OPEN ACCESS
Scholars International Journal of Linguistics and Literature
Abbreviated Key Title: Sch Int J Linguist Lit
ISSN 2616-8677 (Print) |ISSN 2617-3468 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

Formulation and Evaluation of Posaconazole Bilayer Delayed Release Tablets Using Solid Dispersion Technique

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DOI: 10.36348/sijll.2022.v05i09.006 | **Received:** 10.08.2022 | **Accepted:** 13.09.2022 | **Published:** 18.09.2022

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Abstract

The aim of present investigation to formulate bilayer tablets of posaconazole by using solvent evaporation technique. Posaconazole belongs to BCS class 2 which has high permeability and low solubility. In order to enhance the solubility of posaconazole solvent evaporation technique was applied where HPMC AS was used as carrier. This tablet consist of two layers of which first layer serves as loading dose which produce immediate release of drug and second layer serves as maintenance dose that provide controlled release of drug. The whole bilayer tablet is coated with Eudragit L30D55 to produce delayed release and protect drug from acid environment in stomach. The drug excipient compatibility study was performed by FTIR and no interaction was found. Croscaramellose was used in immediate release layer as superdisintegrant. Methocel K100M and Methocel E5M are used for sustain drug release in control release layer. The powder blend for evaluated for flow properties like angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio which showed good results. Invitro dissolution studies was performed with USP dissolution apparatus 2-Paddle type. Invitro dissolution was performed for 2 hours in 0.1N HCl which showed no drug release followed by 6.8 phosphate buffer for 12 hours. The bilayer tablet showed initial release to provide loading dose of drug followed by controlled release up to 12 hours. Change in concentration of polymer and superdisintegrant showed impact on drug release profile. Increase in concentration of superdisintegrant in immediate release layer showed increased % drug release. Whereas increase in sustain release polymers in controlled release layer showed decrease % drug release. F9 batch showed satisfactory release up to 100% for 12 hours and was selected as best formulation. Reproducible batch for F9 was formulated and called F10 which also showed satisfactory results.

Keywords: Posaconazole, Bilayer tablet, Control release, Sustain release, FTIR, Dissolution and Drug release profile.

INTRODUCTION

Over 1 billion people around world gets infected with fungi every year out of which condition of 90% patients is not fatal. Fungi are opportunistic in nature they infect people with weakened immunity or patients who are immunocompramised. This include certain conditions like HIV-AIDS, organ transplantation, chemotherapy treatment to treat cancer, Autoimmune disorders like SLE, other conditions like diabetes, COVID 19 and long term treatment with medications like steroids, immunosuppressants or antibiotics [1].

Bilayer tablets technology has been used to formulate and develop control release formulations. Bilayer tablets offer biphasic drug release where release of drug can be chronologically controlled with polymers. In biphasic systems drug can be release in different rates like immediate release and controlled release. Bilayer tablets provide various advantages over conventional tablets like maximum efficacy and minimize the dosing frequency [2-4].

The basic concept of biphasic drug delivery systems is to alter the drug release. Drug is released at different rates or to different extent. This is also called as Quick/Slow release system which provides initial loading dose by burst of immediate release layer followed by maintenance dose from control release layer. This system is used to reduce dosing frequency. Main advantage of biphasic systems is it provides immediate relief followed by controlled release. It is known that many disorders like panic attacks, body pain, schizophrenia etc. require drug to be release immediately for faster relief and then drug

concentration is maintained through controlled release layer. Hence avoids repeated administration [5-7].

Bilayer tablets are used to combine two incompatible drugs for combination therapy or chronological release of single drug. Bilayer technology is often used in formulation of analgesics, antihypertensive, antimicrobial, anti-inflammatory and diabetic drugs. Introduction of bilayer technology into pharmaceutical industry lead to faster development of delivery systems with predetermined release profiles of drugs [8, 9].

Posaconazole is a triazole antifungal agent. It has broad spectrum of activity against most of Candida species, Cryptococcus neoformans, Aspergillus species, Fusarium species, Zygomycetes and certain endemic fungi. Reports support usage of Posaconazole in immunocompramised patients. It slows down the fungal growth. Posaconazole has already received US FDA approval in treatment of conditions like oropharyngeal candidiasis. Posaconazole is also used in patients who are refractory or resistant to Itraconazole and Fluconazole. Posaconazole acts by inhibiting ergosterol production in fungal cell by binding and inhibiting lanostrerol 14 α- demethylase which results in fungal cell wall disruption. Posaconazole is instable in acidic environment hence delayed release forms of posaconazole are formulated. There are only three marketed formulations of posaconazole in market they are 1) immediate release oral suspension (liquid), 2) Delayed release tablet – to prevent breakdown of drug in stomach acids, 3) Delayed release oral suspension [10-13].

Reports have been supported usage of Croscaramellose sodium as superdisintegrant in formulation of bilayer tablets [14, 15]. There are lots of reports on usage of HPMC K100M and HPMC E5M as control release polymers to formulate sustain release layers in bilayer tablets [16, 17]. Reports also supported use of Eudragit L30D55 as enteric coating polymer to coat the tablets [18].

Posaconazole belong to BCS class 2 that is posaconazole is practically insoluble in water. Drugs with low solubility usually result in poor bioavailability. Solid dispersion is an efficient way to improve drug solubility. There are various effective technique to enhance solubility like salt formation, co-solvent, formation of cyclodextrin complexes etc. formulation of drugs which are poorly water soluble with solid dispersion technique overcomes the drawbacks of other approaches [19, 20].

MATERIALS AND METHODS

Posaconazole kindly gifted by Neuheit Pharma Technologies, ALEAP Industrial Area, Gajularamaram, Hyderabad, and Telangana was used as active pharmaceutical ingredient. HPMC AS used as vehicle in Solid Dispersion Technique, Microcrystalline cellulose 302 and 102 were used as Diluents, Hydroxy propyl cellulose and Sodium Carboxy Methyl Cellulose were used as Binders. Croscaramellose sodium was used as superdisintegrant. Hypromellose K100M and E5M were used as Control Release Polymers, Magnesium stearate and Colloidal Silicon dioxide were used as Lubricant and Glidant. Eudragit L30D55 was used as enteric coting agent and Opadry II was used as colorant. All the above excipients were received as gift sample from Neuheit Pharma Technologies.

