FORMULATION DEVELOPMENT AND IN VITRO IN VIVO CHARACTERIZATION OF VORICONAZOLE TABLET

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INTRODUCTION

Oral drug delivery is the most convenient and preferred route of drug administration, because of the greater stability, smaller bulk, accurate dosage and easy production. Among the different oral dosage forms, solid dosage form possesses several advantages over other types of oral dosage forms. Last few decades, most of the new chemical entities under development are intended to be used as a solid dosage form which produces an effective reproducible in vivo plasma concentration after oral administration. In fact, most new chemical entities are poorly water soluble drugs, not well-absorbed after oral administration, which can distract from the drug’s inherent efficacy. The major rate-limiting steps for absorption of drug from the gastrointestinal tract are aqueous solubility and membrane permeability. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can permeate the membranes of the gastro-intestinal tract to reach systemic circulation. Hence, to improve the oral bioavailability of active agents, the pharmaceutical scientists mainly focus on suitable approaches for enhancing solubility and permeability of poorly water soluble drugs. One of the major current challenges of the pharmaceutical industry is related to develop suitable strategies that improve the water solubility of drug. Solid dispersions are one the most successful and interesting techniques for the improvement of drugs solubility and bioavailability1,2. Solid dispersion can be defined as a molecular mixture of poorly water soluble drugs with hydrophilic carriers, either in amorphous, crystalline or molecularly form.

Voriconazole is a second-generation azole antifungal agent indicated for use in the treatment of fungal infections including invasive aspergillosis, esophageal candidiasis and serious fungal infections1. Voriconazole is a lipophilic drug with a low aqueous solubility (maximum 2.7 mg/mL), which classifies it to Biopharmaceutical Classification System (BCS) class II (4-7). Its limited solubility in water classified voriconazole as drug with low bioavailability, which limits its effectiveness. This major problem can be solved only by developing suitable pharmaceutical formulations3,4,5.

In the present study, tablets of containing voriconazole solid dispersion were prepared by wet granulation technique and the different quality control parameters of tablets were investigated. Further, stability and in vivo pharmacokinetic study were performed on selected best tablet formulation.

MATERIALS AND METHODS

Materials

Voriconazole was collected as a gift sample from MSN House, Hyderabad, India. Gelucire® 44/14 was procured from Coroda, Navi Mumbai, Maharashtra, India. Poloxamer 188 was procured from Merck, Bangalore, India.

Methods

Fabrication of voriconazole tablets

The solid dispersions of voriconazole were fabricated in our laboratory and different characteristics of solid dispersion were evaluated. Among the different solid dispersions, suitable solid dispersion for the formulation of voriconazole tablets was selected based on faster release of voriconazole in release medium. In this context, solid dispersions contained Gelucire® 44/14 and Poloxamer 188 as carrier were considered as they were released whole voriconazole within short period of time.
Solid dispersions were prepared by combination of hot-melt and solvent evaporation technique. Voriconazole tablets containing solid dispersion were prepared by wet granulation technique. The composition of voriconazole tablet formulations is presented in Table 1. Lactose and microcrystalline cellulose were used as diluents and disintegrating agent, respectively. The amount of microcrystalline cellulose and lactose were varied in different formulations. Accurately weighted amount of solid dispersion containing voriconazole equivalent to 50 mg was taken in a glass mortar and then all the excipients except starch, magnesium stearate and talc were blended with the help of a pestle for 30 min and passed through sieve no. 60. Granulation was done with sufficient amount of starch paste. Wet mass was passed through sieve no. 18 and dried at 50-60°C for 2 h. Dried granules were further sized by sieve no. 14 and blend with magnesium stearate and talc in polyethylene bag for 10 min. The lubricated granules obtained were compressed by a single punch-tabletting machine (Kilburns, Allahabad, India) under constant pressure using 13 mm punch. The weights of the tablets were kept constant in each formulation.

