PREPARATION AND EVALUATION OF SUSTAINED RELEASE MATRIX FORMULATIONS OF VORICONAZOLE

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ABSTRACT

Voriconazole is a triazole antifungal with a half-life of 1.7 hours and 96% oral bioavailability. The oral route is the most popular of drug delivery routes. However, there are a few limitations to the traditional dosage form, for instance, fluctuations in plasma drug level. Sustained drug delivery system overcomes these limitations; it helps to maintain stable plasma drug concentrations by decreasing drug r elease and extending the duration of the effect. The main purpose of this study was to formulate voriconazole sustained release dosage form to enhance efficacy, decrease dose frequency, decrease its side effects, and improve patient compliance. The study explored various formulations for producing the sustained-release (S.R) dosage form, as well as assessed the drug's release kinetics and its stability.

Methodology: Fourier-transform Infrared Spectroscopy was used to investigate drug-polymer compatibility. The micromeritics of voriconazole powder and its blends were evaluated. Different sustained release tablets were formulated utilizing a wet granulation process and acrylic polymers (Eudragit) i.e., Eudragit RL100 and RS100 alone and as mixtures with different ratios, in different concentrations. In-vitro drug release of formulae was performed for 24 hours. The formula with desired control of drug release and complied with dissolution specifications for SR dosage forms was further evaluated for its stability by storage for 3 months at 30^{o} C and 40^{o} C and 75% relative humidity.

Results: no interaction was observed between voriconazole and polymers using FTIR. The powder blends micromeritics were found to be in accordance with the specification. Tablets showed release from 37.29 to 76 % up to 24 hr using USP type I technique. It was found that as polymer concentration increased, the drug release from tablet decreased. The selected formulation F13 which containing 5% of Eudragit RL100:RS100 at a ratio of (10:1) was found to be stable.

Conclusion: The obtained data concluded that the F13 formula gave more prominent S.R effect than using Eudragit RL100 or RS 100 alone.

Keywords: Voriconazole, Sustained Release Matrix Tablets, Micromeritics, Eudragit RS100, Eudragit RL100

1. Introduction:

Sustained-release drug delivery systems offer several advantages over traditional forms, and along with a drug manufacturing strategy, they can help address many problems associated with conventional drug delivery. For instance, sustained-release formulations promote patient compliance by requiring less frequent dosing and maintaining steady-state plasma concentration, which can lead to better adherence to the prescribed treatment regimen (***Adepu et al, 2021***). This has the potential to improve treatment outcomes and reduce the likelihood of therapy failure or disease progression. In addition, sustained-release formulations can provide controlled release of the medicine, which can reduce the incidence of adverse events, especially for medications with a narrow therapeutic index or known for serious side effects (***Belamkar et al, 2022***).

Furthermore, sustained-release formulations improve drug efficacy by delivering the drug in a consistent and controlled manner, which can maintain therapeutic drug levels for an extended period of time (***Kompella et al, 2021***). They also enhance drug stability by protecting the drug from degradation, increasing the product's shelf-life, and ensuring consistent drug delivery. Moreover, sustained-release formulations can be tailored to a specific rate or region in the body, or provide a specific drug release profile, which can further improve therapeutic efficacy and reduce the likelihood of drug resistance or toxicity. Overall, sustained-release drug delivery systems have the potential to improve the safety, efficacy, and patient adherence of chronic illness medication regimens (***Cao et al, 2019***). Therefore, in this study, voriconazole is intended to be formulated in sustained-release form.

Voriconazole is an antifungal drug belonging to the triazole class and has a broad-spectrum activity against fungi ***(Cao et al, 2019).*** It is freely soluble in acetone and methylene chloride and very slightly soluble in water ***(USP37 NF32, 2014).*** It has a half-life of 1.7 hours and an oral bioavailability of 96%. Voriconazole works by inhibiting the fungal ergosterol biosynthesis, specifically by inhibiting cytochrome P-450-mediated alpha lanosterol demethylation ***(Oren, 2005; Rosam et al, 2020).***

Different polymers are widely used to formulate S.R dosage forms ***(Ainurofiq & Choiri, 2015; Khan et al, 2022)***. However, careful selection of a suitable polymer or a combination of polymers is required to achieve the desired performance of these dosage forms ***(Merkle, 2015).*** In this study, Eudragit is used to extend the release of Voriconazole. Eudragit is an acrylic polymer and one of the most commonly used types of sustained-release polymer for incorporating the active substance into an inert matrix, particularly suitable for making matrix tablets due to their range of properties and ease of use ***(Nikam et al, 2023).*** Eudragit RS100 and RL100 are two different types of Eudragit polymers that are composed of poly(ethylacrylate, methylmethacrylate, and a quaternary ammonium group-R). The percentage of quaternary ammonium groups in Eudragit RS 100 ranges from 4-8%, while in Eudragit RL 100, it is between 8.8% and 12%. Eudragit RS is not soluble in physiological pH levels, but it can swell and become permeable to water, which makes it useful for controlled oral medication delivery. On the other hand, Eudragit RL is also not soluble in physiological pH levels, but it has limited swelling capacity, which makes it suitable for drug dispersion. Eudragit RL

100 is commonly used to coat medicines meant for the gastrointestinal tract (***Pignatello, 2001***; ***Singh & Pai, 2016***).

In this study, Voriconazole SR matrix tablets were developed to sustain its action, leading to better patient compliance and reducing the incidence of adverse side effects. The aim was to achieve an optimum release profile with once-daily dosing of Voriconazole sustained-release tablets over a 24-hour period ***(Nikam et al, 2023).***

2. Materials and Methods.

2.1. Materials

Voriconazole was supplied by Chromo Laboratories Pvt Limited, India. Eudragit RS100, Eudragit RL100 and Colloidal Silicon dioxide (Aerosil 200) were provided from Degussa Ltd, Germany. Magnesium stearate was provided by Acto-Corp, New York, USA. Lactose monohydrate was provided by Meggle GmbH, Germany. Povidone K30 was provided from ISP, UK. Purified talc was supplied by Pumex Limited, UK. The remaining reagents and chemicals were of analytical grade. The commercial tablet was provided by Mash company.