Preformulation Study

Confirmation of drug was performed by UV Spectroscopy [21, 22].

UV Spectroscopy Study – Identification of Absorption Maxima

Equipment- a Shimadzu (Kyoto, Japan) double beam spectrometer, 1800 model with 1cm Quartz cells.

Diluent- Methanol: Water- 90:10

- Absorption maxima was studied for 4µg/ml concentration and was found to be 260nm

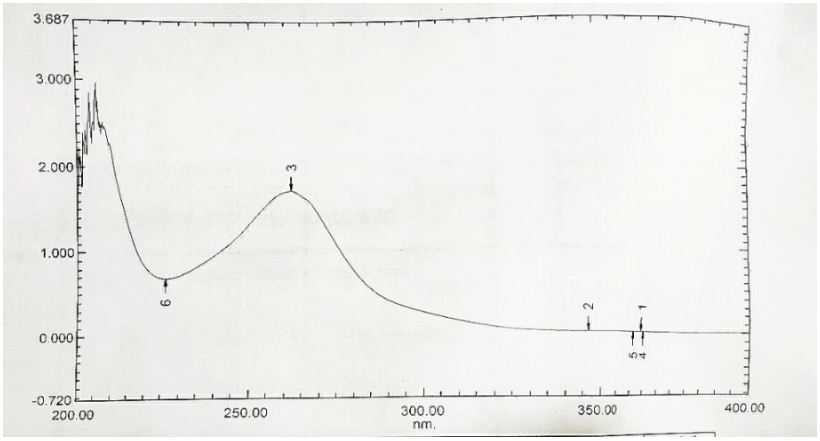


Figure 1: Absorption maxima of Posaconazole

Method

Posaconazole belongs to BCS class II. It is practically insoluble in nature. Hence HPMC AS is mixed with Posaconazole in Solid dispersion technique to improve its solubility. Daily dose of Posaconazole is 300mg per day i.e. Posaconazole DR tablets 100mg thrice a day. To improve the patient compliance Posaconazole 300mg bilayer tablet was formulated in which first layer contain 100mg of drug which serves as immediate release layer and second layer contain 200mg which serves as extended release layer. Posaconazole is pH dependent, it is destroyed in stomach. Hence bilayer tablet is coated with Eudragit L30D55 an enteric coating polymer [23-25].

Solid Dispersion Technique:

Preparation of solid dispersion for a drug is an efficient way to improve the solubility of insoluble drugs. For practically insoluble drug like posaconazole solid dispersion technique is used to enhance its solubility. HPMC Acetate succinate was used as carrier for posaconazole. Acetone and ethanol were used as solvents [26-28].

Step 1: Posaconazole and HPMC AS were dispensed in different polybags

Step 2: Acetone and ethanol were dispensed in beaker and placed under mechanical stirrer for 15 mins.

Step 3: HPMC AS was added to vortex of acetone and ethanol until it forms clear solution.

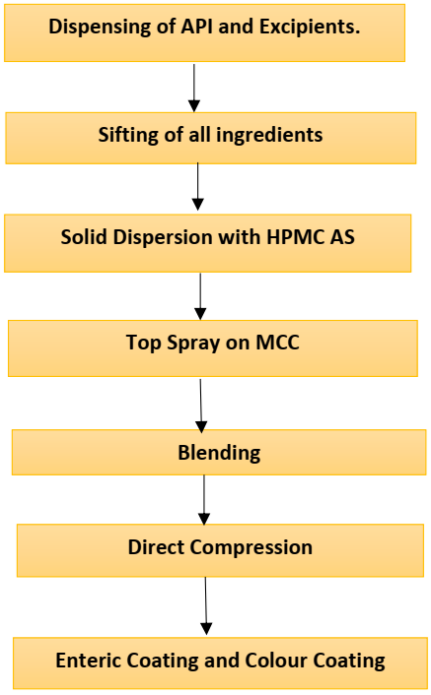
Step 4: To above solution add Posaconazole to form clear drug- polymer solution.

Manufacturing method

Steps involved in manufacturing process for Posaconazole bilayer tablets by using Solid Dispensing of API and excipients at controlled temperature and humidity conditions [29, 30].

- Solid dispersion of Posaconazole with HPMC AS
- Top spray of above dispersion on MCC
- Blending of top sprayed powder with other excipients
- Direct compression of bilayer tablet using two different punches.
- Enteric coating and Colour coating was performed.

Manufacturing flow chart



Manufacturing procedure of Immediate Release layer:

All excipients along with drug were dispensed. Solid dispersion was formed with Posaconazole, HPMC AS, ethanol and acetone. Dispersion is sprayed on Microcrystalline Cellulose 302 through Top Spray Granulation in GPCG. Sifting is performed after unloading. 40# passed Hydroxy Propyl Cellulose, Croscaramellose Sodium, Colloidal Silicon dioxide, were added to octagonal blender along with top sprayed Posaconazole- HPMC AS- MCC mixture. Blending was performed for 15 minutes at 13 RPM. The 60# passed Magnesium stearate was added to prelubricated blend. Blending was then continued for 5 minutes at 13RPM to prepare lubricated blend. Prepared IR layer blend was studied for its flow properties [31].

Manufacturing procedure of Extended Release layer:

All excipients were dispensed and solid dispersion was formed. Dispersion is sprayed on to Microcrystalline Cellulose 102 by Top Spray Granulation in GPCG. 40# passed Sodium Carboxy methyl cellulose, Colloidal silicone dioxide, 30# mesh

passed Hypromellose K100M and Hypromellose E5M were added to octagonal blender along with top sprayed drug-polymer-MCC mixture. Blending was performed for 15 minutes at 13 RPM. The Magnesium stearate which is 60# passed was added to prelubricated blend. Blending was performed for another 5 mins at 13 RPM to form lubricated blend. Flow properties of ER layer blend for all trails was studied, evaluated and tabulated in results.

Compression of Bilayer Tablet

Parle Elizabeth Tablet compression machine was used to compress Posaconazole Bilayer tablets. Compression machine was fixed with two hoppers and two feed frames. 80# passed Opadry II was blended along with First layer and loaded in first hopper whereas the maintenance dose which is second layer was loaded in second hopper. Compression was performed with oval punches with LA79 embossing. During compression weight, thickness and hardness of tablet was set and checked every 5 minutes. It was also observed that no layer separation observed in any tablets compressed. Friability test was also performed in between compression and at the end of compression.

