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FORMULATION AND EVALUATION OF POSACONAZOLE-LOADED NANOPARTICLES FOR TOPICAL DRUG DELIVERY SYSTEM

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ABSTRACT

Nanostructured drug delivery systems offer significant advantages in improving the efficacy of therapeutics by enhancing drug solubility, controlling release, and reducing required doses. The nanoparticles were formulated under 9 different concentrations by emulsification method. From that best formulated nanoparticles F4 will be selected for the nanogel formulation based on the invitro dissolution studies. This study explores the development of posaconazole-loaded nanoparticles (PNPs) incorporated into a nanogel formulation, utilizing TPGS as a permeation enhancer for enhanced antifungal activity. Posaconazole nanoparticles were prepared using an electrostatic stabilization method and characterized for size (70.89–144.5 nm), zeta potential (-26.9 to 1.86), and polydispersity index (PDI 0.284–0.700). The nanoparticles exhibited improved solubility and dissolution rate compared to the pure drug, which showed limited release (41.5% in 0.1 N HCl). The nanoparticle formulations demonstrated a controlled, biphasic drug release profile, with an initial burst phase followed by sustained release, indicating diffusion and degradation-based mechanisms. DSC and FTIR analysis revealed that posaconazole was molecularly dispersed in an amorphous form within the nanoparticles, ensuring no significant interactions with excipients. The nanoparticles were further incorporated into a nanogel formulation with Carbopol 940 as a polymer matrix, showing uniform spreadability,

controlled diffusion, and no irritation upon testing. The formulation showed excellent biocompatibility and enhanced antifungal activity. These results suggest that the nanoparticle-based delivery system significantly improves the solubility, stability, and controlled release of posaconazole, offering a promising solution for the treatment of chronic fungal infections. This study highlights the potential of nanotechnology in overcoming the limitations of poorly soluble drugs, particularly BCS class-II drugs.

KEYWORDS: Posaconazole, Nanoparticle, *in-vitro* evaluation, hydrogel, poor soluble drug.

INTRODUCTION

Nanoparticles are one of the forms of novel drug delivery systems having the capability to release the drug at an optimum rate at the desired site of action. Nano formulations provide the liberty to use a wide range of polymers like synthetic, natural, bio degradable and non-biodegradable polymers. The size range of the nanoparticles is 1 to 1000 nm, but nanoparticles in the range of 50 – 500 nm are acceptable depending on the route of administration.

A skin conveyance framework we can characterized as the substance which conveys a particular kind of medication into contact with and through the skin. The test to skin drug conveyance is the vehicle across the skin boundary. Effective conveyance incorporates two essential sorts of item: External sort of effective that are spread, splashed, or in any case scattered on to cutaneous tissues to cover the influenced zone. Internal kind of effective that are applied to the mucous layer orally, vaginally or on anorectic tissues for nearby action.

Fungal infection is also known as mycosis. This is disease caused by fungi. Types of fungi classified according to the part of the body affected i.e., superficial, subcutaneous and systemic. In 500BC, an apparent account of ulcers in the mouth by Hippocrates may have been thrush. The Hungarian microscopist based in Paris David Grubby first reported that human disease could be caused by fungi in the early 1840s. During the 2003 SARS outbreak, 14.8–33% of people affected by SARS, and it were the cause of death in 25–73.7% of people.

Fungi are everywhere, but only some cause disease fungal infection occurs fungi either breathed in, come into contact with skin or enter the body through the cut, wound or injection on skin. It is more likely to occur in people having weak immune system. This includes people having illnesses like HIV/AIDS, and people with cancer treatments.

Posaconazole is an antifungal medication used to prevent and treat fungal infections, particularly in immunocompromised patients (e.g., those undergoing chemotherapy, stem cell transplants, or with HIV/AIDS). It belongs to the class of triazole antifungals and works by inhibiting fungal ergosterol biosynthesis, an essential component of fungal cell membranes. This action disrupts the integrity of the cell membrane, leading to the death of the fungus.

MATERIALS AND METHODS

Active Pharmaceutical Ingredients (API): Posaconazole-Sisco Research Laboratories, Maharashtra.

Excipients: Glyceryl monostearate-**SVP Chemicals,** oleic acid, TPGS-**HIMEDIA, Mumbai,** Carbopol 940, Triethanolamine-**LOBA Chemie, Maharashtra,** Castor oil- **Fisher scientific, Mumbai,** Tween 80-**Richell international,** Distilled water-**LEO Scientific, Erode.**

PRE-FORMULATION STUDIES

Pre-formulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of pre-formulation testing is to generate information useful to the formulator in developing stable dosage forms, which can be mass-produced.

Organoleptic properties

The sample of posaconazole was studied for organoleptic characters such as colour, Odor and appearance.

Determination of solubility

Solubility of posaconazole pure drug was tested in distilled water and phosphate buffer pH 7.4, ethanol, DMF. An excess amount of posaconazole pure drug was added in 20 ml of the pertinent media. The mixtures were stirred in a mechanical shaker.

Melting point determination

Melting point of the drug sample (Posaconazole) was determined using capillary tube method. Small amount of powdered drug was filled inside the thin capillary tube and sealed from one side by melting. The capillary was placed into the melting point apparatus. Thermometer was also placed in the apparatus which was already immersed into the liquid paraffin in the apparatus. After some time at specific temperature drug was melted, that was the melting

point of the drug.

Determination of absorption maximum (λ max)

To determine the wavelength of maximum absorption (λ max), Posaconazole 1mg/ml was prepared in ethanol, then 0.15ml was made up to 10ml using phosphate buffer pH7.4 and scanned in UV wavelength range of 200-400nm utilizing phosphate buffer pH7.4 as a blank. The absorption maxima obtained in the graph was considered as λmax for the pure drug solution.

Calibration Curve of Posaconazole

Preparation of Posaconazole calibration curve

Stock-1 solution

10mg of Posaconazole was weighed accurately and transferred in 100ml volumetric flask and dissolved in 10ml of ethanol and the volume is made up to the mark with pH 7.4 phosphate buffer (1000µg/ml).