2.2. Construction of calibration curve of Voriconazole using UV spectrophotometer

UV scanning of Voriconazole was carried out using UV Spectrophotometer (Schimadzu, Japan) ***(Rangasamy et al, 2013)***. An amount of 100 mg of Voriconazole was dissolved in 50 ml of Acetonitrile as an organic solvent to enhance the solubility ***(USP37 NF32, 2015)***; making stock solution of 2 mg/ml. (Stock solution I).

2.2.1. Calibration curve in 0.1 N HCl

A measure of 10 ml of stock solution I was collected and diluted to 200 ml with 0.1 N HCl (100 µg/ml) (Stock solution II). 5, 10, 15, 20, 25, 30, and 35 ml were taken from Stock solution II in different 100 ml volumetric flasks and made up the volume by 0.1 N HCl; giving concentrations of 5, 10, 15, 20, 25, 30 and 35 µg/ml of Voriconazole respectively. The absorbance of each sample was measured using a UV spectrophotometer at wavelength (λ max) = 255 nm, in accordance with Voriconazole monograph ***(USP37 NF32, 2014).***

2.2.2. Calibration curve in Phosphate buffer pH 6.8

A measure of 10 ml of stock solution I was taken and diluted to 200 ml with phosphate buffer pH 6.8 (100 µg/ml) (Stock solution III). 5, 10, 15, 20, 25, 30, and 35 ml were taken from Stock solution III in different 100 ml volumetric flasks and made up the volume by phosphate buffer pH 6.8; giving concentrations of 5, 10, 15, 20, 25, 30 and 35 µg/ml of Voriconazole respectively. The absorbance of each sample was measured using UV spectrophotometer at wavelength (λ max) = 255 nm, in accordance with Voriconazole monograph ***(USP37 NF32, 2014).***

2.3. Drug-excipient compatibility study

Physical mixtures of Voriconazole with various excipients namely; Eudragit RS100, Eudragit RL100, Aerosil 200, Lactose monohydrate, Povidone K30, Purified talc and Magnesium stearate in 1:1 w/w ratio were prepared by mixing together using mortar and pestle. Compatibility of Voriconazole with polymers and additives was checked by Fourier-transform Infrared Spectroscopy (FTIR) (Schimadzu, Japan) Samples with a powder of dry potassium bromide (around 200-400 mg) (as window material) in a ratio of 1:100. By using a hydrostatic press, the mixture was compressed into transparent discs under a pressure of 10 tons **.**The discs were places in the sample holder to scan from 4000 to 400 cm^{-1} ***(Range et al, 2009).***

2.4. Characterization of Voriconazole powder and its blends:

The micromeritics study (including angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio) were carried out for Voriconazole powder alone and its blend.

2.4.1. Angle of repose

The fixed funnel and free-standing cone method was adopted ***(Sharma et al, 2013).*** The tangent of the angle of repose and the mean diameter of the powder cone's base were measured, representing the coefficient of friction. Three determinations were carried out. The angle of repose expressed in degrees, using the following equation

$$\tan \theta = h / r \quad (1)$$

Where Ɵ is angle of repose, h is pile's height, and r is powder cone's radius

2.4.2. Bulk density and tapped density

The bulk density and tapped density were measured using a Tapped Volumeter (Erweka Type: SVM202, lift height 3 mm, Germany) according to ***Kukadiya et al, (2014)***. Three determinations were carried out. They expressed in g/ml and according to the following equations:

$$P\ bulk = \frac{Weight\ of\ the\ powder}{Initial\ volume} \quad (2)$$

$$P\ tap = \frac{Weight\ of\ the\ powder}{Final\ volume} \quad (3)$$

2.4.3. Carr's compressibility index

Carr's compressibility index is used for evaluating the powder flowability. This can be achieved through comparing the bulk density and the powders tapped density in addition to the rate at which it is packed down ***(Kukadiya et al, 2014)***. According to the coming formula, it's represented as a percentage % :

$$\text{Carr's index } (\%) = \frac{(Tapped\ density - bulk\ density\ \times 100)}{Tapped\ Density} \quad (4)$$

2.4.4. Hausner's ratio

The powder flowability is evaluated by Hausner's ratio. The following equation is used to calculate Hausner's ratio ***(Kukadiya et al, 2014)***.

$$\text{.Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density} \quad (5)$$

2.5. Preparation of Voriconazole SR matrix tablets

Different tablet formulations containing 400 mg Voriconazole were prepared (Table 1). Eudragits were used at three concentrations (5, 10 and 15%) of total tablet weight. The formulations were prepared using the wet granulation technique (***Tejashwini et al, 2015)***. The drug, matrix polymer (Eudragit RS100 & Eudragit RL100), diluent (lactose monohydrate), and binder (Povidone K30) were mixed together in a plastic bag till a homogenous mixture was attained. Then the mixture was granulated with purified water and sieved on a sieve of 2000 µm size. The bulk granules were dried for 15 minutes at 40°C in an oven (Heraeus UT5060E, Germany). The dried granules were milled using a sieve of 850 microns size. The glidants (Purified Talc and Colloidal silicon dioxide "Aerosil 200") and the lubricant (Magnesium stearate), were sieved on a sieve 180 µm size, and added to the dried blend & mixed for 2 minutes. The blend formulations were first tested for micrometric study as previously mentioned, then were compressed using Tablet Compression Machine, a single punch tablet machine (Korsch XP1, Germany) on an oblong punch with a diameter (20 mm) into 1200 mg tablets. The force of compression was kept constant during the whole experiment.