Coating of Bilayer Tablets

After compression enteric coating was performed on bilayer tablets with Eudragit L30D55. Before enteric coating was performed tablets were cured for 30 minutes at 3-5 RPM. Then enteric coating was performed at 12-16 RPM. Tablets were kept for curing for 30 minutes after enteric coating. The final colour coating was performed with Opadry II and cured for another 30minutes. Percentage buildup of weight before and after each coating was determined. Both enteric and colour coating were performed in Mec-Well Auto Coating Pan.

Coating Parameters [37]
Inlet temperature- 55ºC
Product temperature- 40°C
Pan RPM for curing- 3-5RPM
Pan RPM for coating- 12-16RPM
Spray rate- 2.0-3.2
Atomization- 0.8
Spray pattern- 0.5

Formulation Trials

Table 1: Formulation trails of Posaconazole Bilayer DR Tablets

INGREDIENTS	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)	F7(mg)	F8(mg)	F9(mg)	F10(mg)
IR LAYER										
Posaconazole	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
HPMC AS	54.00	64.00	74.00	104.00	94.00	84.00	84.00	84.00	84.00	84.00
Acetone	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Ethanol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Microcrystalline Cellulose 302	40.00	30.00	20.00	20.00	20.00	30.00	20.00	30.00	20.00	20.00
Hydroxy Propyl Cellulose	30.00	30.00	30.00	15.00	25.00	25.00	25.00	20.00	25.00	25.00
Croscaramellose sodium	20.00	20.00	20.00	5.00	5.00	5.00	15.00	10.00	15.00	15.00
Colloidal silicon dioxide	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Magnesium Stearate	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
IR layer weight	250.00	250.00	250.00	250.00	250.00	250.00	250.00	250.00	250.00	250.00
ER LAYER										
Posaconazole	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00
HPMC AS	94.00	84.00	140.00	114.00	120.00	100.00	100.00	104.00	104.00	104.00
Acetone	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Ethanol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Sodium carboxy methyl cellulose	110.00	90.00	90.00	90.00	84.00	100.00	104.00	105.00	100.00	100.00
Hypromellose K100M	225.00	265.00	245.00	235.00	235.00	239.00	235.00	230.00	235.00	235.00
Hypromellose E5M	48.00	38.00	38.00	38.00	38.00	38.00	38.00	38.00	38.00	38.00
Microcrystalline cellulose 102	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Colloidal silicon dioxide	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00
Magnesium Stearate	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
ER layer weight	792.00	792.00	792.00	792.00	792.00	792.00	792.00	792.00	792.00	792.00
Coat materials										
Eudragit L30D55	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Opadry II	33.00	33.00	33.00	33.00	33.00	33.00	33.00	33.00	33.00	33.00
Coating weight	133.00	133.00	133.00	133.00	133.00	133.00	133.00	133.00	133.00	133.00
Total weight of Bilayer Tablet	1175.00	1175.00	1175.00	1175.00	1175.00	1175.00	1175.00	1175.00	1175.00	1175.00

- 10^{th} batch showed same results as 9^{th} batch.
- Total weight of tablet is maintained constant in all trails.

Characterization of powder

Lubricated blend was subjected to pharmacotechnical characterization before compression. They were evaluated for Angle of Repose, Bulk density, Tapped density, Carr's index and Hausner's ratio [32-34].

Bulk Density:

Bulk density of blend was determined by taking 20gm of powder into 100ml graduated cylinder. Initial volume in cylinder was recorded.

$$\text{Bulk Density} = \frac{\text{Weight of sample in grams}}{\text{Bulk volume}}$$

Tapped Density:

Tapped density is measured with Electro Lab Density tester. Here Graduated cylinder is mounted on tapping device. Initial volume of powder was recorded. Tapping continued until there was no further reduction in volume. Then final volume was recorded and tapped density wad calculated.

$$\text{Tapped Density} = \frac{\text{Weight of sample in grams}}{\text{Tapped volume}}$$

Carr's Index

It indicates the compressibility of powder. Depends on Bulk density and tapped density

$$\text{Carr's index} = \frac{\text{Tapped density- Bulk density}}{\text{Tapped density}} * 100$$

Hausner's Ratio

It indicates the flowability of powders. It depends on both Bulk density and Tapped density.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of Repose

Angle of repose is determined by Fixed Funnel method.

$$\text{Ø} = \tan^{-1} h/r$$

Where,
h= height of pile
r = radius of pile

Evaluation of Bilayer tablets

The prepared bilayer tablets were evaluated for properties like hardness, thickness, friability and drug content. In- Vitro dissolution study was also performed [38-43].

- **Weight Variation Test**:

Here 10 tablets were weighed individually using Electronic Pan Balance. The average weight of 10 tablets was calculated. The uniformity of weight was evaluated by specifications mentioned in IP.

- **Thickness**

Twenty tablets were randomly selected from each formulation and for every tablet thickness is determined individually. Thickness was determined with Vernier Calipers.

$$\text{MSR+VSR} * \text{LC}$$

MSR= Maim Scale Reading, VSR= Vernier Scale Reading, LC= Least Count

- **Hardness**

Hardness of tablet is determined by crushing the tablets in diametric direction with Labindia hardness tester. Hardness was determined for 10 tablets.

- **Friability**

Roche friabilator was used to determine friability of tablets. Initially ten tablets were taken and weighed. Ten tablets were dropped in friabilator which is rotated at 25 RPM for 4 mins. Tablets were dedusted and weighed.

$$\% \text{ Friability} = W_1 - W_2 / W_1 * 100$$

W_1= Initial weight of tablets

W_2= Final weight of tablets

Drug content

Instrument- High Performance Liquid Chromatography equipped with PDA/ UV- detector and data handling system.

Five tablets were crushed to make fine powder in motor with pestle. Powder equivalent to 500mg of posaconazole was weighed and transferred to 250ml volumetric flask to this add 190ml diluent and sonicate for 30mins with intermediate shaking. Then make up the volume with diluent and centrifuge the above solution for 5 minutes at 5000 RPM. 5ml of liquid was taken into 100ml volumetric flask and diluent was added and solution was filtered through 0.45µm. Blank, Standard and sample were injected separately into chromatographic system and analyzed.

