointments, tablets, gels etc. However, buccal patch offers greater flexibility and comfort than

the other forms. Apart from it buccal patches can overcome problems like short residence time as that of gels which is easily washed away by saliva.<sup>[2]</sup>

Buccal route of drug delivery provides high bioavailability as it has direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism. Apart from it, it has excellent accessibility, low enzymatic activity, suitable for drugs or excipients that mildly and reversibly damage or irritate the mucosa. Other advantages include painless drug administration, easy withdrawal. Facility to include permeation enhancer / enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action.<sup>[3]</sup> Voriconazole is a triazole anti fungal drug which is used to treat serious fungal infections. It has a very low aqueous solubility and extensively metabolized by the liver. Buccal route offers several advantages as it bypasses first pass metabolism, easy withdrawal, rapid absorption. Hence it leads to significant reduction of dose and related side effects. Here in the present work, an attempt was made to formulate and evaluate voriconazole buccal patches for

buccal drug delivery system. The main objectives of the present study are to formulate Voriconazole muco-adhesive patches for buccal drug delivery system, Voriconazole buccal patches were prepared using some mucoadhesive polymers by Solvent casting technique and The prepared patches will be evaluated for parameter related to buccal drug delivery system like weight uniformity, thickness, folding endurance, swelling index, surface pH, bio-adhesive time, drug content estimation, *in-vitro* release study, stability, drug polymer interaction.

## MATERIALS

Voriconazole procured from Natco Laboratories Pvt Ltd, Hyderabad, and Telangana, India. HPMC K-4M, HPMC K-100M, PEG-400 and Tween-80 from SD fine chemical, Mumbai, India. Dichloromethane and Methanol from Merck Specialities Pvt Ltd, India and other chemicals were consumed of laboratory grade.

## METHODS

### Determination of UV Absorption maxima<sup>[6]</sup>

Voriconazole solution was prepared with 6.8 pH phosphate buffer and diluted suitably. The UV spectrum of the solution was taken on Lab, India 3200 UV/Vis double beam Spectrophotometer. The solution exhibited UV maxima at 274 nm. The procedure was repeated with pH 6.8 phosphate buffer.

### Preparation of Standard Calibration Curve of Voriconazole<sup>[5]</sup>

100 mg of Voriconazole was accurately weighed and dissolved in a little amount of Methanol and the final volume is made up to 100 ml with pH 6.8 phosphate buffer to prepare a stock solution. The 10 ml of stock solution was further diluted with pH 6.8 phosphate buffer in 100ml to get 100µg/ml (working standard). Then 0.5,1,1.5,2and 2.5 ml of working standard was taken in

10 ml standard volumetric flask and made up the volume with pH 6.8 phosphate buffer. Then the absorbance was measured in a UV spectrophotometer at 274 nm against pH 6.8 phosphate buffer as blank.

### Drug Excipients interaction studies<sup>[6]</sup>

**FT-IR spectrum interpretation:** IR spectral analysis was carried out using FT-IR by the KBr disc method. The sample and KBr were triturated and compressed to get the discs. The samples of pure drug, dummy formulation and optimized formulation were analyzed between wave numbers 4000.0 and 400.0 cm<sup>-1</sup>.

### Selection of drug and other ingredients<sup>[7]</sup>

- Voriconazole was selected as model drug based on its physico-chemical and biological properties and also based on its suitability for Buccal drug delivery system.
- HPMCK4M(mg), HPMCK100M(mg) were selected as matrix forming polymers.
- Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer.

### Formulation of Buccal patches<sup>[8]</sup>

**Development of Buccal patches:** Buccal drug delivery patches were prepared by solvent casting method.

**Solvent casting method:** Polymers HPMCK<sub>4</sub>M and HPMCK100M were weighed accurately and dissolved in dichloromethane and methanol as solvent using magnetic stirrer.