Table 1: Composition of Voriconazole SR matrix tablets

	Amount (mg/tablet)														
Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**
Voriconazole	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400
Povidone K30	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Purified Talc	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Colloidal Silicon dioxide	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Magnesium stearate	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14
Eud. RL100	60	120	180	---	---	---	---	---	---	---	---	---	---	---	---
Eud. RS100	---	---	---	60	120	180	---	---	---	---	---	---	---	---	---
Eud.RL100 : Eud.RS100 (1:1)	---	---	---	---	---	---	60	120	180	---	---	---	---	---	---
Eud.RL100 : Eud.RS100 (5:1)	---	---	---	---	---	---	---	---	---	60	120	180	---	---	---
Eud. RL100 : Eud.RS100 (10:1)	---	---	---	---	---	---	---	---	---	---	---	---	60	120	180
Lactose monohydrate	600	540	480	600	540	480	600	600	540	480	600	540	480	600	540
Total tablet weight	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200

2.6. Characterization of Voriconazole matrix tablets

2.6.1. Uniformity of weight

Twenty tablets were weighed individually from each formula. Then, the mean tablet weight was calculated. The results were presented as mean values. According to European pharmacopeia no more than two of the individual weights may deviate from the average weight by more than 5% (percent deviation), and none deviate by more than twice that percentage ***(EP, 2019).***

2.6.2. Uniformity of content

Ten tablets were powdered. A Quantity of the powder equivalent to 100 mg of voriconazole was weighed, then transferred to a 250 ml volumetric flask. A 150 ml of Phosphate buffer pH 6.8 was added, shacked well, then sonicated for 25-30 min. The volume was made up to 250 ml with Phosphate buffer pH 6.8. After that the dispersion was filtered, suitably diluted, and measured spectrophotometrically at 255 nm (***Tejashwini et al, 2015).***

2.6.3. Tablet friability

Ten tablets were weighed from each formulation and subjected to abrasion and shock by placing them in the friabilizer drum (Erweka type TAR200, Germany). For four minutes, the tablets were spun at 25 rpm. The tables were then taken apart, detached, de-dusted, and re-weighed precisely. The % decrease in weight was determined and used as a measure of friability ***(Kaoud et al, 2021)***.

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100 \quad (6)$$

2.6.4. Tablet hardness

Tablets should have specific hardness or strength that could withstand handling, packing, and shipping. The force required to crush the tablet by the compression applied radially is called tablet hardness. Ten tablets were tested from each formula for their hardness using a Tablet hardness tester (Erweka TBH 220TD, Germany) ***(Nasrin et al, 2011).*** The mean hardness in Kg/Cm^2 for each formula was calculated.

2.6.5. *In vitro* dissolution study

The USP basket technique was used to determine the dissolution profiles of Voriconazole in each tablet formulation in a dissolution tester (Erweka DT-700 Dissolution Tester, Germany) ***(Rangasamy et al, 2013)***. The experiments were carried out for two hours at 37 ± 0.5ºC in 900 ml of 0.1 N HCl (pH = 1.2) at 100 rpm speed. After that, the studies continued in 900 ml of phosphate buffer pH = 6.8 for twenty-two hours after successfully shifting the pH from 1.2 to 6.8 ***(Rangasamy et al, 2013).*** Five ml samples were obtained after 1, 2, 3, 4, 5, 6, 7, 8, 10, 11 12 and 24 hours. The withdrawn samples were replaced with fresh media at each time interval. The samples

were then filtered to be analyzed for Voriconazole content UV assay method; where the detection wavelength (λ_{max}) was 255 nm ***(Rangasamy et al, 2013).*** In addition, commercial tablets have been subjected to the same conditions of the study for the purpose of comparison. Formula which gave the desired control of drug release which is the release between 40-60% at 12 hours and not less than 75% at 24 hours have been chosen in order, to study its stability

2.6.6. Drug release kinetics:

The drug release data of in-vitro dissolution was analyzed with various kinetic equations in order to determine the drug release mechanism from this formulation. The data were treated according to: Zero order and first order kinetic equations, and also according to the Diffusion model. The equation's suitability is judged based on the best fit to the equation. This can be achieved by using statistical indicators such (r) value ***(Singh et al., 2011).***

2.6.7. Accelerated stability study:

Adequate samples from the formula with desired control of drug release and complied with dissolution specifications for sustained-release dosage forms were stored at temperatures of 30°C and 40°C in thermostatically controlled hot air ovens accurate to ± 2°C, and relative humidity 75% (***Tejashwini et al, 2015)***. Adequate samples of this formula, at each elevated temperature, were collected at the beginning of the experiment and at time intervals at 0.5, 1, 1.5, 2, 2.5, and 3 months and evaluated for Voriconazole content via a validated stability-indicating Reversed Phase-HPLC analytical method (Waters alliance PD, USA). Voriconazole HPLC method was conducted with UV detector (255nm). The mobile phase consisting a mixture of acetonitrile and 0.05M disodium hydrogen phosphate buffer, pH5.5 (1:1, v/v) with a flow rate of 1.0 ml per min., ambient temperature, 20µl injection volume using RP column C18 ***(Badr Eldin et al, 2010)***.

3. Results and discussion:

3.1. Calibration curve of Voriconazole using UV-spectrophotometer

In all media, 0.1 N HCl pH 1.2 and Phosphate buffer pH 6.8, linear regression analysis was carried out and results showed that Voriconazole obeys Beer-Lambert's Law. Correlation coefficient values (r) were found to be 0.99485 and 0.9999 respectively which indicate good linearity.