In-Vitro Dissolution Study

Bilayer tablets were studied for Invitro drug release to determine their ability to provide desired controlled drug release in simulated gastric fluid and intestinal fluids. Drug release was studied in simulated

gastric fluid as gastric emptying time is about 2 hours then dissolution medium is replaced with 6.8pH buffer and drug release is determined upto 12 hours.

Apparatus- USP type II apparatus, Paddle type

Instrument- High Performance liquid Chromatography equipped with PDA/UV detector and data handling system.

Table 2: Dissolution parameters

Acid Stage
Medium – 0.1N HCl Volume- 750ml Type- USP type II paddle apparatus RPM – 75RPM Bath temperature – 37.5^{o}C Bowl temperature – 37.0^{o}C Time points- 2 hours
Buffer stage
Medium- pH 6.8 buffer Volume- 1000ml Type- USP apparatus II, paddle type RPM- 75RPM Bath temperature- 37.5^{O}C Bowl temperature- 37.0^{O}C Time points- 1hr, 2hr, 4hr, 6hr, 8hr, 10hr and 12hr.

750ml of preheated 0.01N HCl was transferred into each dissolution vessel. One tablet was transferred into each dissolution vessel. After 1 hour and 2hours time intervals 10ml of sample was withdrawn from each dissolution vessel and aliquots of sample was replaced. 0.1N HCl was replaced with preheated 6.8 pH buffer. At specific time points 10ml of sample was withdrawn for analysis up to 12 hours while maintaining sink conditions.

RESULTS AND DISCUSSION

Posaconazole bilayer tablets were formulated with immediate release for loading dose and controlled release layer for maintenance dose. Bilayer tablet is coated with enteric polymer to protect drug in gastric environment. Total 10 batches were designed with varying concentrations of superdisintegrant and control release polymers. Before compression lubricated blend was evaluated for pharmacotechnical characterization.

Standard Graph of Posaconazole in HPLC

Table-3: Linearity of Posaconazole in HPLC

Concentration (µg/ml)	Sample ID	Peak Area
0.1024	Standard 1	504260
0.2048	Standard 2	1310063
0.4096	Standard 3	2411319
0.5120	Standard 4	2950435
1.0243	Standard 5	6525062

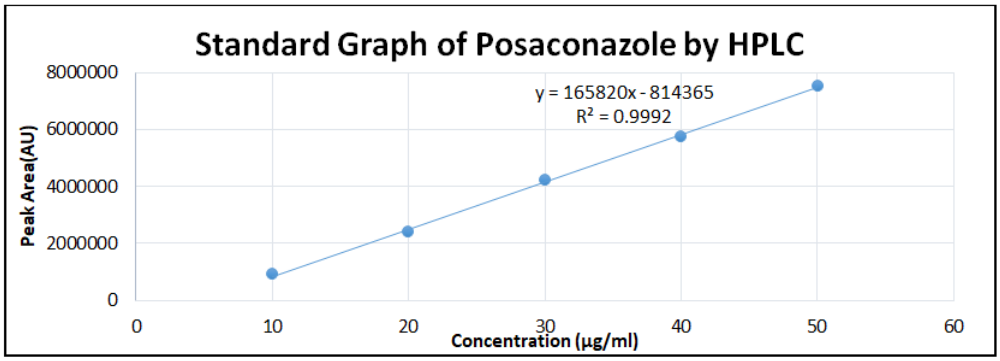


Fig-2: Posaconazole standard graph in HPLC

FTIR GRAPHS

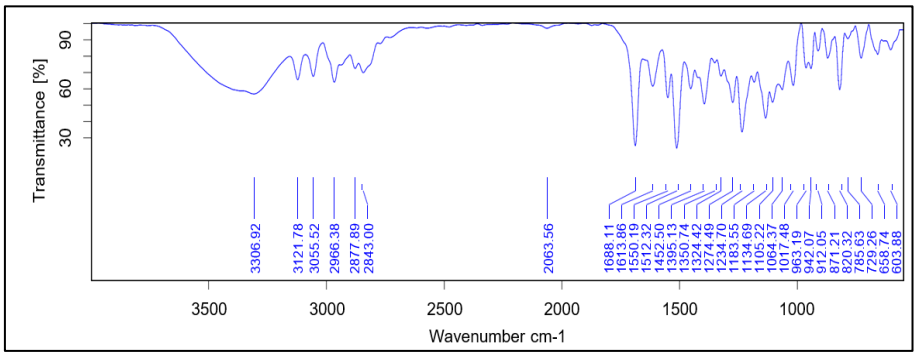


Fig-3: FTIR of Posaconazole Drug

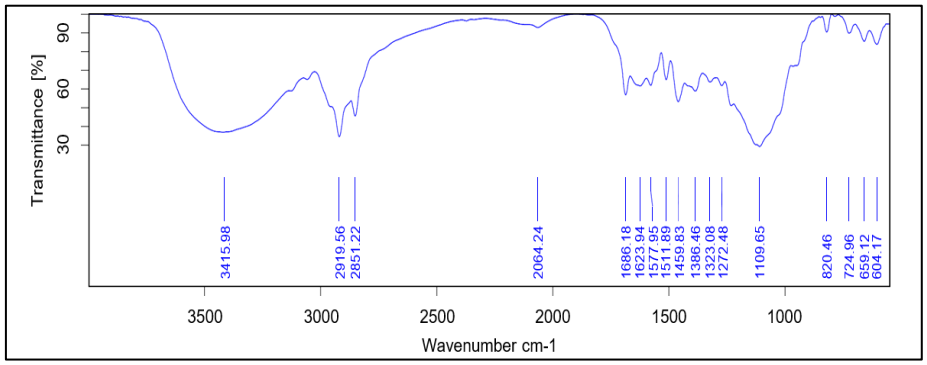


Fig-4: FTIR of Posaconazole Formulation

Table 4: Interpretation of FTIR Spectrum of Drug and Formulation

Functional Group	Posaconazole Drug Wave Number cm $^{-1}$	Posaconazole DR Bilayer Tablet formulation wave number $^{-1}$
OH	3306.92	3315.98
C-H alkyl	2916.38	2919.56
C=O	1688.11	1686.18
N=N & C-N triazole	1452.50	1459.83
C-H aromatic	1274.49	1272.48
C-O-C aromatic	1234.70	1232.53
C-H Benzene & Triazole	820.32	820.46