Voriconazole, Propylene glycol, Tween80 is added to the above dispersion with continuous stirring. The uniform dispersion was poured on the Petri plate. The rate of evaporation of solvent was controlled by inverting cut funnel over the patches.

**Table 1: Formulations of Voriconazole Buccal Patch.**

| Ingredients     | F1     | F2     | F3     | F4     | F5     | F6     |
|-----------------|--------|--------|--------|--------|--------|--------|
| Drug            | 300    | 300    | 300    | 300    | 300    | 300    |
| HPMCK 4M        | 300    | 400    | 500    | -      | -      | -      |
| HPMCK 100M      | -      | -      | -      | 300    | 400    | 500    |
| Dichloromethane | 10ml   | 10ml   | 10ml   | 10ml   | 10ml   | 10ml   |
| Methanol        | 13.2ml | 13.2ml | 13.2ml | 13.2ml | 13.2ml | 13.2ml |
| PEG 400         | 1ml    | 1ml    | 1ml    | 1ml    | 1ml    | 1ml    |
| Tween 80        | 1ml    | 1ml    | 1ml    | 1ml    | 1ml    | 1ml    |

### Evaluation of Buccal patch of physical methods<sup>[9]</sup>

**Physical appearance:** All the Buccal patches were visually inspected for color, clarity, flexibility and smoothness.

**Thickness:** This thickness of the patches was assessed at 3 different points using screw gauze. For each formulation, three randomly selected patches were used.

**Weight variation:** The three disks of 2x2 cm<sup>2</sup> were cut and weighed on an electronic digital balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

**Flatness:** Longitudinal strips were cut out from each patch, one at the center and two from either side. The length of each strip was measured and the variation in the length because of the uniformity in flatness was

measured by determining present constriction, considering 0% constriction equivalent to 100% flatness.

**Folding endurance:** The folding endurance was measured manually for the preparation patch. A strip of the films (4x3 cm<sup>2</sup>) was cut evenly and repeatedly folded at the same place till it is broken.

**Moisture uptake:** The percent moisture absorption test was carried out to check the physical stability and integrity of the patch at high humid conditions. In the present study the moisture absorption capacities of the patch were determined in the following manner. The patches were placed in the desiccators containing 200 ml saturated solution of potassium chloride, to get the humidity inside the desiccators to 84 % RH. After 3 days the films were taken and weighed the percentage moisture absorption of the patch was found.

$$\text{Percentage moisture absorbed} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

**Moisture content:** The patches were weighed individually and kept in a desiccator containing fused calcium chloride at 40 °C for 24 h. The patches were reweighed until a constant weight was obtained. The moisture content was calculated in percentage based on the difference between the initial and the constant final weights of the patches.

**Swelling study:** Completely dried patches with a specified area (3.83 cm<sup>2</sup>) were weighed and put in desiccators for 24 h. They were removed and exposed to relative humidity conditions of 75 % (containing saturated solution of sodium chloride) in desiccators. Weight was taken on a single pan balance periodically until a constant weight was obtained. The swelling capacity of the patch (in weight %) was calculated in terms of percentage increase in weight of the patch over the initial weight of the specimen. The experiments were carried out in triplicate and the average values were used for the calculation. The percentage degree of swelling (DS) was calculated as:

$$\text{DS (\%)} = \frac{W_s - W_d}{W_d} \times 100$$

Where, W<sub>s</sub> and W<sub>d</sub> indicate the weight of the swollen and dry patch respectively.<sup>[8]</sup>

**Drug content determination:** The patch of area 3.83 cm<sup>2</sup> was cut and dissolved in phosphate buffer solution with pH 6.8. Then solvent methanol and dichloromethane, to make polymer soluble, were added to the mixture and the remaining volume was made up with buffer pH 6.8 to 100 ml in 100 ml volumetric flask. Then 1 ml was withdrawn from the solution and diluted to 10 ml. The absorbance of the solution was taken at 274 nm and concentration was calculated. By correcting dilution factor, the drug content was calculated.