Stock-2solution

1ml from the stock-1 solution was pipette out and diluted to 10ml with pH 7.4 phosphate buffer (100µg/ml). From this solution 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5 and 4.0 ml were pipette out and diluted to 10 ml using pH 7.4 phosphate buffers to get aliquots of 5, 10, 15, 20, 25, 30, 35 and 40 µg/ml respectively pH7.4 phosphate buffer was used as blank solution. Three sets of standard solutions were prepared to repeat the standard graph. The absorbance was measured at 262 nm using UV-Visible Spectrophotometer.47 The obtained data was plotted by taking concentration on X-axis and average absorbance (n=3) on Y-axis.

Drug-Excipients Compatibility study

Compatibility of the drug with the excipients is determined by subjecting the physical mixture of drug and the excipients of the main formulation to infrared absorption spectral analysis (FT-IR). Any change in chemical composition of the drug after combining it with the excipients was investigated with IR spectral analysis.

PROCEDURE

Weighed amount of drug (Posaconazole) and excipients (GMS and Tween 80) were mixed with IR grade KBr (1:10) and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned by IR spectrophotometer over a range of

4000cm-1 to 500cm-1 range.40

Formulation of Solid lipid nanoparticles

Emulsification technique is the method used to prepare solid lipid nanoparticles (SLNs). The lipid phase containing (GMS or Oleic acid) was heated to 60 ℃ above their melting points (GMS - 500C and Oleic acid – 160C). Then 1% w/w Posaconazole was dissolved with 5ml of ethanol and then added with the lipid matrix to obtain a drug-lipid mixture. While the aqueous phase was obtained by dissolving the surfactant (Tween 80) in deionized water and heated up to the temperature of the melted lipid phase 600C. Afterwards, the melted lipid phase was poured into the warm aqueous phase slowly and was stirred at 2000 rpm for 4hr using Magnetic stirrer. Posaconazole loaded SLNs were obtained by allowing the hot nano emulsions to cool gradually to room temperature, forming solid lipid nanoparticles.38

COMPOSITION OF POSACONAZOLE

Formulation of posaconazole nanoparticle (F1 - F8) formulations.

S. No	Batch Code	Posacona zole (mg)	Glyceryl Monostea rate (mg)	Oleic Acid (ml)	Castor Oil (ml)	Tween 80 (ml)	Distilled Water(ml)
1	F1	100	1.5	-	1.5	0.5	25
2	F2	100	1.5	-	1.5	1	25
3	F3	100	3	-	1.5	0.5	25
4	F4	100	3	-	1.5	1	25
5	F5	100	-	1.5	1.5	0.5	25
6	F6	100	-	1.5	1.5	1	25
7	F7	100	-	3	1.5	0.5	25
8	F8	100	-	3	1.5	1	25

FORMULATION OF DRY NANOPARTICLES

The prepared posaconazole nanoparticles were freeze dried to increase the shelf life of the nanoparticle and to study the dissolution behaviour. 1% mannitol solution was added to each formulation as a cryoprotectant at the time of lyophilization. Vertis freeze drier was used for lyophilization of nanoparticles. At first the sample was kept overnight in a deep freezer at -70 °C and then sample was kept in Vertis freeze drier for two days at -50 °C at 2 millitorr.

EVALUATION OF NANOPARTICLES

Particle size analysis and polydispersity index

The average particle size and size distribution are important parameters because they influence the physicochemical properties and biological fate of the NPs. The particle size

must be in the range of 10nm - 100nm. Polydispersity index is a parameter to define the particle size distribution of nanoparticles obtained. It is a dimensionless number extrapolated from the autocorrelation function and ranges from a value of 0.01 for mono dispersed particles and up to values of 0.5-0.7 for broad particle size distribution. The prepared nanoparticles sample was collected and 1 ml of the sample was diluted with 10 ml of double distilled water. Then, the sample was transferred to cuvette and kept inside the instrument. Then, the laser scattering light was passed through cuvette tube and the particle size and size distribution was analysed by using Horiba Scientific (Nanoparticle) - SZ100.34 From each formulation particle size was measured 3 times and the mean and standard deviation was carried out (n=3).

Zeta-potential determination

The surface charge (zeta potential) was determined by measuring the electrophoretic mobility of the nanoparticles. It is a useful parameter to predict the physical stability of colloidal systems. 1 ml of the prepared solid lipid nanoparticles sample was diluted with 10 ml of Double Distilled water. Then, the samples were transferred into the cuvette which contains electrodes and kept inside the instrument. Then, the laser scattering light was passed through cuvette tube and analysed the zetapotential using Horiba Scientific (NanoPartica –SZ100).38 The procedure is repeated 3 times and the mean and standard deviation was carried out (n=3).

Drug content

1ml of the dispersed nanoparticles sample was dissolved in 5 ml of acetone by sonication and volume was made up to 100ml using phosphate buffer pH 7.4. From this solution 1.5 ml was diluted with phosphate buffer pH 7.4 solution in a 10ml volumetric flask to get the concentration in the standard graph range and the drug content was estimated by using UV-Spectrophotometry at 262 nm.

Drug entrapment Efficacy

The Entrapment efficiency was determined by measuring the concentration of the drug in the supernatant after centrifugation. The unentrapped Posaconazole (PCZ) was determined by adding 2 ml of PCZ loaded nanoparticles to 0.5 ml of ethanol into centrifuge tubes. This dispersion was centrifuged at 6000rpm for 30 mins at 250C. The supernatant was diluted with phosphate buffer pH 7.4 and measured spectrophotometrically at 262 nm. The entrapment efficiency was calculated using the following equation.47 The procedure is repeated 3 times and the mean and standard deviation was carried out (n=3).

$$Percentage\ Entrapment\ Efficiency\ (\%EE) = \frac{W_{Total} - W_{Free}}{W_{Total}} \times 100$$

Saturation solubility studies

The saturation solubility studies were carried out for both the posaconazole and posaconazole nanoparticle formulations. 10 mg of posaconazole and posaconazole nanoparticle formulations equivalent to 10 mg of posaconazole were weighed and separately introduced into25 ml of stoppered conical flask containing 10 ml of distilled water. The flasks were sealed and placed in a rotary shaker for 24 hours at 37 °C. The samples were collected after the specified time interval and it was filtered and analysed using UV spectrophotometer at 262 nm.