Table 5: Precompression Flow Properties of IR layer and ER layer

Formulation	Angle of Repose	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index	Hausner's Ratio	Flow property
Posaconazole API	47.42±0.03	0.32	0.43	25.58	1.35	Poor
IR (F1)	40.08±0.01	0.34	0.47	27.65	1.38	Poor
IR (F2)	41.36±0.04	0.29	0.37	21.62	1.27	Passable
IR (F3)	37.82±0.02	0.31	0.41	24.39	1.32	Passable
IR (F4)	36.13±0.01	0.30	0.41	26.82	1.36	Poor
IR (F5)	23.30±0.03	0.35	0.44	20.45	1.25	Fair
IR (F6)	31.56±0.04	0.43	0.52	17.30	1.20	Fair
IR (F7)	38.93±0.02	0.33	0.41	19.50	1.24	Good
IR (F8)	27.04±0.05	0.35	0.41	14.61	1.17	Good
IR (F9)	26.03±0.03	0.31	0.35	11.42	1.12	Excellent
IR (F10)	26.43±0.02	0.32	0.35	8.57	1.09	Excellent
ER (F1)	44.24±0.01	0.31	0.45	31.11	1.43	Poor
ER (F2)	36.84±0.01	0.35	0.42	16.67	1.20	Fair
ER (F3)	36.39±0.04	0.36	0.44	18.18	1.22	Fair
ER (F4)	32.70±0.02	0.34	0.40	15.00	1.17	Good
ER (F5)	37.29±0.04	0.37	0.46	19.56	1.24	Fair
ER (F6)	36.51±0.01	0.37	0.45	17.77	1.21	Fair
ER (F7)	31.11±0.05	0.33	0.37	10.81	1.12	Good
ER (F8)	28.33±0.03	0.34	0.39	12.82	1.14	Good
ER (F9)	27.42±0.02	0.32	0.35	8.57	1.09	Excellent
ER (F10)	26.89±0.01	0.36	0.39	7.64	1.08	Excellent

Pure drug has poor flow properties. Solid dispersion technique not only improved solubility of posaconazole but also improved the flow properties of drug.

Table 6: Post Compression Parameters of Posaconazole Bilayer tablets

Batch No.	Weight variation (mg)	Thickness (mm)	Hardness (kp)	Friability (%)	Drug Content (%)
F1	1178 ± 3.6	8.03 ± 0.04	33.3 ± 4.2	0.51 ± 0.08	96.8 ± 0.42
F2	1180 ± 3.0	8.04 ± 0.02	33.3 ± 2.5	0.32 ± 0.02	92.5 ± 0.23
F3	1177 ± 4.7	8.02 ± 0.01	33.3 ± 2.1	0.29 ± 0.02	97.8 ± 0.26
F4	1174 ± 4.5	8.07 ± 0.03	38.0 ± 4.4	0.23 ± 0.06	95.2 ± 0.33
F5	1172 ± 3.0	8.08 ± 0.01	37.3 ± 2.1	0.22 ± 0.03	103.2 ± 0.10
F6	1174 ± 4.5	8.04 ± 0.01	33.7 ± 2.1	0.21 ± 0.02	102.0 ± 0.71
F7	1173 ± 2.0	8.08 ± 0.02	36.7 ± 3.1	0.22 ± 0.01	96.5 ± 0.81
F8	1174 ± 3.5	8.06 ± 0.03	34.0 ± 3.0	0.21 ± 0.13	96.9 ± 0.71
F9	1173 ± 4.0	8.04 ± 0.01	40.3 ± 0.6	0.23 ± 0.13	100.2 ± 0.81
F10	1174 ± 3.6	8.05 ± 0.04	40.0 ± 3.0	0.29 ± 0.03	99.8 ± 0.73

Post Compression parameters of Posaconazole Bilayer DR Tablets like weight variation, thickness, hardness, friability and drug content were represented in table 6.

The hardness of all formulations varied between 30-40kp.

Friability of all formulations ranged between 0.20% w/w to 0.52% w/w.

The drug content of all formulations varied between 97%- 102%

Bilayer DR Tablets of Posaconazole were subjected to In-Vitro drug release studies in simulated gastric fluid for 2 hours followed by pH 6.8 buffer for 12 hours to study their ability to provide preferred drug delivery.

Tablets were dropped into 0.1N HCl dissolution study was performed for 2 hours 0.1N HCl was completely replaced with 6.8pH buffer and dissolution study was performed for 12 hours. As tablets were coated with Eudragit enteric polymer none of tablets showed drug release in 0.1N HCl. Drug release started only in 6.8 pH phosphate buffer.

F1 and F2 formulations showed complete release of 95.5 and 99.2 upto 8 hours, F3 showed complete release of 99.5 of upto 10 hours.

F4- F10 showed complete release of at 98-102 within 12 hours.

F9 was found to be best batch and F 10 formulation is reproducible batch of F9 batch. All results of F10 batch matches F9 batch.

Drug release profile of all formulations is represented in Table 7.

Table 7: % Drug Release of Posaconazole Bilayer DR tablet in 0.1N HCl followed by 6.8 pH buffer

TIME IN HOURS	F1 (%Drug Release)	F2 (%Drug Release)	F3 (%Drug Release)	F4 (%Drug Release)	F5 (%Drug Release)	F6 (%Drug Release)	F7 (%Drug Release)	F8 (%Drug Release)	F9 (%Drug Release)	F10 (%Drug Release)
1	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0
3	19.8	18.5	25.5	11.5	14.9	12.9	28.9	28.5	35.5	31.8
4	45.5	39.9	38.9	25.9	24.5	20.8	38.5	45.9	48.9	45.5
6	69.8	68.5	55.8	50.5	48.2	35.5	58.5	70.9	65.8	61.8
8	87.4	88.5	79.9	62.8	65.8	62.9	80.9	85.5	86.9	85.9
10	95.5	99.2	88.5	75.6	72.9	75.9	89.2	89.6	92.8	93.8
12	-	-	99.5	89.6	88.2	85.9	95.2	90.2	96.5	96.2
14	-	-	-	100.5	98.9	98.6	101.2	98.9	100.9	100.8