**Surface pH:** For the determination of surface pH of the patch, each formulation is allowed to swell for 2 hrs in a

petri dish containing 5 ml of phosphate buffer pH 6.8. The surface pH was measured by pH paper placed on the surface of patches and allowed to equilibrate for 1 min. Evaluation of Buccal patch of permeation studies.<sup>[10]</sup>

**Diffusion cell:** Permeation studies were carried out in Franz diffusion cells. The Franz diffusion cell contains two compartments, the donor and receptor compartment. The receptor compartment is 5mm and holds a volume of 15 ml. The receptor compartment is attached to a collecting tube which allows easy collection of the sample every hour during the process of diffusion. The donor and the receptor compartment are held together with the help of a clamp and the diffusion cell was placed on the magnetic stirrer while diffusion studies carried. The total area of the receptor compartment that is exposed to the buccal patch for diffusion is 3.83 cm<sup>2</sup>.

#### ***In vitro* permeation studies using dialysis membrane<sup>[11]</sup>**

*In vitro* permeation of Voriconazole from Buccal patches through the dialysis membrane (Hi-Media) with molecular weight cut off of 12000 was studied. The membrane was mounted over a Franz diffusion cell along with the buccal patch. The receiver compartment of the diffusion cell was filled with 15 ml of phosphate buffer solution pH 6.8 and the setup were placed over a magnetic stirrer with temperature maintained at 37°C. Samples of 3 ml were withdrawn and replenished immediately from the receiver compartment at 1, 2, 3, 4, 6 and 12hrs. They were stored in refrigerated condition till the analysis was performed. The content of Voriconazole in the samples was analyzed by UV-Visible spectrophotometer. The concentrations of drug were determined at 274 nm.

#### **Kinetic modeling of drug release<sup>[12]</sup>**

**Mechanism of drug release:** Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted in zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

**A. Zero order release model:** To study the zero-order release kinetics the release rate data are fitted to the following equation.

$$Q = K_0 t$$

Where, Q= amount of drug released at time t, K<sub>0</sub>=zero order release rate constant. The plot of % drug release versus time is linear.

**B. First order release model:** The release rate data are fitted to the following equation.

$$\ln(100 - Q) = \ln 100 - k_1 t$$

Where, Q= percent drug release at time t, K<sub>1</sub>= first order release rate constant. The plot of log % drug release versus time is linear.

**C. Higuchi's Release Model:** To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$Q = K_H t^{1/2}$$

Where, Q= percent drug release at time t,  $K_H$ = Higuchi's (diffusion) rate constant. In Higuchi's model, a plot of % drug release versus the square root of time is linear.

**D. Korsmeyer-peppas release model:** The release rate data were fitted to the following equation.

$$F = (M_t/M) = K_m t^n$$

Where,  $M_t$ = drug release at time t,  $M$ = total amount of drug in dosage form,  $F$ = fraction of drug release at time t,  $K_m$ =constant dependent on the geometry of dosage form,  $n$ =diffusion exponent indicating the mechanism of drug release.

If  $n$  is equal to 0.89, the release is zero order. If  $n$  is equal to 0.45 the release is best explained by Fickian diffusion, and if  $0.45 < n < 0.89$  then the release is through anomalous diffusion or non-fickian diffusion (Swellaible & Cylindrical Matrix). In this model, a plot of  $\log(M_t/M)$  versus  $\log(\text{time})$  is linear.

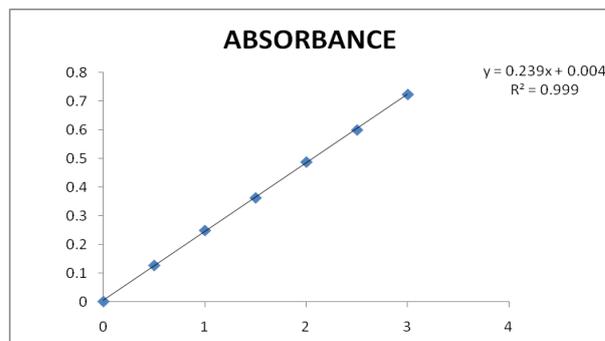
## RESULTS AND DISCUSSION

**The standard Calibration curve of Voriconazole:** It was found that the estimation of Voriconazole by UV spectrophotometric method at  $\lambda_{\text{max}}$  274 nm in 6.8 pH phosphate buffer had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2-10  $\mu\text{g/ml}$ .