Fourier Transform Infra-Red Spectroscopy analysis

The Fourier transform infra-red analysis was performed for the analysis of lyophilized nanoparticle interaction and stability of drug during the formulation process. The FT-IR spectra of formulated nanoparticles were recorded using FT-IR spectrophotometer (Shimadzu 8400 S, Japan). About 2-3 mg samples were mixed with dried potassium bromide of equal weight and compressed to form a KBr pellets. The pellets were placed in the light path scanned over a frequency range 4000-400 cm- 1 and the spectrum was obtained.

***In-vitro* drug release studies**

The *in-vitro* drug release of PCZ nanoparticle was studied by using dialysis bag method in phosphate buffer pH 7.4. The PS nanoparticle (equivalent to 10 mg of drug) was taken in dialysis bag having (molecular cut off between 12000 to 14000 and pore size 2.4 nm) dialysis membrane was soaked in the distilled water for 24 Hr. PCZ sample was added into the dialysis bag and both end of the bag was tied and placed in 100 ml of dissolution medium (glass rod was used to immerse the dialysis bag to avoid the floating of the bag) which was continuously stirred at 100rpm at 37^0C using magnetic stirrer. Definite aliquots of dissolution medium pH 7.4 phosphate buffers were withdrawn at every 2hr of time interval and the same volume of fresh dissolution medium was added to maintain a sink condition. The samples were analyzed spectrophotometrically at 262 nm.

***In-vitro* drug release kinetic behaviour**

There are number of kinetic models, which describe the overall release of drug from the dosage forms. Model dependent methods like zero order, first order, Higuchi and Korsmeyar peppas

were studied to elucidate the release rate and its mechanics. The results of *in-vitro* release release profile obtained for all the formulations were plotted in modes of data treatment as follows:

1. Zero order kinetic model – Cumulative percentage drug release vs. Time
2. First order kinetic model – Log cumulative percentage drug remaining vs. Time
3. Higuchi's model – Cumulative percentage drug release vs. square root of time
4. Korsmeyer peppas model – Log cumulative percentage drug release vs. Log time

1) Zero order kinetic model

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation,

$$Q = K_0 t$$

Where,

Q = fraction of drug release at time 't'

K0 = Zero order release rate constant

A plot of fraction of drug released against time will be linear, if the release obeys zero order release kinetics.

2) First order kinetic model

The first order equation describes the release from system where release rate is concentration dependent. The first order kinetic can be expressed by the following equation,

$$\ln(1 - Q) = -K_1 t$$

Where,

SSQ = fraction of drug released at time't'

K1 = first order release rate constant

A plot of logarithm of the fraction of drug remained against time will be linear if the release obeys first order kinetics.

3) Higuchi kinetic model

Higuchi proposed the first example of kinetic model aimed to describe drug release from a matrix system. The simplified Higuchi equation is as follows,

$$Q = K_2 t 1/2$$

Where,

K2 = release rate constant

A plot of fraction of drug released against square root of time will be linear thereby, the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on Fick's law, square root of time dependent.

4) Korsmeyer equation/Peppa's kinetic model

To study the mechanism of drug release date fitted to the well-known exponential equation (Korsmeyer equation/Peppa's equation), which is often used to describe the drug release behaviour from polymeric systems.

$$M_t/M_a = K_t n$$

Where,

Mt/Ma = the fraction of drug released at time 't'

K = constant incorporating the structural and geometrical characteristics of the drug/polymer system. n = diffusion exponent related to the mechanism of the release.

Selection of best formulation

To be select the best formulation with high bioavailability based on characterization of nanoparticle such as particle size and poly-dispersity index, zeta potential, percentage drug content, percentage encapsulation efficiency, saturation solubility, fourier transform-infrared spectroscopy, scanning electron microscopy, differential scanning calorimetry, *in-vitro* drug release and its release kinetic profile.

Surface morphology

Microphotograph were taken on different magnification was used for surface morphology done by scanning electron microscopy. The scanning electron microscopy of posaconazole nanoparticle was carried out to confirm the nano-sized formulation with their morphological structure. The sample was lightly sprinkled on a double side adhesive tape stuck to an aluminium stub and the stubs were coated with platinum of thickness to about 10 A° under an argon atmosphere using gold sputter module in a high vaccum evaporator. The stubs containing the coated samples were placed in scanning electron microscopy chamber and analyze the surface morphology.

FORMULATION OF POSACONAZOLE NANOPARTICLE INCORPORATED TPGS STABILIZED CARBOPAL NANOGEL.

Ingredients	Gel I	Gel II	Gel III
Posaconazole	100 mg	-	-
Posaconazole nanoparticle	-	100 mg	100 mg
Carbopol 940	1 gm	1 gm	1 gm
TPGS	-	-	1 gm
Water	100 ml	100 ml	100 ml
Triethanolamine	q.s	q.s	q.s

CHARACTERIZATION OF GEL PREPARATIONS

The posaconazole incorporated gel and posaconazole loaded nanoparticle incorporated carbopol gels were subjected to physical appearance, pH measurement, homogeneity, spreadability, swelling index, rheological measurements and *in-vitro* drug diffusion study.

Physical appearance

The prepared nanogel formulations were inspected for clarity, color and transparency. The prepared nanogel will be evaluated for the presence of any particles. Smears of gels will be prepared on glass slides and observed under the microscope for the presence of any particles or grittiness.

pH measurements

The pH measurement was carried out by using calibrated digital type pH meter by dipping the glass electrode and the reference electrode completely into the gel system.

Homogeneity

The prepared nanogel was tested for homogeneity by visual inspection after the gels have been store in the container. Nanogel was test for their appearance and presence of any aggregates.

Spreadability

A sample of 0.5 gm of nanogel formulation was pressed between two slides (divided into square of 5 mm slides) and left for 5 minutes. Spread circles were measured in cm and it taken as comparative values for spreadability.