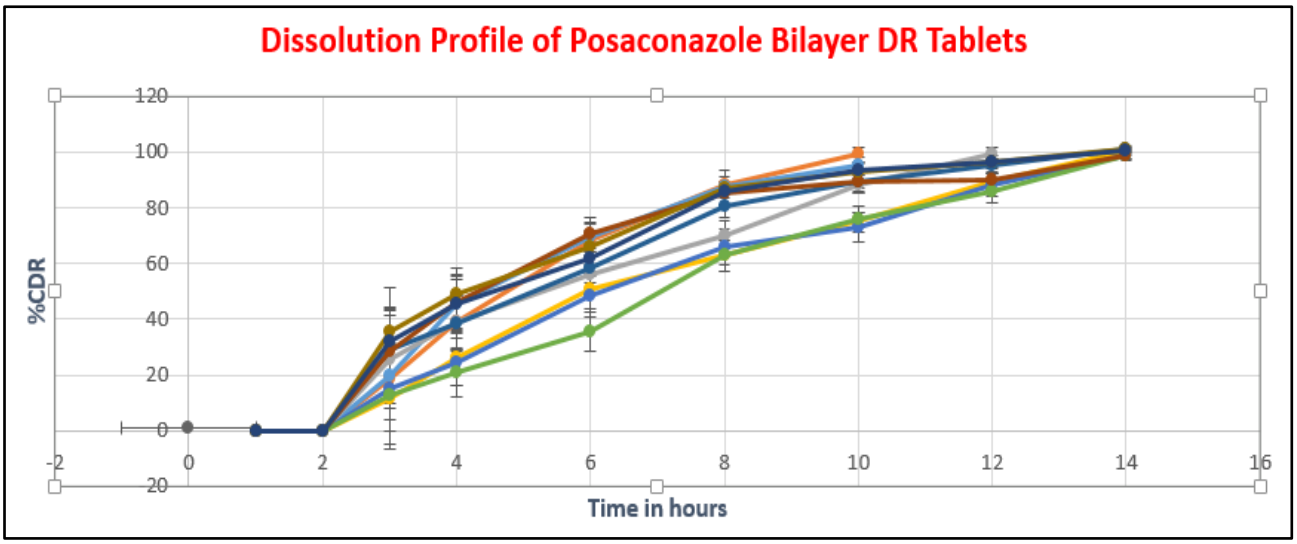


Figure 4: Dissolution profile of Posaconazole Bilayer DR tablets

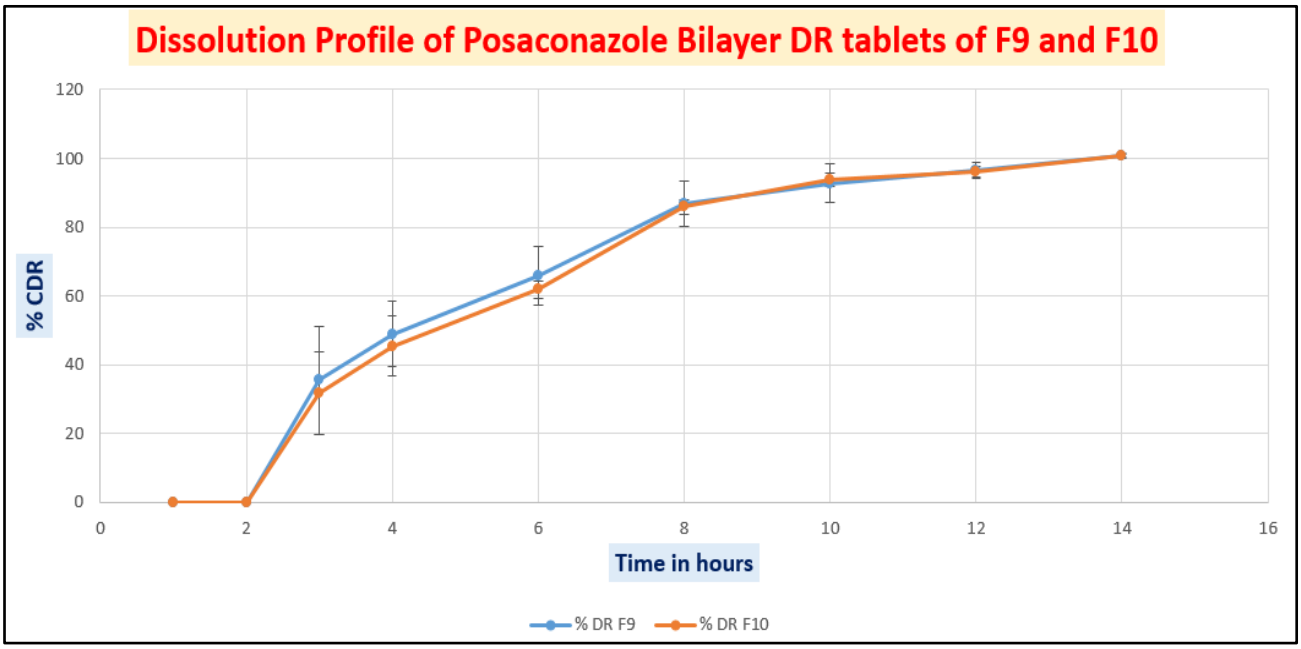


Figure 5: Dissolution Profile of Posaconazole Bilayer DR Tablets of F9, F10 formulations

Release kinetic Data Analysis of Posaconazole Bilayer DR tablets

Table 8: Release kinetics of Posaconazole Drug

Time in hours	%CDR	Log %CDR	% Cumulative Drug Remaining	Log Cumulative % Drug Remaining	Square root of Time	Log t	Cube root Of CDR	W0-Wt
2	0	0	100.9	2.003891	1.414	0.301029996	4.66008142	0
3	33.5	1.52504481	67.4	1.828660	1.732	0.477121255	4.27812944	0.38195198
4	45.9	1.66181269	55	1.740363	2	0.602059991	4.09561312	0.56466842
6	65.8	1.81822589	35.1	1.545307	2.449	0.778151256	3.77275690	0.88732452
8	8.09	1.90794852	20	1.301030	2.828	0.903089987	3.37079953	1.28928189
10	91.8	1.96284268	9.1	0.959041	3..162	1	2.80203933	1.85804209
12	97.5	1.98900462	3.4	0.531479	3.464	1.079181246	1.81712059	2.84296083
14	100.9	2.00389117	0	0	3.742	1.146128036	0	4.66008142