**Construction of calibration curve:** The absorbance was measured in a UV spectrophotometer at 274 nm against 6.8 pH buffer. The absorbance so obtained was tabulated as in table 2. Calibration curve was plotted as shown in figure 1.

**Table 2: Standard calibration curve values of Voriconazole in 6.8 pH.**

| S. No | Concentration ( $\mu\text{g/ml}$ ) | Absorbance (at 274 nm) |
|-------|------------------------------------|------------------------|
| 1     | 0                                  | 0                      |
| 2     | 0.5                                | 0.126                  |
| 3     | 1                                  | 0.248                  |
| 4     | 1.5                                | 0.362                  |
| 5     | 2                                  | 0.487                  |
| 6     | 2.5                                | 0.599                  |



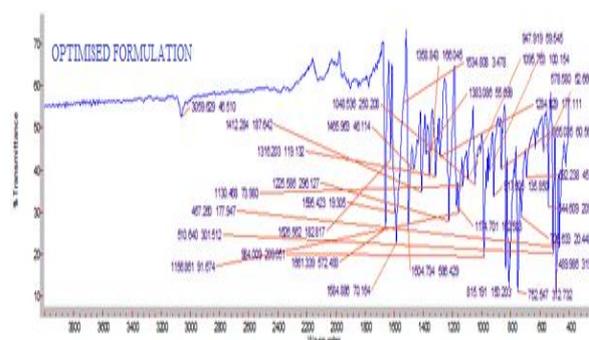
**Fig 1: Calibration curve of Voriconazole in pH 6.8 Phosphate buffer.**

### FT-IR Spectrum study

The FT-IR spectrum did not show the presence of any additional peaks for new functional groups, indicating no chemical interaction between drug and polymers. The FT-IR results were shown in the figure number 2 –3.



**Fig 2: FT-IR of Pure Drug.**



**Fig 3: FT-IR of Optimized Drug.**

### Selection of Drug and other ingredients

Voriconazole is selected based on suitability for buccal drug delivery system, biological and physico-chemical properties. Polymers HPMC K4M, HPMC K100M were selected. FT-IR studies showed there were no interactions between drug and polymers. Propylene glycol, Tween 80 was selected as permeation enhancer and plasticizer as given good results in studies observations.

### Formulation of Voriconazole buccal patches

Buccal patches were prepared by solvent casting method. The prepared patches were as shown in the figure 4.



Fig 4: Voriconazole buccal patches.

#### Evaluation of Voriconazole Buccal patches

The prepared Voriconazole Buccal patches were evaluated for Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake and Moisture content and all the results were found to be within the pharmacopeia limits as shown in the table 3.

**Physical appearance:** All the Buccal patches were visually inspected for colour, clarity, flexibility.

**Flatness:** All the Buccal patches were found to be flat without any foams.

Table 3: Evaluation of Buccal patch by physical methods.

| Formulation Code | Thickness (mm) | Folding endurance | Drug content (%) | Moisture uptake (%) | Moisture content (%) | Surface pH | Weight variation |
|------------------|----------------|-------------------|------------------|---------------------|----------------------|------------|------------------|
| F1               | 0.3569         | 20                | 45               | 7.98                | 3.77                 | 6.59       | 2.09             |
| F2               | 0.3520         | 25                | 65               | 25.05               | 9.2                  | 6.34       | 1.97             |
| F3               | 0.3470         | 27                | 57.5             | 13.09               | 5.16                 | 5.89       | 2.13             |
| F4               | 0.3496         | 24                | 60               | 15.63               | 5.66                 | 6.34       | 2.11             |
| F5               | 0.3460         | 30                | 67.5             | 11.73               | 4.87                 | 6.18       | 1.97             |
| F6               | 0.3517         | 32                | 92.5             | 19.65               | 12.67                | 5.98       | 2.18             |