3.2. Drug-excipient compatibility study

Compatibility of voriconazole with the used polymers was confirmed by FTIR spectroscopy. The FT-IR spectrum of voriconazole was shown in figure (1A). Main characteristic peak showed OH stretching at 3167.76 cm^{-1}. From other main spectra, C-N stretching at 1054.28 cm−1, C=C stretching which appears at 1450.73 cm^{-1}, and C-F stretching at 1589.23 cm^{-1}. The FTIR spectrum obtained for each of the mixtures confirmed the presence of the basic peaks of voriconazole with only a minor shift or decrease in peak intensity due to relative dilution of the mixture as shown in figures

(1B-1D). This may indicate the absence of incompatibility between voriconazole and the used polymers.

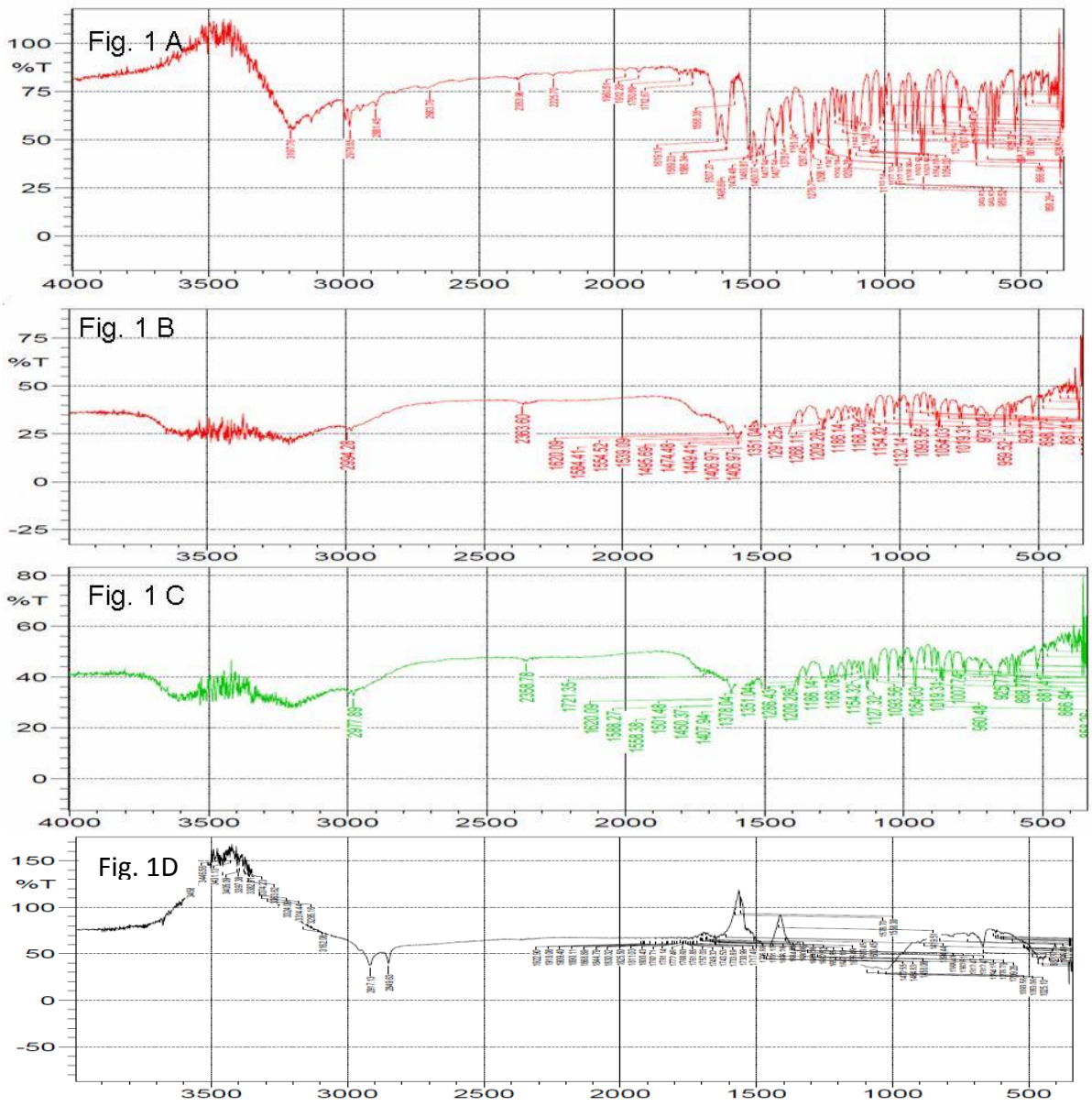

Figure (1A): FTIR spectrum of Voriconazole; (1B): FTIR spectrum of Voriconazole/Eudragit RS100; (1C): FTIR spectrum of Voriconazole/Eudragit RL100 & (1D): (I) FTIR spectrum of Voriconazole/Eudragit RS100, Eudragit RL100 &Excipients.

3.3. Micromeritics study of the Voriconazole powder and its SR matrix tablets formulae:

The micromeritics (including angle of repose, bulk density, tapped density, Carr's index and Hausner ratio) were dedicated for Voriconazole powder and bulk powder of all tablets formulae as demonstrated in Table (2). For voriconazole powder, it was found that the angle of repose was 34.56º. The bulk density was 0.32 gm/ml and the

tapped density was 0.47 gm/ml. Hausner's ratio was found to be 1.48, while Carr's index was 32.2%. These data indicate very poor flowability and compressibility properties as shown in table (3); which was the main cause of adopting wet granulation technique in all tablet formulae to improve the flowability and compressibility properties of the Voriconazole (***Shah et al, 2021***, ***Agarwal et al, 2021***)

For powder blends, the angle of repose measurements ranged from 25 to 29° which indicates very good flowability. Both the bulk and tap density of the bulk powder of the tablet formulae decrease with the increase of the percentage of the sustained release matrix polymer. However, the difference in bulk and tapped densities was relatively low when comparing with the different formulae of Eudragit RL100, Eudragit RS 100, and their mixtures in different ratio. Flowability and compressibility properties of the bulk formulae are relatively enhanced when compared with Voriconazole powder. The micromeritics results showed that the value of Carr's index and Hausner's ratio increased with increasing matrix-former polymer concentration, which was also correlated with the suitable value of angle of repose results. The results of Hausner's ratio for the tested blends revealed that all formulations had values of around 1.2, indicating little interparticle friction.