Swelling index of nanogel

Swelling of the polymer depends on the concentration of the gel polymer, ionic strength and

the presence of water. The swelling index was measured prepared nanogel taken 1 gm on porous aluminium foil and then placed separately in a 50 ml of beaker containing 10 ml of 0.1N NaOH. The samples were removed from the beaker at different time intervals and put it on dry place for some times after it reweighed. The swelling index was calculated as follows,

$$Swelling\ index(SW)\% = \frac{w_t - w_o}{w_0} \times 100$$

Where,

Wt = Weight of swollen gel after time t, W0 = Original weight of gel at zero time.

Rheological measurements

The rheological measurements were performed on Brookfield Rheometer. All measurements were carried out in room temperature. The rheological properties of formulated nanogel were studied at various shear rates (rpm) and the viscosity measure in cP.

***In-vitro* diffusion (or) skin permeation studies**

The *in-vitro* diffusion studies for posaconazole nanogel were performed in phosphate buffer 7.4 pH for 2 hours in nitrocellulose as a dialysis membrane in franz-diffusion cell. Accurately weigh the samples from the prepared nanogel was added to a dialysis membrane and immersed into the dissolution medium (phosphate buffer 7.4 pH) and the temperature was maintained at 37.0 ºC. The dissolution medium fluid agitated at 50 rpm. Withdraw the 5 ml of dissolution medium in every one hour and withdrawal volume was replaced with equal quantity of fluid so as to maintain constant volume. After suitable dilution, the sample was analyzed in UV spectrophotometrically at 262 nm.

RESULT AND DISCUSSION

Posaconazole is BCS Class – II drug with low aqueous solubility and has high permeability. Thus, it was challenging to enhance the solubility and dissolution rate of posaconazole particles in an aqueous solution. Emulsification techniques were employed to produce posaconazole loaded nanoparticles formulation.

PREFORMULATION STUDIES

Characterization of drug

The sample of posaconazole was evaluated by physical characters and by determining the melting point. The Ultra-violet (UV) absorption spectra and FT-IR spectra of pure

posaconazole were recorded, which was compare and matched with reference spectra.

Physical observation

Physical observation of posaconazole was appeared in powder form in a light-yellow colour. The description of the substance is appropriate to the specifications informed by the manufacturer.

Melting point determination

The melting point of the posaconazole was determined by capillary method. The melting point was found to be 171 °C. which complies with the literature47. Thus, indicating the purity of the drug sample.

ULTRA-VIOLET ABSORPTION SPECTRA

The posaconazole was analyzed by spectrophotometrically in between 400nm to 200nm. The maximum absorbance (λ max) was found for posaconazole at 262 nm which was used for quantitative analysis. From the below figure.15 and figure.16, it was observed that the posaconazole UV spectrum was mentioned in 0.1 N HCl and phosphate buffer.

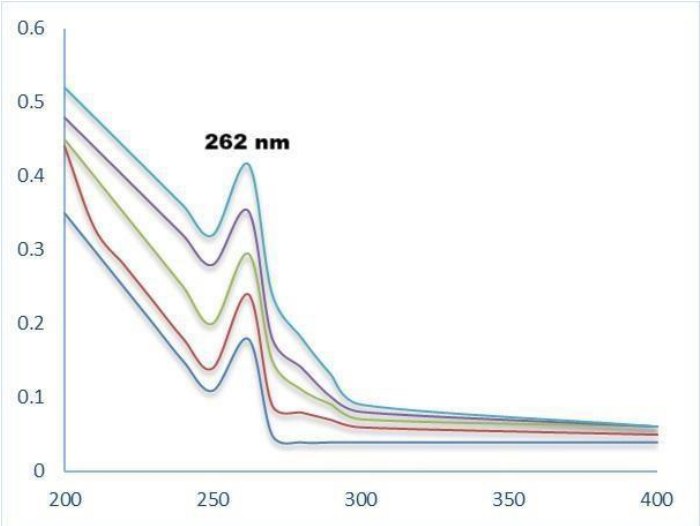


Figure 15: UV Spectrum of Posaconazole in 0.1 N HCl (pH 1.2).

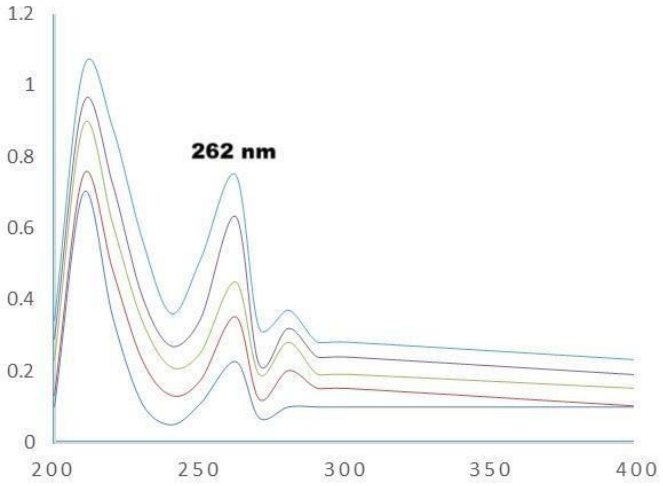


Figure 16: UV Spectrum of Posaconazole in phosphate buffer pH 7.4.

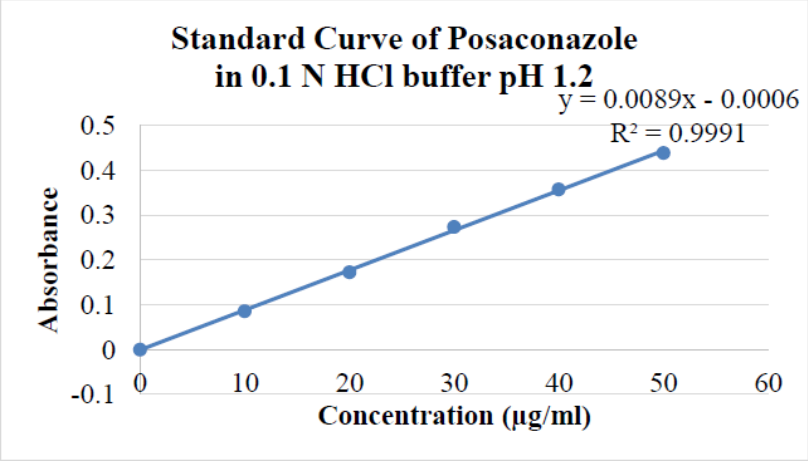
PREPARATION OF POSACONAZOLE STANDARD CURVE

Standard curve of posaconazole in 0.1 N HCl buffer (pH 1.2)

Standard curve was prepared by using various concentration of posaconazole vs absorbance at 262 nm. The standard curve was found linear at different concentration at the range in 10 to 50 µg/ml from the below data (Table 6, Figure 17) it was observed that the drug obeys beer's law in concentration range of 10 to 50 µg/ml in 0.1N HCl buffer (pH 1.2). The slope value is 0.0089, the correlation co-efficient is 0.9991 it follows fit curve since r2 is below 1.