#### Evaluation of buccal patches by *In-vitro* permeation studies using a dialysis membrane

The prepared Voriconazole Buccal patches were evaluated for *In-vitro* permeation studies using dialysis membrane. Among all the 6 formulations F6 formulation which contain HPMC K 100M had shown a 94% cumulative drug release within 12 hours, HPMC K 100M showed a better drug release profile and the results are as shown in the table 4.

Table 4: Evaluation of Buccal patch by *In-vitro* permeation studies using dialysis membrane.

| Time (hrs) | F1   | F2   | F3   | F4   | F5   | F6   |
|------------|------|------|------|------|------|------|
| 1          | 9.05 | 15.1 | 10.1 | 9.49 | 10.9 | 20.2 |
| 2          | 13.3 | 19.8 | 12.8 | 11.3 | 19.6 | 27.8 |
| 4          | 14.6 | 28.3 | 21.5 | 22.6 | 24.9 | 42.8 |
| 6          | 21.9 | 34.1 | 25.9 | 32.3 | 31.2 | 53.5 |
| 8          | 32.7 | 41.1 | 33.4 | 43.9 | 38.0 | 66.3 |
| 10         | 40.4 | 50.1 | 44.5 | 56.3 | 50.3 | 82.0 |
| 12         | 54.2 | 65.8 | 56.7 | 69.4 | 65.9 | 94.7 |

#### *In vitro* permeation studies using a dialysis membrane

The results were plotted to assess the permeation pattern as given in Figure 5 and table 5. All results suggest that the permeation was similar to the *in vitro* dissolution studies in most cases and the amount permeated is slightly less than the actual amount of drug dissolved under similar conditions.

Table 5: kinetics of *In-vitro* permeation studies using a dialysis membrane.

| Cumulative (%) Release Q | Time (T) | Root (T) | Log (%) Release | Log (T) | Log (%) Remain |
|--------------------------|----------|----------|-----------------|---------|----------------|
| 0                        | 0        | 0        | -               | -       | 2.000          |
| 20.2                     | 1        | 1.000    | 1.305           | 0.000   | 1.902          |
| 27.8                     | 2        | 1.414    | 1.444           | 0.301   | 1.859          |
| 42.8                     | 4        | 2.000    | 1.631           | 0.602   | 1.757          |
| 53.5                     | 6        | 2.449    | 1.728           | 0.778   | 1.667          |
| 66.3                     | 8        | 2.828    | 1.822           | 0.903   | 1.528          |
| 82                       | 10       | 3.162    | 1.914           | 1.000   | 1.255          |
| 94.7                     | 12       | 3.464    | 1.976           | 1.079   | 0.724          |

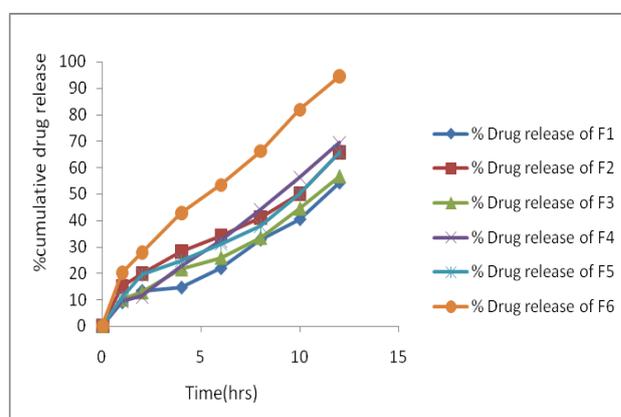


Fig 5: Release profile of *In-vitro* permeation studies using dialysis membrane.