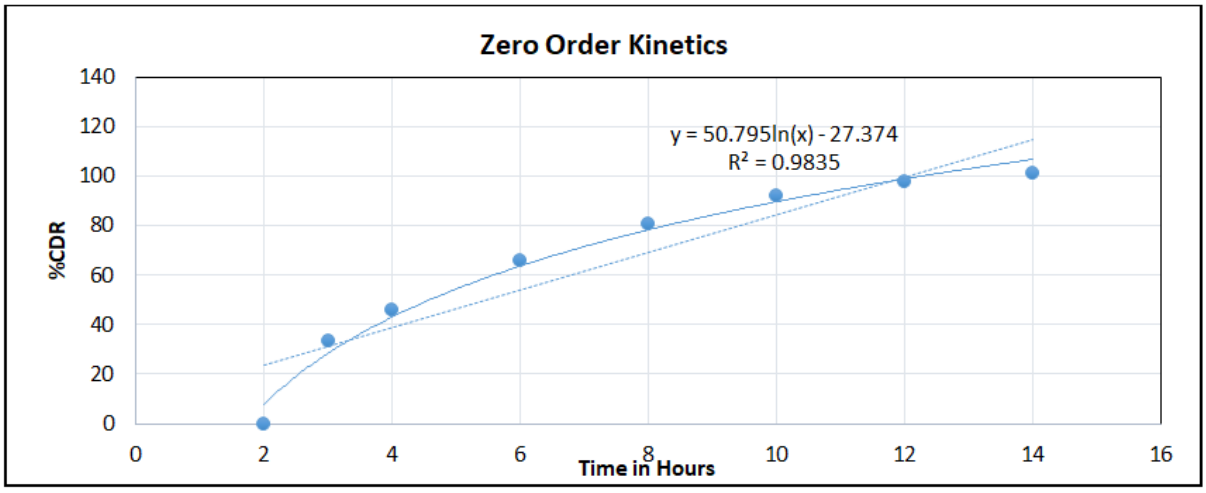


Fig-6: Zero Order Release Kinetics Graph

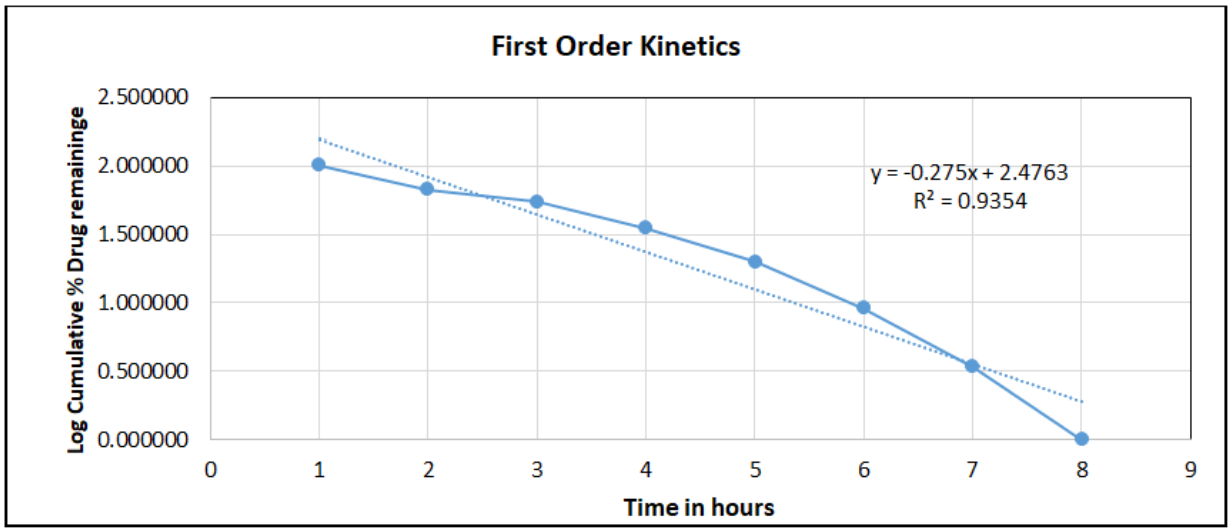


Fig 7: First Order Release Kinetics Graph

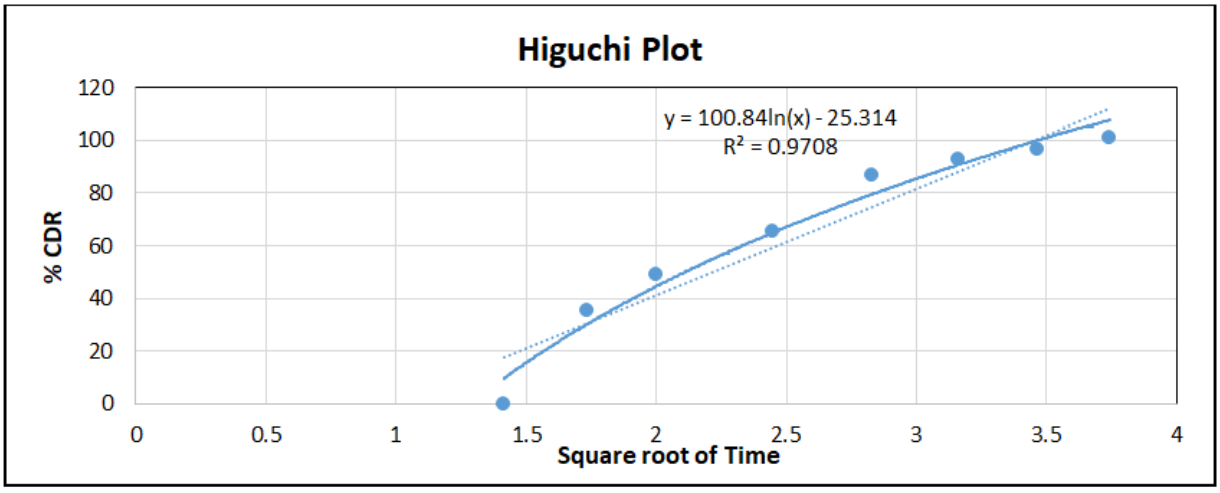


Fig 8: Higuchi Plot

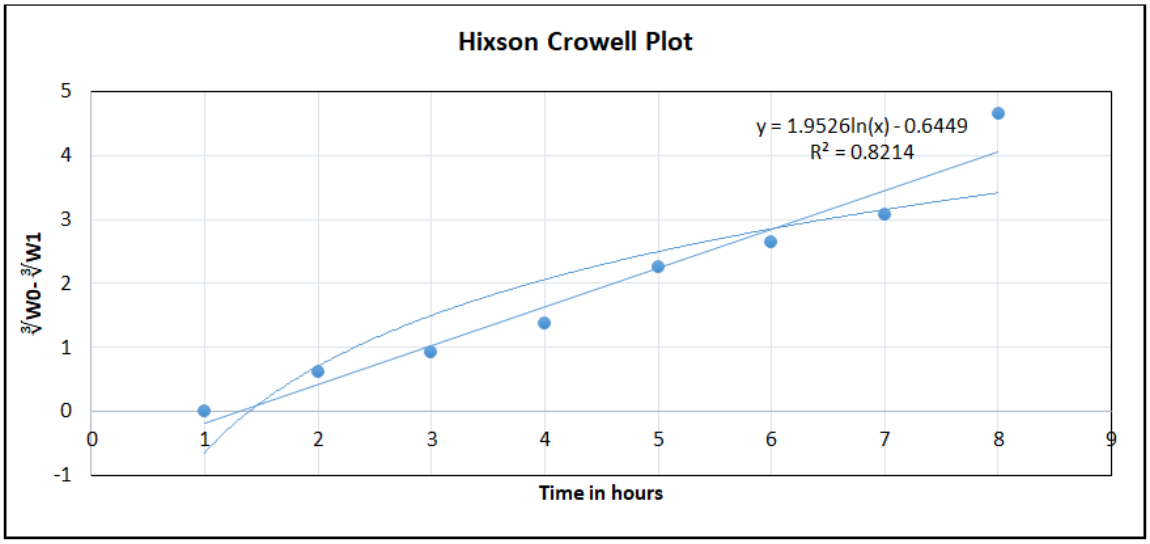


Fig 9: Hixson Crowell Plot

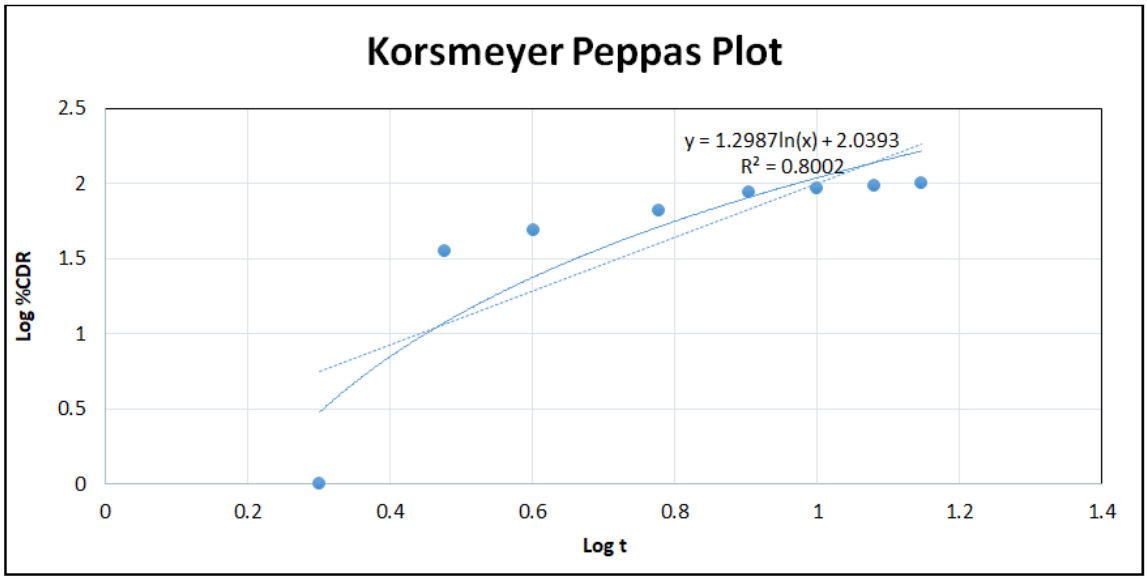


Fig 10: Korsmeyer Peppas Plot

Table-9: Results of Kinetic Studies for Optimized Formulation F-9

S. No	Formulation	Zero order R^2	First Order R^2	Higuchi R^2	Hixson Crowell R^2	Korsmeyer Peppas R^2	n value
1	9	0.9835	0.9354	0.9708	0.8214	0.8002	0.624

Mechanism: Zero Order, Non Fickian Diffusion.

CONCLUSION

The present research work was carried out to develop Posaconazole Bilayer DR tablets by Solid Dispersion technique using HPMC AS. Here immediate release layer was prepared by direct compression method using Croscaramellose sodium as superdisintegrant which produced immediate drug release. Extended release layer was prepared using direct compression method by using combination of Hypromellose K100M and E5M as controlled release polymers. Pharmacotechnical studies shows Pure API has poor flow properties but upon formulation flow properties were improved. Concentration of superdisintegrant and control release polymers influenced the drug release. Increase in concentration of superdisintegrant showed increase % drug release and increase in concentration of control release polymer resulted in decrease % drug release. Bilayer tablet stayed intact with no drug release in 0.1N HCl and provided initial drug release to provide loading dose of drug, which is followed by controlled release upto 12 hours in 6.8 pH buffer. F9 and F10 batches were chosen as best formulation. Results of In vitro drug release was applied in various mathematical model and evaluated by correlation coefficient R^2. From above results drawn,

it was found that system follows Zero Order kinetics with Non Fickian Diffusion. Above study concluded that Posaconazole Bilayer DR Tablets achieved the objective of research work to treat invasive fungal infections. Posaconazole DR Tablets dosage frequency is thrice a day and Dosage Frequency was also reduced to one time.

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