Table 1: Composition of voriconazole tablets containing solid dispersion

| Ingredients (mg) | TGF1 | TGF2 | TPF1 | TPF2 |
|------------------|------|------|------|------|
| Solid Dispersion* (equivalent to 50 mg voriconazole) | Gelucire®(8) carrier | 44/14 as Poloxamer 188 as carrier |
| Microcrystalline cellulose | 70 | 100 | 70 | 100 |
| Starch | 20 | 20 | 20 | 20 |
| Lactose | 100 | 70 | 100 | 70 |
| Magnesium stearate | 5 | 5 | 5 | 5 |
| Talc | 5 | 5 | 5 | 5 |
| Total | 600 | 600 | 600 | 600 |

*Solid dispersion prepared by combination of hot-melt and solvent evaporation technique in the drug to carrier ratio of 1:5.

Evaluation of pre-compressed lubricated granules
The blended lubricated granules of all formulations before compression were subjected to evaluate following different physico-chemical properties like: bulk density, tapped density, angle of repose (θ), compressibility index and Hausner's ratio as per method reported earlier.  

Evaluation of compressed tablets
The formulated tablets were evaluated for following quality control tests:

Shape of tablets
The shape of compressed tablets was examined under the magnifying lens.

Tablet dimensions
Thickness and diameter were measured using a calibrated dial caliper. Three tablets of each formulation were taken randomly and thickness was measured individually.

Hardness
The hardness of three randomly selected tablets from each formulation was determined using Monsanto hardness tester (Monsanto, Mumbai, India). Hardness of tablets was expressed in kg/cm².

Friability test
The friability test of tablets of each formulation were carried out in triplicate by taking ten tablets from each formulation and weighed. The tablets were placed in Roche friabilator (Labotech, Mumbai, India) and operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were then dedusted and reweighed. The friability was calculated as the percent weight loss of ten tablets.

Weight variation test
The weight variation test of tablets of all formulations batches were carried out by randomly selecting twenty tablets from each formulation and weight of twenty tablets was determined. The average weight of individual tablet was calculated. Then individual tablets were weighed and the individual weight was compared with an average weight.

Content uniformity
Twenty tablets of each formulation were placed in a mortar and powdered with pestle. An amount equivalent to 200 mg of voriconazole was taken in a volumetric flask and shaken with 70 ml of water and diluted to 100 ml with water. The solution was filtered through a membrane filter (0.22 μm). One milliliter of the filtrate was withdrawn and suitably diluted to 100 ml with water. The absorbance of the solution was measured using UV-Visible spectrophotometer (Shimadzu, Tokyo, Japan) at 255 nm. The content uniformity test of each formulation was carried out in triplicate.

In vitro release study
In vitro release study of tablet (n = 6) of each formulation was carried out using USP XXIII paddle dissolution test apparatus (Campbell Electronics, Mumbai, India) at 100 rpm. The release study was performed in 900 ml simulated gastric fluid (0.1N HCl, pH 1.2) and the temperature of the release media was maintained at 37 ± 0.5°C. Samples (1 ml) were withdrawn at predetermined intervals up to 2 hrs and replaced with equivalent volume of fresh medium. The samples were filtered through Whatman filter paper (0.22 μm) and analyzed the drug content after appropriate dilution by UV-Visible spectrophotometer (Shimadzu, Tokyo, Japan) at 255 nm.

Drug release kinetics
To evaluate the release kinetics of voriconazole from physical mixtures and solid dispersions, the release data were subjected to different kinetic models like: zero-order, first-order and Higuchi.  

Zero order: Q = k0t  
First order: lnQ = lnQ0 - k1t  
Higuchi’s square root at time: Q = k0t½

Where, Q0 is the initial amount of drug present in the physical mixtures and solid dispersions, Q is the percent of drug released at time t and k0, k1, and k0 are the zero-order, first-order and Higuchi rate constant, respectively. In order to evaluate the voriconazole release mechanism from physical mixtures and solid dispersion, the release data was further analyzed by Korsmeyer-Peppas equation: Mt/M∞ = ktⁿ  

Where, Mt is the amount of drug released at time t and M∞ is the amount of drug released at infinite time, M∞/M₀ is
the fraction of drug released at time t. k is the kinetic constant and n is the diffusional exponent. In case of value of diffusional exponent, n > 0.45 indicates Fickian or Case I release; 0.45 < n < 0.89 for non-Fickian or anomalous release; n = 0.89 for Case II release; and n > 0.89 indicates Super Case II release.