Table 6: Standard curve of posaconazole in 0.1 N HCl (pH 1.2).

Concentration (µg/ml)	Absorbance (Mean±SD)
10	0.086
20	0.173
30	0.274
40	0.358
50	0.439



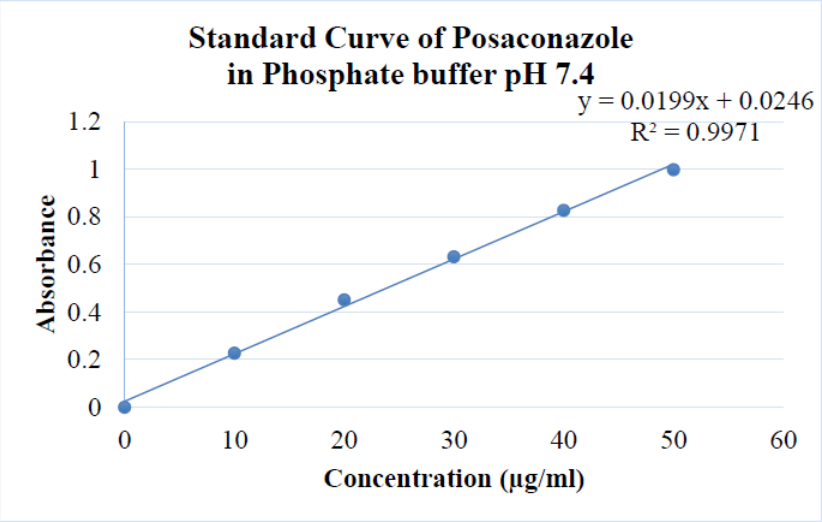
Regression coefficient (r2) = 0.9991, Slope (y) = 0.0089.

Standard curve of posaconazole in phosphate buffer (pH 7.4)

Standard curve was prepared by using various concentration of posaconazole vs absorbance at 262nm. The standard curve was found linear at different concentration at the range in 10 to 50 µg/ml from the below data (Table 7, Figure 18) it was observed that the drug obeys beer's law in concentration range of 10 to 50 µg/ml in phosphate buffer (pH 7.4). The slope value is 0.0199, the correlation co-efficient is 0.9971 it follows fit curve since r2 is below 1.

Table 7: Standard curve of posaconazole in phosphate buffer (pH 7.4).

Concentration (µg/ml)	Absorbance (Mean±SD)
10	0.277
20	0.451
30	0.632
40	0.827
50	0.998



Regression coefficient (r2) = 0.9971, Slope (y) = 0.0199.

DRUG – POLYMER COMPATIBILITY STUDY

The FT-IR spectroscopy was used to study the possible interaction between pure posaconazole, glyceryl monostearate, preformulation mixture PF1, PF2, carbopol 940 and TPGS. The characteristic peaks for posaconazole can be observed at a wave numbers showed the presence of ~3357.84 cm-1, ~3382.91 cm-1 (Alcohol, Phenol O-H stretching vibrations), ~2937.38 to ~2893.02 (Alkane C-H stretching vibrations), ~2937.38 cm-1, ~2893.02 cm-1 (Amine N-H Stretching vibrations),~1697.24 cm-1 (α, β, unsaturated aldehyde, ketones C=O stretching vibrations), ~1649.02cm-1 (1° Amine N-H Bend vibrations), ~1417.58 cm-1 (Aromatic C-C Stretching vibrations), ~1336.58 cm-1 to 1043.42

cm-1(Flouro Compound C-F Stretching vibrations), ~1315.36 cm-1 to 1043.42 cm-1 (Alcohol, carboxylic acid, ester, ether C-O Stretching vibrations) and ~887.19 cm-1 to 746.40 cm-1 (Aromatic C-H Stretching).

The posaconazole similar peaks were seen in physical mixture of posaconazole and polymers. There was no discrimible shift/disappearance/appearance of peaks in combined spectra that indicates good drug-polymer compatibility and no chemical interaction between posaconazole and polymers. Hence, the selected polymers were found suitable for development of the nanoparticle formulation. The values are represented in table.8 and table.9.

Table 8: Interpretation of IR spectrum of Posaconazole, Glyceryl Monostearate (GMS), Carbopol 940 and TPGS.

Transition with IR Range (cm^{-1})	Absorption wave number (cm^{-1})			
	Posaconazole	GMS	Carbopol 940	TPGS
O-H Stretching Alcohols, phenols 3500 - 3200	3357.84, 3382.91	3442.70 – 3398.34	3469.70 – 3373.27	3485.49 – 3396.76
O-H Stretching Carboxylic acid 3300 - 2500	-	3031.89 - 2848.67	3126.40 – 2661.58	3130.57- 2507.54
C-H Stretching Aromatic 3100 - 3000	-	3031.89	3089.75 – 3002.96	3097.78, 3078.49
C-H Stretching Alkanes 3000 - 2850	2937.38, 2893.02	2866.02	2962.46	2924.18 – 2870.17
N – H Stretching Amine salt 2800 - 3000	2937.38, 2893.02	2933.53- 2848.67	2962.46	2870.17- 2924.18
C=O Stretching α, β, unsaturated aldehydes, Ketones 1710 - 1665	1697.24	1701.10, 1670.24	1695.31	1701.27, 1685.84
N-H Bend 1° amines 650 - 1580	1649.02	1622.02	1635.52- 1604.66	1626.05
C-C Stretching Aromatic 1500 - 1400	1417.58	1465.80, 1438.80	1446.51 – 1409.87	1460.16
C – F Stretching Flouro Compound 1400 - 1000	1336.58 – 1043.42	1379.01- 1022.20	1259.43- 1163.00	1348.29- 1111.03
C-O Stretching Alcohol, carboxylic acid, ester, ether 1320 - 1000	1315.36 – 1043.42	1315.36- 1022.20	1259.43 – 1163.00	1282.71 – 1111.03
C-H Stretching Aromatic 900 - 675	887.19 – 746.40	885.27- 738.69	891.05 – 773.40	881.50- 680.89