#### Drug release kinetics studies

Table 5 represents the kinetic parameters of *in vitro* dissolution studies. The zero order, first order, Higuchi

diffusion and Korsmeyer – Peppas drawn as represented in Figures 6 –9. Results suggest that the Voriconazole buccal patches could release the drug following first order.

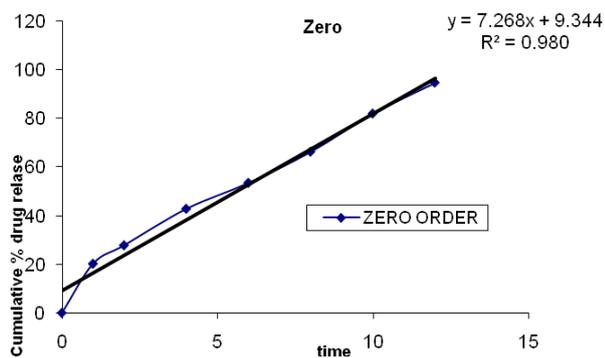


Fig 6: Zero order kinetics.

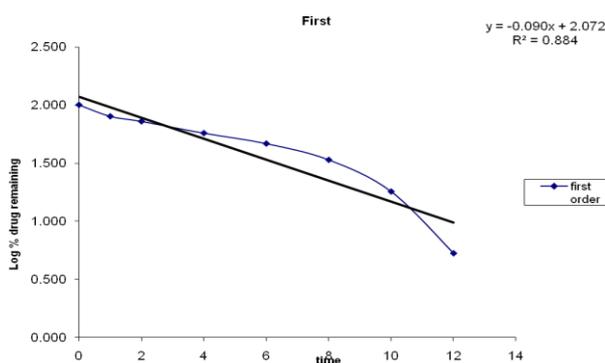


Fig 7: first order kinetics.

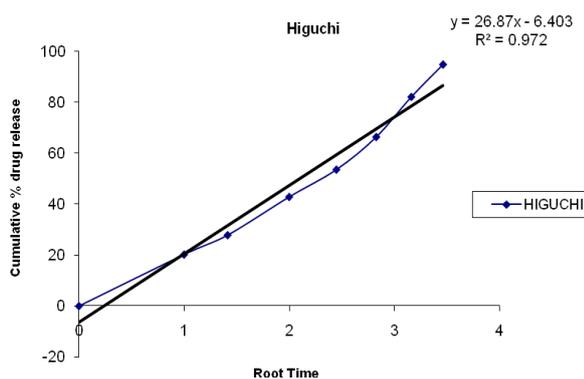


Fig 8: Higuchi plot.

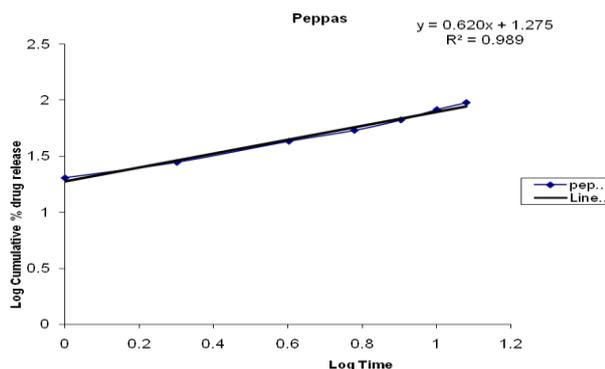


Fig 9: Korsmeyer – Peppas plot.