Table 2: **Micromeritics of Voriconazole powder of tablets formulae**

Formula		**Angle of repose (q)**	**Bulk density (gm/ml)**	**Tapped density (gm/ml)**	**Carr's index**	**Hausner's Ratio**
Vor Powder		34.56	0.32	0.47	32.2	1.48
Eudragit RL100	F1	26	0.492	0.562	12.47	1.143
	F2	27.75	0.471	0.561	15.98	1.19
	F3	28.75	0.451	0.549	17.83	1.217
Eudragit RS100	F4	26.1	0.496	0.566	12.34	1.141
	F5	27.42	0.478	0.568	15.73	1.187
	F6	28.32	0.459	0.549	16.37	1.196
Eudragit RL100:	F7	26.51	0.495	0.565	12.42	1.142
	F8	28.06	0.477	0.564	15.31	1.181
Eudragit RS100 (1:1)	F9	28.96	0.458	0.559	18.05	1.22
Eudragit RL100:	F10	27.03	0.494	0.564	12.44	1.142
	F11	28.28	0.476	0.563	15.33	1.181
Eudragit RS100 (5:1)	F12	29.78	0.457	0.549	16.74	1.201
Eudragit RL100:	F13	26.1	0.491	0.561	12.47	1.143
	F14	27.86	0.471	0.561	16.04	1.191
Eudragit RS100 (10:1)	F15	28.86	0.451	0.541	16.63	1.2

Table 3: **Relationship of Angle of Repose, Carr's Index & Hausner's Ratio with Flow Properties**

Flow Properties	Angle of repose	Carr's Index	Hausner's Ratio
Excellent	25-30	< 10	1 – 1.11
Good	31-35	11-15	1.12 – 1.18
Fair	36-40	16-20	1.19 – 1.25
Passable	41-45	21-25	1.26 - 1.34
Poor	46-55	26-31	1.35 - 1.45
Very poor	56-65	32-37	1.46 – 1.59
Very very poor	> 66	> 38	> 1.6

3.4. Characterization of Voriconazole SR matrix tablets:

The physiochemical characteristics of all of the produced tablets were confirmed to be in accordance with the specifications. The average percentage of Voriconazole in compressed tablets is within accepted limits (90-110%) for all formulations. The proportion of friability in all equations was less than 1%. Furthermore, hardness was greater than 13 Kg / cm^2, indicating high mechanical resistance. Also, the average tablet weight for the produced tablets was found to be uniform according to European Pharmacopeia 10.5 ***(2019)*** as shown in Table (4).

Table 4: Characterization of Voriconazole matrix tablets

Formulae	Total Weight (mg) ± SD	Hardness (Kg/Cm^2) ± SD	Friability (%) Loss± SD	Drug Content (%) ± SD
F1	1200 ± 0.72	13.8 ± 0.2	0.19 ± 0.02	98.94% ± 1.94
F2	1200 ± 0.71	14.67 ± 0.8	0.15 ± 0.01	98.76% ± 1.68
F3	1200 ± 0.65	15.94 ± 0.7	0	98.80% ± 1.75
F4	1200 ± 0.25	17.29 ± 0.55	0.13 ± 0.015	100.1% ± 1.98
F5	1200 ± 0.5	19.12 ± 0.12	0.1 ± 0.009	97.80% ± 1.27
F6	1200 ± 0.42	20.76 ± 0.22	0	100.1% ± 1.98
F7	1200 ± 0.45	16.34 ± 0.95	0.14 ± 0.008	101.65% ± 1.43
F8	1200 ± 0.35	17.34 ± 0.66	0.1 ± 0.016	96.37% ± 2.64
F9	1200 ± 0.5	17.78 ± 0.36	0	97.80% ± 1.27
F10	1200 ± 0.52	15.41 ± 0.45	0.15 ± 0.007	100.1% ± 1.98
F11	1200 ± 0.95	16.75 ± 0.6	0.12 ± 0.008	100.99% ± 3.17
F12	1200 ± 0.35	17.01 ± 0.52	0	98.49% ± 2.35
F13	1200 ± 0.51	14.12 ± 0.75	0.17 ± 0.02	102.74% ± 1.40
F14	1200 ± 0.7	15.41 ± 0.8	0.13 ± 0.01	100.81% ± 1.76
F15	1200 ± 0.63	16.7 ± 0.64	0	99.54% ± 1.46

3.5. *In vitro* dissolution results of Voriconazole matrix tablets

The drug release depends not only on the nature of matrix but also upon the polymer content. As the percentage of polymer increased, the drug release decreased (***Shah et al, 2021***). The release of Voriconazole from matrix tablets containing Eudragit (RS100, RL100 and their mixtures at different ratios) with concentrations 5, 10 and 15% was studied. The results showed that Eudragit RS100 hindered the drug release at different polymer concentrations with a maximum of 60% drug release over a 24 hours period at 5% polymer concentration. As for Eudragit RL100, it hampered the release of Voriconazole over 24 hours period at different concentrations with a maximum of 73%