Stability study
Stability study of formulation TPF1 was carried out under the different stress conditions and the method was followed as earlier mentioned by some researchers6-13. Formulation TPF1 was stored at 40ºC with 75 ± 5% RH. After 30, 60 and 90 days all the quality control tests of tablet including drug contents of that formulation were determined. In vitro release study was also carried out for the same formulation after stipulated time period of time intervals. Methods followed for all the quality control tests were discussed in earlier section.

Pharmacokinetic study
The pharmacokinetic study were conducted under approval of the Institutional Animal Ethical Committee. The present study was carried out in accordance with that concerned recommendations and with standard institutional guidelines.

Animal study design and method
The in vivo pharmacokinetic studies9-13 were conducted under approval of the Ethical Committee of the Institution. For the experiment, healthy rabbits (New Zealand albino) of male; weighing between 25-30 Kg were acclimatized in the animal room for 10 days and fasted for 12 h before dose administration with free access to drinking water. The pharmacokinetic parameters of TPF1 tablet were determined with the following study design: Single dose, open label, randomized and complete crossover design under fasted condition. Animals were randomly divided into three groups, each group comprising of four rabbits. First group was received formulation TPF1 containing voriconazole equivalent to 6 mg/kg body weight, while second group received the mixtures pure drug prepared with 25 mL of purified water (6mg/kg body weight) and third group treated as control.

After an overnight fasting, animals were given a single dose of dosage form in a randomized fashion with approximately 25 mL of water. Food and drinks (other than water) were not allowed for 4 hrs after dosing to all animals. For oral administration, the rabbits were placed in a restraining device specially designed to protect the rabbits from spinal injury. A wooden biting block with a central opening was placed between the upper and lower teeth. The tube was passed through the opening and inserted carefully in the oesophagus. Once the tube was properly inserted to the oesophagus, the formulation TPF1 was placed into the tube and it was administered through 4-5 times flushing of small volume (5 mL) of water repeatedly.

Blood samples (1ml) were withdrawn from ear vein of each animal with a 24G-1 inch needles and collected directly in heparinized tubes. Blood samples were collected at 0 (pre-treatment), 0.5, 1, 2, 4, 6, 8, 12, 24 and 36 h. The blood samples were centrifuged at 4,000 rpm (Remi Cooling Centrifuge, Mumbai) for 10 min at 4ºC and the separated plasma samples were stored in a clean screw capped 5 mL polypropylene plasma tubes (Labsro, Mumbai) at -8ºC in a deep freezer, until further analysis.

Sample preparation and extraction
Liquid-liquid extraction procedure was used for the extraction of the drug from the plasma9-13. Blood samples were collected in disposable glass tubes (100 × 16 mm) and centrifuged at 4500 rpm for 5 min. The plasma samples were stored at -22ºC until analysis. Hundred microliter of plasma sample was taken in a 2 mL glass centrifuge tube; 10 µL of pure drug solution (100 µg mL⁻¹) was added and the mixture was vortexed for 10 sec using multipulse vortexer (Glas-COL, USA). The above solutions were treated with 1.5 mL of acetonitrile. After vortex-mixed for 10 min in a spinix vortexer (M37610-33, Barnstead International, USA) and centrifugation (Biofuge Fresco centrifuge, Heraeus, Germany) at 4ºC for 5 min at 10,000 rpm, the organic layer was aspirated off and transferred to a second tube by means of disposable Pasteur pipette. The collected organic layer was then transferred to a clean test tube and evaporated under the nitrogen gas. The residue was reconstituted in 100 µL with respective mobile phase mixed well and 20 µL of the final clear solution was injected in to the HPLC system.