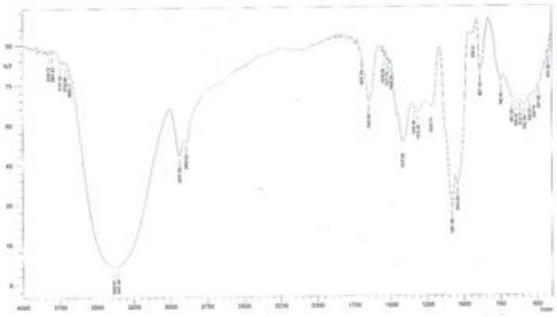


Figure 12: FTIR Spectrum of Posaconazole.

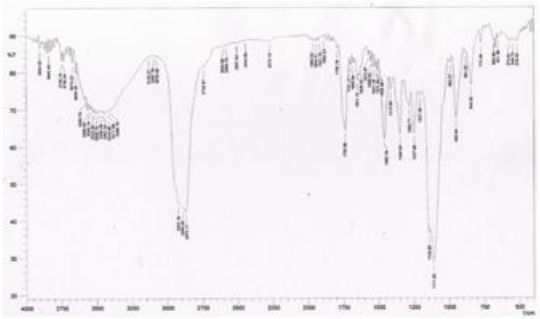


Figure 12: FT-IR spectrum of TPGS.

Figure 12: FTIR Spectrum of Carbopol 940.

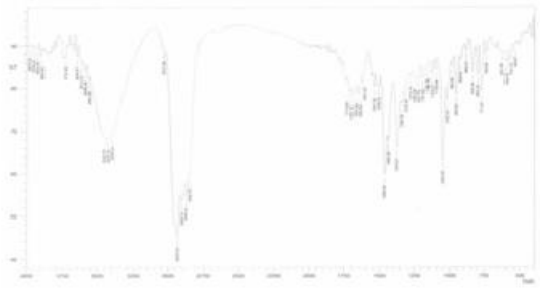


Figure 12: FTIR Spectrum of Glyceryl Monostearate (GMS).

Table 7: Interpretation of IR spectrum of Posaconazole, physical mixture-I and physical mixture-II.

Transition with IR Range (cm-1)	Absorption wave number (cm-1)		
	Posaconazole	Physical mixture-I	sical mixture- II
O-H Stretching Alcohols, phenols 3500 -3200	3357.84, 3382.91	3288.40 – 3217.04	3278.76
O-H Stretching Carboxylic acid 3300 - 2500	-	3288.40 – 2626.87	3278.76 – 2515.00
C-H Stretching Aromatic 3100 - 3000	-	3058.89 – 3033.82	3056.96 – 3033.82
C-H Stretching Alkanes 3000 - 2850	2937.38, 2893.02	2968.24 – 2921.96	2977.89 – 2918.10
N – H Stretching Amine salt 2800 - 3000	2937.38, 2893.02	2833.24-2968.24	2977.89-2831.31
C=O Stretching α, β, unsaturated aldehydes, Ketones 1710 - 1665	1697.24	1697.24	1697.24
N-H Bend 1° amines 1650 - 1580	1649.02	1635.52, 1605.74	1633.69, 1602.74
C-C Stretching Aromatic 1500 - 1400	1417.58	1494.73 – 1419.51	1498.59-1421.44
C – F Stretching Flouro Compound 1400 - 1000	1336.58 – 1043.42	1390.58-1012.56	1390.56-1012.58
C-O Stretching Alcohol, carboxylic acid, ester, ether 1320 - 1000	1315.36 – 1043.42	1313.43 – 1012.56	1313.43-1012.58
C-H Stretching Aromatic 900 - 675	887.19 – 746.40	889.12 – 729.04	889.12-729.08

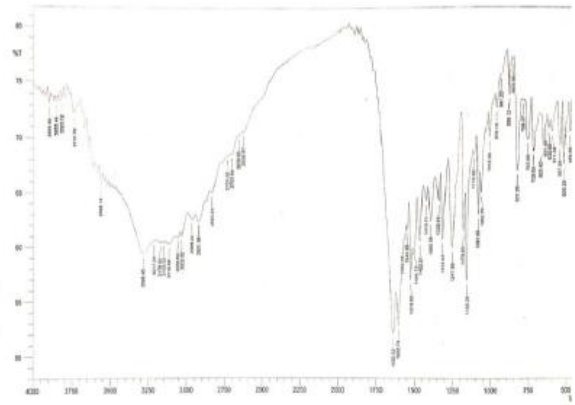


Figure.13: FT-IR spectrum of physical mixture-I

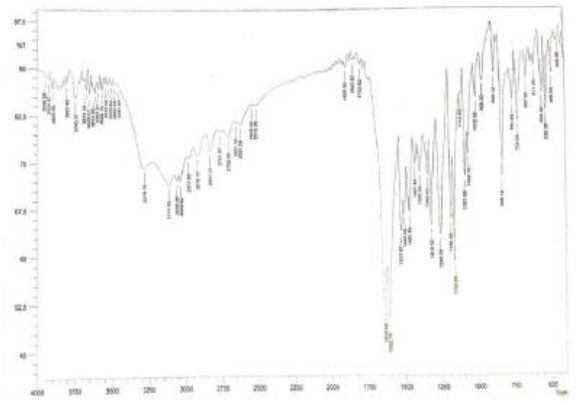


Figure.14: FT-IR spectrum of physical mixture-II

FORMULATION OF POSACONAZOLE LOADED NANOPARTICLE

Various posaconazole nanoparticle formulations were successfully prepared by electrostatic stabilization method as emulsification techniques. The drug and castor oil are constant ratio and glyceryl monostearate, oleic acid, tween 80 in various proportions. The polymers were selected based on the literature review and preformulation studies. It was also observed nanoparticle system, which greatly improved the saturation solubility, *in-vitro* dissolution and *in-vitro* diffusion. The ratio posaconazole nanoparticle formulations are represented in table.9.