release at 5% concentrations. The release profile of the formulae with the two mixed polymers has different sustained release effect using different percentage of Eudragit RS100 to RL100 as shown in figure (2) and tables (5 & 6). Formula (F13) containing of 5% Eudragit mixture of RL100: RS100 at ratio of (10:1) achieved the SR required criteria release 52% after 12 hours and 75.67% over 24 hours. On the other hand, the commercial tablet has fast release characters, as drug completely released after 15 minutes. The effect on release was found to be higher for Eudragit RS100 than RL100. However, the release profiles of the formulations containing both mixed polymers differed in their sustained-release effects, indicating a possible inter-polymer complex effect. Inter-polymer complex (IPC) is an intermolecular interaction between polymers that can change the physicochemical and physico-mechanical characteristics of the polymers ***(Jeganathan & Prakya,2015; Robertis et al, 2015; Terashima et al, 2015; Kubova et al, 2017)***. IPC can achieve this interaction through hydrogen bonding, ionic, or Van der Waals interactions. Positive or negative interactions may also occur ***(Khutoryanskaya et al, 2014)***. Several IPCs have been reported e.g between Copovidone and Carbopol ***(Zhang et al, 2017)***, between Polyox and Carbopol ***(Zhang et al, 2016)***, between polyethylene oxide and polyacrylic acid ***(Zhang et al, 2016)***, and inter polyelectrolyte complexes utilizing different polymers, for example; Eudragit L, Eudragit E, Hydroxypropylmethylcellulose, chitosan, and polyacrylic acid ***(Jeganathan & Prakya, 2015; Moustafine et al, 2012).***

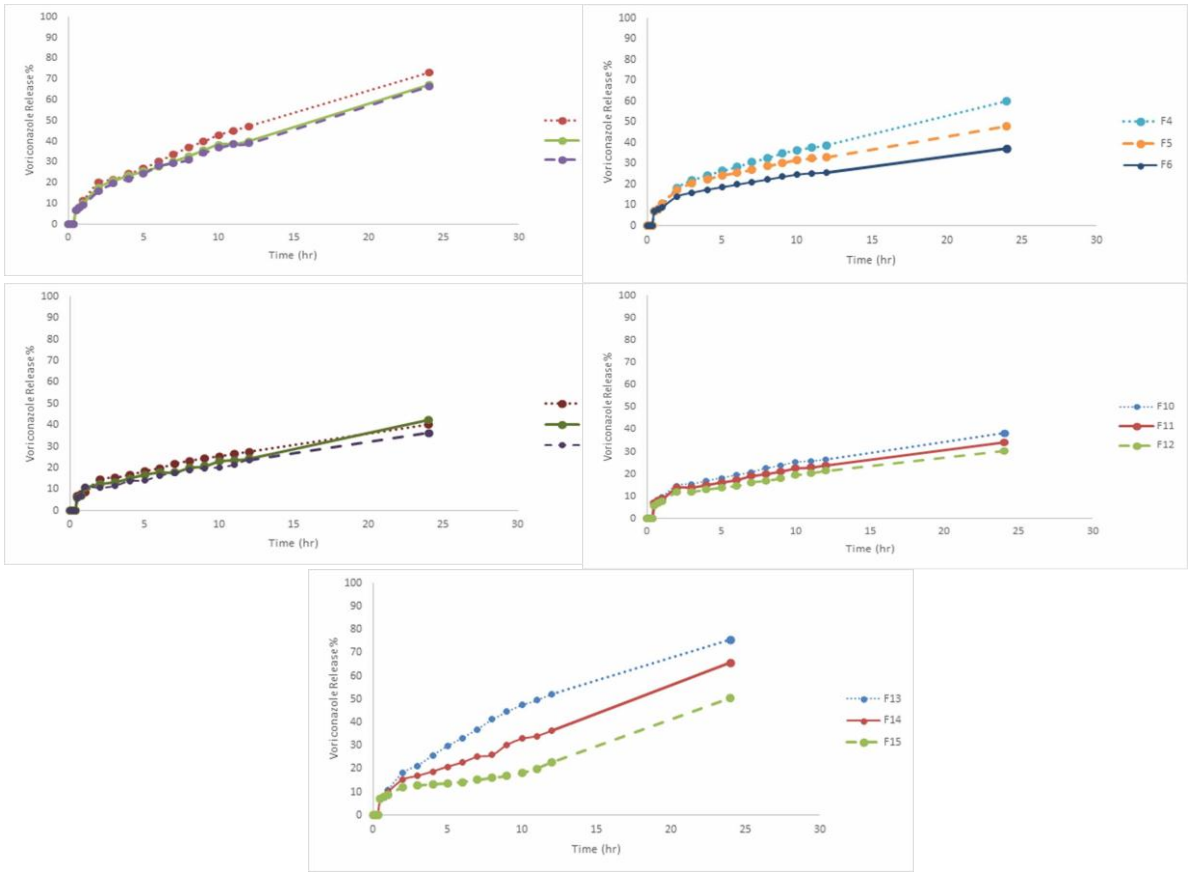

Figure (2): Dissolution Release Profiles of Voriconazole Sustained Release Tablets

Formulae

Table (5): Dissolution Results of Eud. RS 100 and RL 100 Voriconazole Matrix Tablets

Dissolution Time		% of release of Vor ±SD					
		Eudragit RL 100			Eudragit RS 100		
		F1	F2	F3	F4	F5	F6
0.1 N HCl pH = 1.2	1hr	11.55 ±0.07	10.33 ±0.21	9.52 ± 0.20	10.21 ± 0.13	10.9 ±0.21	8.9 ±0.03
	2 hrs.	20.145 ± 0.40	17.85 ± 0.19	16.07 ±0.32	18.48 ± 0.66	17.38 ±0.30	14.15 ±0.22
Phosphate buffer pH = 6.8	4 hrs.	24.32 ±0.57	23.46 ±0.29	22.12 ± 0.48	24.4 ± 0.61	22.54 ± 0.20	17.49 ±0.30
	6 hrs.	30.35 ± 0.49	27.69 ±0.24	28.2 ± 0.37	28.33 ±0.46	25.62 ±0.42	19.91 ±0.21
	8 hrs.	37.21 ± 0.38	32.87 ±0.31	31.18 ± 0.65	32.64 ±0.72	28.83 ±0.23	22.37 ±0.27
	10 hrs.	43.15 ± 0.40	38.54 ± 0.64	37.01 ± 0.31	36.52 ±0.50	31.88 ±0.35	24.83 ±0.25
	12 hrs.	47.3 ± 0.28	40.12 ± 0.84	39.05 ±0.66	38.89 ±0.57	33.2 ± 0.63	25.88 ± 0.55
	24 hr	73.07 ± 0.31	67.16 ±0.58	66.66 ± 0.45	59.92 ± 0.88	48.17 ±0.71	37.29 ± 0.33