## CONCLUSION

In the present study buccal drug delivery of Voriconazole patches was developed to overcome the first pass metabolism and to reduce the frequency of dosing compared to oral route. Matrix type of buccal patches was developed by using polymers HPMCK4M and HPMCK100M. Buccal patches were prepared by employing solvent casting method. Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions. The formulations were prepared with the varying concentrations of polymers ranging from F1-F6, and all the formulations were evaluated for parameters like Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Surface pH, Drug content, Moisture uptake, Moisture content and Swelling study and all the results were found to be within the pharmacopeial limits. *In vitro* drug release studies are carried out by using a dialysis membrane. Among all the 6 formulations F6 formulation which contain HPMC K100M 500mg had shown 94% cumulative drug release within 12 hours. For F6 formulation release kinetics were plotted and the Regression coefficient value was found to be high for Korsmeyer-peppas release model i.e., 0.989.

## REFERENCES

1. P. Sandhya, Nazera Tazyeen, M. Sunitha, M. Sirisha, R. Sunil, Formulation and Evaluation of Buccal Films of Ketorolac Tromethamine Journal of Global Trends in Pharmaceutical Sciences, 2013; 4(3): 1184-1192.
2. Nagaveni Somepalli, Chandra Sekhar Moru, Dinesh Babu Gottipati, Vamshi Krishna Voruganti, Formulation and Evaluation of Buccal Films of Salbutamol Sulphate, Mintage journal of Pharmaceutical and Medical Sciences, 2013; 2(3): 37-40.
3. N. G. Raghavendra Rao, Sunil Firangi, Keyur Patel Formulation and *in-vitro* evaluation of mucoadhesive buccal patches containing zolmitriptan using gel forming polymers, Pelagia Research Library Der Pharmacia Sinica, 2012; 3(1): 47-57.
4. S.Himabindu, D.Sathish and Shayeda Formulation and *In-vitro* Evaluation of Mucoadhesive Buccal Patches of Cyproheptadine Hydrochloride, Journal of Applied Pharmaceutical Science, 2012; 02(07): 196-201.
5. Navneet Verma and Pronobesh Chattopadhyay Preparation of Mucoadhesive Patches for Buccal Administration of Metoprolol Succinate, *In Vitro and In Vivo* Drug Release and Bioadhesion Tropical Journal of Pharmaceutical Research, 2012; 11(1): 9-17.
6. Tiwari D, Goldman D, Town C, Sause R, Madan PL, *In vitro-in vivo* evaluation of a controlled

- release buccal bioadhesive device for oral drug delivery, *Pharm Res.*, 1999; 16: 1775–1780.
7. Rohit Chaudhary, Md. Shamim Qureshi, Jitendra Patel, Uttam Prasad Panigrahi, I.C. Giri Formulation, Development and *In-Vitro* Evaluation of Mucoadhesive Buccal Patches of Methotrexate, *International Journal of Pharma Sciences and Research(IJPSR)*, 2010; 1(9): 357-365.
  8. Khanna R, Agrawal SP and Alka Ahuja. Preparation and evaluation of mucoadhesivebuccal films of clotrimazole for oral candida infections, *Indian Journal of Pharmaceutical Sciences*, 1997; 59(6): 299-6.
  9. Murthy TK., Reddy MN, Shankar DG. Several analytical methods for the estimation of tizanidine, *Ind J Pharm Sci.*, 2001; 63: 179-191.
  10. Rajesh Khanna, Suraj P. Agarwal Rajesh Khanna, Suraj P. Agarwa, Alka Ahuja, Muco-adhesive Buccal Tablets of Clotrimazole for Oral Candidiasis. *Drug Development and Industrial Pharmacy*, 1997; 23(8): 831–837.
  11. Mohana K, Srivalli R, Lakshmi P, Balasubramaniam J. K, Design of a novel bilayered gastric mucoadhesive system for localized and unidirectional release of lamotrigine *Saudi Pharmaceutical Journal*, *AAPS Pharm Sci Tech*, 2013; 21(1): 45–52.
  12. Shaila Lewis, G Subramanian, S Pandey, N Udupa. Design, Evaluation and Pharmacokinetic Study of Mucoadhesive Buccal Tablets of Nicotine for Smoking Cessation. *Indian Journal Pharm Science*, 2006; 68(6): 829-831.