Table 9: Composition of drug loaded nanoparticle formulations.

S. No	Batch Code	Posaconazole (mg)	Glyceryl Monostearate (mg)	Oleic Acid (ml)	Castor Oil (ml)	Tween 80 (ml)	Distilled Water(ml)
1	F1	100	1.5	-	1.5	0.5	25
2	F2	100	1.5	-	1.5	1	25
3	F3	100	3	-	1.5	0.5	25
4	F4	100	3	-	1.5	1	25
5	F5	100	-	1.5	1.5	0.5	25
6	F6	100	-	1.5	1.5	1	25
7	F7	100	-	3	1.5	0.5	25
8	F8	100	-	3	1.5	1	25

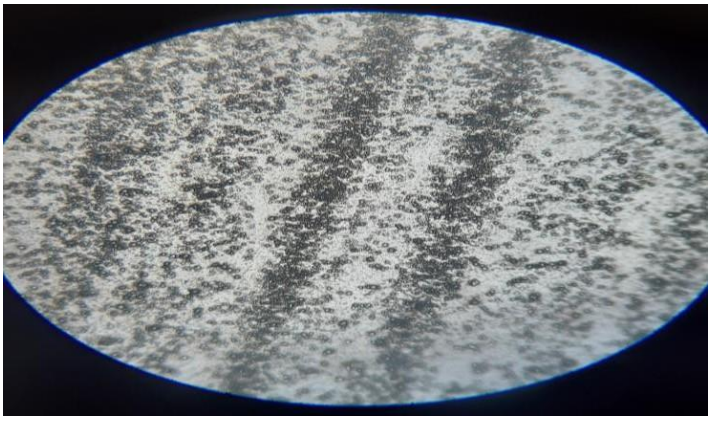


Figure 17: Different formulations of posaconazole nanoparticles.

LYOPHILIZATION

The lyophilized nanoparticle was performed to increasing the stability. The prepared nanoparticle was lyophilized using free dryer at -70 °C for 3days. Then vacuum was applied. 1 % mannitol was added as a cryoprotectant. Degassing was carried out in between prevent explosion.

EVALUATION OF NANOPARTICLES

PARTICLE SIZE ANALYSIS AND POLYDISPERSITY INDEX MEASUREMENT

The particle size distribution has most important characteristics affecting the *in*-vitro fate of nanoparticle. The particle size was measured by Malvern particle size analyzer. The prepared nanoparticle formulations mean particle size ranges from 70.89 nm to 144.5 nm as shown in table.10.

The poly dispersity index (PDI) gives degree of particle size distribution and promotes the physical stability of nanoparticles. The poly dispersity index was a measurement for distribution of nanoparticles and gave a distribution range from 0.00 to 0.50. The value of PDI close to zero indicates homogenous distribution of nanoparticles, which is highly desirable. Exceptionally small particles can obtain adequate energy through Brownian motion to keep them agitated which can prevent precipitation of nanoparticle and thus enhance stability. The PDI vale ranges from 0.284 to 0.700.

It indicates good uniformity in particle size distribution. The choice of suitable polymers and its concentration are the most important factors to control the size and stability. All nanoparticle formulations showed low particle size and poly dispersity index and this low value will indicate good stability of the nanoparticle. The particle size and poly dispersity

index data represented in table.10.

Table 10: Particle size and poly dispersity index of various nanoparticle formulations.

S.No	Formulations	Average particle size (d.nm)	Poly dispersity index
1.	F1	74.37	0.327
2.	F2	129.0	0.422
3.	F3	110.7	0.318
4.	F4	144.5	0.393
5.	F5	80.52	0.284
6.	F6	117.3	0.700
7.	F7	70.89	0.293
8.	F8	95.94	0.359

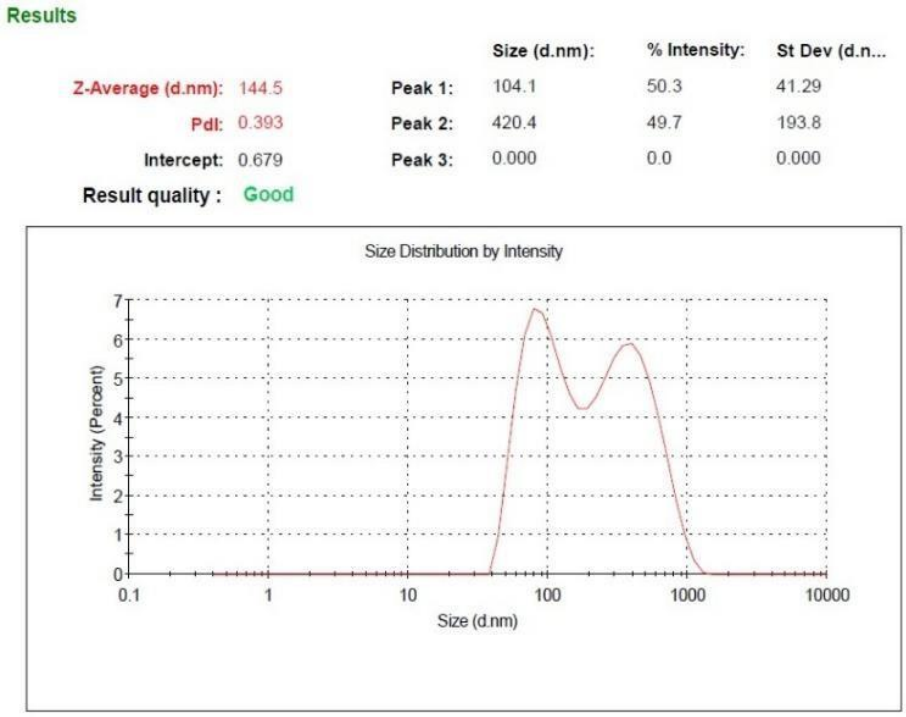


Figure 20: Particle size distribution and poly dispersity index of nanoparticle F4.