Determination of pharmacokinetic parameters and statistical analysis
The pharmacokinetic parameters9-13 were assessed maximum plasma concentration (Cmax), time to reach peak plasma concentration (tmax), area under the plasma concentration-time curve (AUC0-12) and apparent elimination and absorption half-life (t1/2) [9-13]. The rate of absorption phase was also evaluated by means of the ratio Cmax/AUC. AUC and MRT values were calculated using the trapezoidal method without logarithmic transformation. The method of Wagner and Nelson was used to calculate the k. Statistical analyses were carried out using Student’s paired t-test, the t-test for independent groups. Student’s t-test was used for statistical analysis of the data and a probability value of p<0.05 was considered statistically significant.

Time to reach the maximal concentration (tmax) = \frac{2.303 \times \log k_a/k_d}{\log k_a/k_d} 
Maximal plasma concentration (Cmax) = \frac{k_{nm} \times F \times X}{V_d} \times e^{-k_{nmax} \times t}
Both Tmax and Cmax were taken from plasma drug concentration profile of each individual.

Area under the plasma concentration-time curve from zero to the last quantifiable concentration (AUC0-12) was calculated using trapezoidal rule.

Area under the plasma concentration-time curve from zero to infinity (AUC0-∞) was the sum of AUC0-12 + AUC12-∞, where AUC12-∞ (extrapolated AUC from t to infinity) was determined as C/Ke, where Ke as equal to 36 hrs.

Half-life (t1/2) was calculated from the formula t1/2 = 0.693/Kd
Elimination rate constant (Kd) = \frac{2.303}{303} \times \log (0.693/Kd)

In vitro-in vivo correlation
At the end of the pharmacokinetic study, the in vitro/in vivo correlations for formulation were assessed by positioning the in vitro released data and the in vivo absorption data on top of each other. Cumulative dissolution released was used as the in vitro parameter. The in vivo concentration versus time curve for each animal was initially transformed to cumulative amounts absorbed at each time point, using the method of Wagner–Nelson method.

Data analysis
Results are expressed as mean values and standard deviation (±S.D.) and the significance of the difference observed was analyzed by the Student’s t-test. In all tests, a probability value of p < 0.05 was considered statistically significant.

RESULT & DISCUSSIONS
Evaluation of pre-compressed lubricated granules
The different micromeritic properties of lubricated granules of different formulations are presented in table 2. Bulk density and tapped density of lubricated granules were found within the range of 0.37 ± 0.09 g/ml to 0.39 ± 0.06 g/ml and 0.45 ± 0.07 g/ml to 0.48 ± 0.08 g/ml respectively. The Hausner’s ratio (< 1.29), compressibility index (%; <22.91%) and angle of repose (°; <34.24°) values indicated that the prepared lubricated granules exhibited good flow properties.
The diameter and thickness from all the tablet formulations were found less than 12 minutes. From the release data it was indicated the release of voriconazole within 105 minutes. The release profile of TPF1 portrayed that the faster release of voriconazole was occurred as compared to other formulations.

In vitro release study
The in vitro release profiles of all the voriconazole tablet formulations are shown in Fig. 1. From the release data it was revealed that the entire tablet formulations were released voriconazole within 105 minutes. The release profile of TPF1 showed minimum disintegration time (2-7 minutes).

Release kinetics
The in vitro release data of all the tablet formulation were subjected to evaluation of release kinetics and release mechanism. The release kinetics and release mechanism of voriconazole of all the tablet formulations are presented in table 4. The release of voriconazole from all the tablet formulations followed first order kinetic. This was indicated the release of voriconazole dependent on the concentration of voriconazole present in the tablets. The high value of R² in Higuchi model revealed that the release of voriconazole from all the formulations followed diffusion controlled. The release data when fitted to the Korsmeyer-Peppas model it was found that formulations TGF1 and TGF2 only followed this model and diffusion exponent was found less than 0.501 indicating the release of voriconazole from the tablet followed non-Fickian transport.
Table 4: Drug release kinetics and release mechanism of voriconazole from different tablet formulations

| Formulation | Release Kinetics |  
|-------------|-----------------|
|             | Zero Order | First Order | Higuchi | Korsmeyer-Peppas |
| TGF1        | 0.814     | 0.938      | 0.976   | 0.977   | 0.407   |
| TGF2        | 0.879     | 0.890      | 0.992   | 0.985   | 0.501   |
| TPF1        | 0.791     | 0.936      | 0.967   | 0.765   | -       |
| TPF2        | 0.781     | 0.936      | 0.963   | 0.765   | -       |