Table (6): Dissolution Results of Eud. RS 100/ RL 100 Mixture Voriconazole Matrix Tablets

Dissolution Time		% of release of Vor ±SD								
		Eudr. RL 100 : Eudr. RS 100 (1:1)			Eudr. RL 100: Eudr. RS 100 (5:1)			Eudr. RL 100 : Eudr. RS 100 (10:1)		
		F7	F8	F9	F10	F11	F12	F13	F14	F15
0.1 N HCl pH = 1.2	1hr	8.65 ± 0.21	10.63 ± 0.04	11.15 ±0.07	9.54 ± 0.14	8.73 ± 0.31	7.86 ± 0.61	10.7 ±0.18	9.94 ±0.20	8.65 ±0.28
	2 hrs.	14.81 ±0.09	12.56 ±0.11	18.66 ± 0.51	14.84 ± 0.35	13.77 ±0.22	11.95 ±0.30	18.26 ± 0.12	15.33 ±0.25	12.23 ±0.15
Phosphate buffer pH = 6.8	4 hrs.	16.82 ± 0.25	15.23 ± 0.19	19.81 ± 0.10	16.84 ± 0.60	15.2 ±0.43	13.13 ± 0.52	25.73 ± 0.09	18.85 ±0.20	13.45 ±0.34
	6 hrs.	19.92 ±0.31	18.01 ±0.39	22.33 ± 0.20	19.48 ±0.21	17.38 ± 0.16	14.73 ±0.62	33.29 ± 0.49	22.77 ±0.55	14.36 ± 0.26
	8 hrs.	23.36 ± 0.51	20.11 ±0.54	24.71 ± 0.49	22.58 ± 0.09	20.09 ± 0.71	16.98 ± 0.63	41.28 ± 0.55	25.97 ±0.22	16.15 ±0.51
	10 hrs.	25.46 ± 0.34	23.17 ±0.25	27.13 ± 0.28	25.37 ± 0.44	22.62 ± 0.20	19.53 ± 0.60	47.56 ± 0.19	33.02 ± 0.51	18.16 ±0.16
	12 hrs.	27.6 ± 0.54	24.48 ±0.29	29.67 ± 0.42	26.52 ± 0.72	23.96 ± 0.51	21.43 ± 0.46	52.13 ±0.36	36.46 ± 0.58	22.78 ±0.91
	24 hr	40.18 ±0.62	42.54 ± 0.59	36.53 ± 0.39	38.27 ± 0.41	34.37 ±0.33	30.46 ± 0.63	75.67 ±0.55	65.76 ± 0.74	50.34 ± 0.69

3.6. Drug release kinetics

Formulations F-1 to F-15 were estimated to examine the kinetics mechanism of drug release. The release data followed zero order kinetics for formulae F2, F3, F8, F14, and F15 while formulae F1, F4, F5, F6, F7, F9, F10, F11, F12, and F13 followed Higuchi's model. For the selected formula F13 it follows the diffusion model, as the graphs exhibit the maximum linearity with r = 0.998638 as shown in table (7). Higuchi model, commonly used to predict drug release from hydrophilic matrices, was used in

this study to analyze the drug release profile (***Wadher et al, 2011; Paolino et al, 2019; Agarwal & Murthy, 2015***). The selected model of the present study is based on its widespread use and the characteristics of the sustained-release dosage form being tested

Table 7: Release kinetics of Voriconazole SR matrix tablet (F13).

Parameter	Zero	First	Diffusion
a	15.44358	1.967338	-7.05493
b	2.806603	- 0.02427	16.94841
r	0.972825	- 0.99958	**0.998638**
k	2.806603	- 0.05589	16.94841
$t_{1/2}$ (hr)	17.81513	-12.3996	8.70326

Where (a) intercept, (b) slope, (r) correlation coefficient, (k) rate constant and ($t_{1/2}$) half-life.

3.7. Accelerated stability study

Formula 13 shows the desired control drug release complied with the dissolution specifications for sustained-release dosage forms. F13 has undergone an accelerated stability study for 3 months.Chromatograms of Voriconazole and its impurities indicate that the excipients used in the formulation do not interfere with Voriconazole peak. Also, all degradant peaks are well resolved from Voriconazole peak. Figure (3) shows HPLC chromatograms of voriconazole. It was found that F13 had no significant difference in drug content after three months at the two elevated temperatures indicating its stability. The percent Voriconazole remained after storage of sustained release tablets at 30ºC and 75% RH and at 40ºC and 75% RH for three months are shown in table (5). The percent of Voriconazole decreased after storage at 30ºC and 75% RH is higher than that stored at 40ºC and 75% RH. This finding needs further studies. The degradation of Voriconazole was found to follow zero- order kinetics reaction based on the mean values of correlation coefficients (r= 0.988). The shelf life at 20^{o}C was found to be 270.58 days based on Arrhenius equation, while K_{20} was (0.0369) days^{-1}. Thus, formula F13 after accelerated stability testing was produced to be stable.