Stability study

The evaluated quality control test parameters of stability studies at different time intervals are presented in Table 5. There were no significant changes in the test parameters like: physical appearance, weight variation, diameter, thickness, hardness, friability, drug content uniformity and disintegration time observed in tablets after 6 months of storage at accelerated stability conditions. The in vitro release data of tablet formulation at initial stage was considered as the reference for release study. The in vitro release profile (Fig. 2) revealed that the release profile after 6 months of storage at accelerated condition was found to be similar to that of reference one. Based on the results it was opined that the tablet was stable after 6 months of storage at accelerated stability conditions.

Table 5: Quality control test parameters of tablets at time different time intervals during accelerated stability study

| Parameters                  | Initial | After 30 days | After 60 days | After 90 days |
|-----------------------------|---------|---------------|---------------|---------------|
| Physical appearance        | White to off white | No change     | No change     | No change     |
| Weight variation (mg)       | 604 ± 0.16 | 604 ± 0.22    | 604 ± 0.24    | 604 ± 0.28    |
| Diameter (mm)               | 13.02 ± 0.06 | 13.02 ± 0.04  | 13.02 ± 0.08  | 13.02 ± 0.14  |
| Thickness (mm)              | 3.50 ± 0.04 | 3.50 ± 0.04   | 3.50 ± 0.04   | 3.50 ± 0.04   |
| Hardness (kg/cm²)           | 4.6 ± 0.22  | 4.6 ± 0.24    | 4.7 ± 0.12    | 4.7 ± 0.28    |
| Friability (%)              | 0.88 ± 0.12 | 0.86 ± 0.14   | 0.94 ± 0.12   | 0.94 ± 0.14   |
| % Drug content Uniformity   | 98.43 ± 0.48| 98.54 ± 0.56  | 98.47 ± 0.46  | 98.52 ± 0.65  |
| Disintegration Time (min)   | 2-7       | 2-7           | 2-8           | 2-8           |

In vitro drug release studies

| Time (min) | % Cumulative drug release | Initial | After 30 days* | After 60 days* | After 90 days* |
|------------|---------------------------|---------|---------------|---------------|---------------|
| 0          | 0                         | 0       | 0             | 0             | 0             |
| 15         | 51.24 ± 0.66              | 50.98   | 50.68         | 50.04         |
| 30         | 72.23 ± 1.28              | 72.12   | 72.02         | 71.56         |
| 45         | 86.96 ± 1.66              | 86.78   | 86.58         | 86.24         |
| 60         | 94.66 ± 1.24              | 94.46   | 94.38         | 94.09         |
| 75         | 97.64 ± 1.12              | 97.62   | 97.46         | 97.08         |
| 90         | 99.95 ± 1.21              | 99.89   | 99.84         | 99.58         |

*In vitro release study at different time intervals were carried out on six tablets and the mean value is presented.

Fig. 2: In vitro release profile of tablet formulation (TPF1) after different time intervals (Mean ± S.D.; n = 6)

Pharmacokinetic study

The results of plasma concentration at different time intervals, after administration of tablet TPF1 and pure voriconazole to rabbits are presented in Fig. 3. The pharmacokinetic parameters were derived from plasma drug concentration versus time profile of all the subjects and the results are shown in Table 6.

The time required to reach maximum plasma concentration (tmax) of tablet TPF1 and pure drug was found 1.24 ± 0.21 hrs and 2.06 ± 0.15 hrs, respectively. This indicated that the rate of absorption of voriconazole from the tablet TPF1 was faster. The average peak plasma concentration (Cmax) of tablet TPF1 and pure drug was found 314.25 ± 124.64 ng/mL and 145.26 ± 55.42 ng/mL, respectively. There was more than 2 fold increased of Cmax of voriconazole was observed from TPF1 as compared to pure voriconazole. The significant difference in tmax (p<0.001) and Cmax (p<0.05) were observed in TPF1 and pure voriconazole. The AUC0-t of TPF1 and pure voriconazole was found 2630.88 ± 287.55 ng. hr./mL and 1689.83 ± 126.34 ng. hr./mL, respectively. There was significant (p < 0.05) difference of AUC0-t was observed between the TPF1 and pure voriconazole. The AUC0-t of voriconazole from TPF1 was found 1.56 times more than pure voriconazole. The significant (p < 0.05) difference in calculated
AUC_{∞} of formulation TPF1 (2704.12 ± 226.69 ng. hr./mL) and pure voriconazole (1747.59 ± 104.23 ng. hr./mL) was exhibited. This revealed that the bioavailability of voriconazole was improved when voriconazole formulated as TPF1. The increased in bioavailability of voriconazole in TPF1 could be attributed to the increased in solubility and dissolution rate of voriconazole. The t_{1/2} of voriconazole was found shorter in TPF1 (6.02 ± 0.16 h) as compared to pure voriconazole (6.60 ± 1.24 h). The significant (p < 0.001) difference of K_{a} was observed between TPF1 (2.64 ± 0.02 h⁻¹) and pure voriconazole (1.34 ± 0.04 h⁻¹).

![Graph](image1.png)

**Fig. 3:** Mean plasma concentration versus time (Mean ± S.E.) profile of voriconazole following oral administration of TPF1 tablets and pure voriconazole solution.

| Pharmacokinetics parameters | Pure drug | TPF1 |
|-----------------------------|-----------|------|
| C_{max} (ng/mL) *           | 145.26 ± 55.42 | 314.25 ± 124.64 |
| T_{max} (h) **              | 2.06 ± 0.15     | 1.24 ± 0.21   |
| AUC_{0-t} (ng. hr./mL) *    | 1689.83 ± 126.34 | 2630.88 ± 287.55 |
| K_{e} (h⁻¹) **             | 0.105 ± 0.04    | 0.115 ± 0.07  |
| t_{1/2} (h) **              | 6.60 ± 1.24     | 6.02 ± 0.16   |
| AUC_{0-∞} (ng. hr./mL) *    | 1747.59 ± 104.23 | 2704.12 ± 226.69 |
| K_{a} (h⁻¹) **             | 1.34 ± 0.04     | 2.64 ± 0.02   |

* p<0.05, ** p< 0.001.

**In vitro-in vivo correlation**

Further, 'cumulative % of drug absorbed' in vivo was plotted against 'cumulative % of drug released' in vitro at the same time and the graph is presented in **Fig. 4**. A linear correlation (R² = 0.822) represent point-to-point relationship between in vitro release and in vivo absorption.

![Graph](image2.png)

**Fig. 4:** Correlation of cumulative % drug released and cumulative % drug absorbed for formulation (TPF1) of voriconazole tablets.

**CONCLUSIONS**

The present work tablets of voriconazole solid dispersion were fabricated and the different quality control parameters were investigated. The quality control tests of all tablet formulations had passed the USP tests for tablets. The in vitro release profile revealed that the faster release of voriconazole from tablet formulation (TPF1) contained solid dispersion using poloxamer in the drug to carrier ratio of 1:5. The stability studies indicated that the tablets were stable in accelerated stability condition up to 3 months. The point-to-point (type A) correlation was observed during investigation of in vitro-in vivo correlation. It can be concluded that the tablet can be formulated using voriconazole solid dispersion is able to enhance the therapeutic efficacy of voriconazole. However, extensive preclinical studies and clinical trials of the presently developed voriconazole tablet needs to be conducted to determine and document the safety profiles of the voriconazole.

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Conflict of Interest:
Authors are hereby declared that there is no conflict of interest for publication of this manuscript.
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