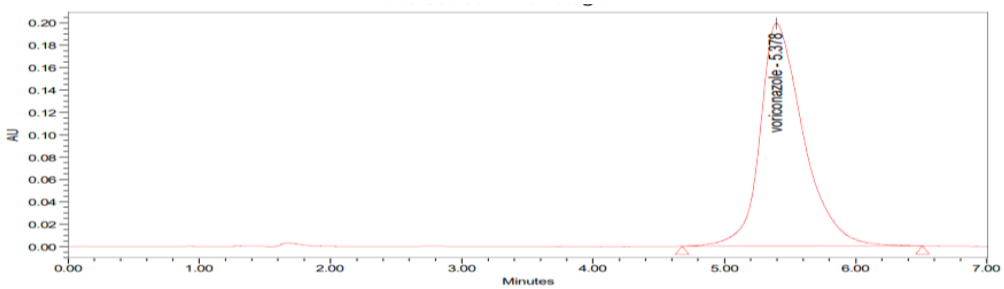

Figure 3: HPLC chromatogram of Voriconazole

Table 5: Accelerated stability testing of Voriconazole tablets stored at 30°C and 40 °C at 75% RH for three months

Time (months)	%Drug remained	
	at 30 °C	at 40 °C
0	100	98.86
0.5	99.6	99.28
1	99.2	99.4
1.5	99.18	99.35
2	98.91	98.13
2.5	98.2	97.95
3	97.31	97.29

4. Conclusion:

The present study successfully formulated sustained-release tablets of voriconazole using a wet granulation technique with the use of Eudragit RS100, Eudragit RL100, and their combination. Compatibility between voriconazole and the suggested excipients was confirmed by FTIR spectroscopy. The micromeritics of the powder blends were in compliance with the specifications as well. The in-vitro dissolution study was carried out for two hours at 37 ± 0.5ºC in 900 ml of 0.1 N HCl (pH = 1.2) at 100 rpm speed and then continued in 900 ml of phosphate buffer pH = 6.8 for twenty-two hours. F13, containing Eudragit RL100:RS100 at a ratio of (10:1), Povidone K30 as the tablet binder, Magnesium stearate as the lubricant, Purified talc and Colloidal silicon dioxide as the glidant, achieved the desired sustained release. Formula (F13) released 52% after 12 hours and 75.67% over 24 hours. The kinetic studies of F13 followed the Higuchi diffusion model. Stability studies showed that the drug content was not significantly affected by storage at 30ºC and 40ºC and RH 75±5% for 90 days. More studies and techniques are required to check the formation of IPC in the formulae with mixtures of Eudragit RL100 and Eudragit RS100.

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تحضير وتقييم صيغ طويلة المفعول لعقار الفوريكونازول

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عقار الفوريكونازول هو مضاد للفطريات من فئة الترايازول، ويتميز بفترة نصف حياة ١.٧ ساعة وبتوافر حيوي بنسبة ٩٦% عن طريق الفم. التوصيل الدوائي عن طرق الفم هو الأكثر شيوعاً في طرق توصيل الدواء، ومع ذلك، هناك بعض المشكلات للاشكال الصيدلية التقليدية، على سبيل المثال، تذبذب في مستوى الدواء في الجسم. يتغلب نظام الصيغ طويلة المفعول على هذه المشكلات؛ حيث يساعد على تقليل حدوث تذبذب في مستوى الدواء في الجسم عن طريق تقليل إطلاق الدواء وإطالة مدة الفعالية. وكان الهدف الرئيسي من هذه الدراسة هو اعداد عدة صيغ من عقارالفوريكونازول طويلة المفعول ، لتعزيز الفاعلية، وتقليل تكرار الجرعة، وتقليل الآثار الجانبية، وتحسين التزام المريض بتناول الدواء. تم تحضير صيغ مختلفة ممتدة المفعول، وتحديد وقت الانطلاق من خلال معدل الإذابة ايضا تم دراسة ثبات الأقراص. تم دراسة خواص التدفق للعقاربمفرده وتم استخدام التحليل الطيفي بالاشعة تحت الحمراء للتحقق من توافق الدواء مع المواد متعددة الجزيئات. كما تم صياغة أقراص مختلفة ممتدة المفعول باستخدام عملية تقنية التحبيب الرطب حيث تم استخدام نوعين مختلفين من إيودراجيت، وهما إيودراجيت RL100 و RS100 بمفردهما وكمزيج بنسب مختلفة وبتركيزات مختلفة. كما تم دراسة إنطلاق الدواء في المختبر لمدة ٢٤ ساعة. تم تقييم ثبات الصيغة التي حققت معدلات التحكم المطلوبة لإنطلاق الدواء حيث تم تخزينها عند درجات حرارة ٣٠ و ٤٠ درجة مئوية ورطوبة نسبية ٧٥%. وقد أظهرت النتائج للدراسات السابقة عدم وجود تفاعل بين فوريكونازول والمواد متعددة الجزيئات المستخدمة بواسطة التحليل الطيفي بالأشعة تحت الحمراء. وكانت نتائج خصائص جسيمات مزيج البودرة بعد الاضافات وفقًا لمواصفات الصيدلية المتعارف عليها. وأظهرت الأقراص إنطلاق للعقار يتراوح بين ٣٧.٢٩% و ٧٦% خلال ٢٤ ساعة باستخدام جهاز USP النوع الأول. وتبين أنه مع زيادة تركيز المواد متعددة الجزيئات ينخفض معدل إطلاق العقار من الأقراص. كما تبين أن التركيبة المختارة F13 (التي تحتوي على ٥% بوليمر بنسبة ١٠ من ايدراجيت RL100 إلى ١ من ايدراجيت RS 100) اعطت قيما مقبولة في دراسة الثبات المعجلة لمدة ٣ أشهر. وبالتالي فإن البيانات التي تم الحصول عليها تشير إلى أن الصيغة F13 قدمت قيما مقبولة في إطلاق العقار ممتد المفعول أفضل بكثير من الصيغ المحتوية على إيودراجيت RL100 أو RS100 بمفردهما.

الكلمات المفتاحية : فوريكونازول، اقراص ممتدة المفعول ، خصائص الجسيمات، ايدراجيت RL100، ايدراجيت RS 100