ZETA POTENTIAL ANALYSIS

The determination of the zeta potential parameter (properly related to the double electrical layer on the surface of colloidal particles) of a nanoparticle is an essential as it provides an indication about the physical stability of nanoparticles. Extremely positive or negative zeta potential values causes larger repulsive forces, whereas repulsion between the particles with similar electrical charges prevent aggregation of the particles and thus ensure easy redispersion. In case of combined electrostatic and steric stabilization, a minimum zeta potential of ± 20 mV is desirable.

In this study of zeta potential of nanoparticle formulation was found to be in the ranges from -26.9 to 1.86, which indicates all nanoparticle formulations shows good physical stability of nanoparticles. The zeta potential data and graphs are represented in table.11 and figure.21 - 23.

Table 11: Zeta potential of various nanoparticle formulations.

S.No	Formulations	Zeta potential
1.	F1	1.86
2.	F2	-26.9
3.	F3	-13.1
4.	F4	-22.5
5.	F5	-8.48
6.	F6	-5.19
7.	F7	-7.84
8.	F8	-5.22

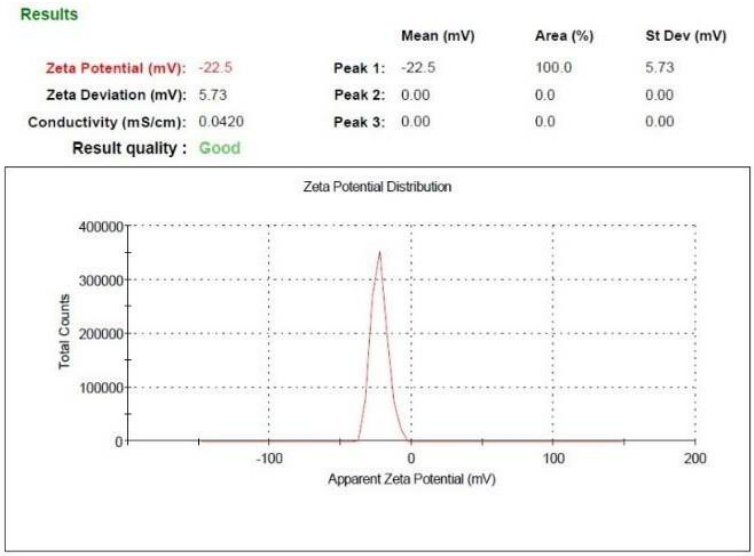


Figure 23: Zeta potential of nanoparticle F4.

DRUG CONTENT

In all nanoparticle formulation, the drug particle was reduced to nano sized from micro scale. In this study of drug content of nanoparticle formulation was found to be in the ranges from 75.73 to 95.27, which was found to be within the theoretical claim. All nanoparticles showed the presence of high drug content. It revealed that the drug was uniformly dispersed in the powder formulation. The drug content values of all formulations represented table.12 and figure.24.

DRUG ENTRAPMENT EFFICIENCY

The percentage drug entrapment efficiency of all the formulations was estimated and repeated three times. All the formulations showed good reproducible results. Entrapment efficiency of posaconazole loaded nanoparticle formulation F1 to F8 was found to be in the ranges 68.26 to 92.74. The posaconazole entrapment efficiency of F4 (92.74) was high entrapment efficiency when compared to other nanoparticle formulations. The entrapment efficiency values of all formulations represented in table.12 and figure.24.

Table 12: Percentage drug content and percentage drug entrapment efficiency of all nanoparticle formulation.

S. No	Formulations	% Drug content	Drug entrapment efficiency (%)
1.	F1	88.61	74.75
2.	F2	79.49	69.00
3.	F3	75.73	68.26
4.	F4	95.27	92.74
5.	F5	88.71	76.89
6.	F6	91.26	84.17
7.	F7	80.27	79.28
8.	F8	82.62	81.94

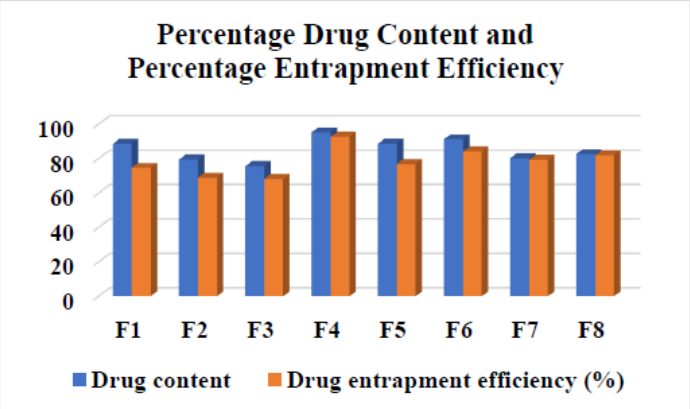


Figure 24: Percentage drug content and percentage drug entrapment efficiency of all nanoparticle formulation.

SATURATION SOLUBILITY STUDIES

The saturation solubility of posaconazole was found 19.67 µg/ml in 0.1N HCl and 25.45 µg/ml in phosphate buffer. The saturation solubility of prepared nanoparticle in 0.1N HCl and phosphate buffer is represented in table.13 and figure.25. The saturation solubility studies of posaconazole show very low solubility due to crystal property; the nanoparticle formulations showing maximum solubility compared to pure drug posaconazole due to the amorphous

nature of nanoparticle formulation from the pure drug. The saturation solubility profile of nanoparticle increases the surface area of drug, leads to increase the saturation solubility also increasing the dissolution velocity, as well as increasing the dissolution rate of posaconazole due to particle size reduction of posaconazole.

Table 13: Saturation solubility studies of pure drug and nanoparticle formulations.

S.No	Formulations	Percentage saturation solubility	
		0.1N HCl buffer	Phosphate buffer
1.	Posaconazole	19.67	25.45
2.	F1	91.73	98.21
3.	F2	73.24	84.31
4.	F3	64.98	75.36
5.	F4	80.47	94.75
6.	F5	76.46	84.46
7.	F6	71.98	80.92
8.	F7	75.84	79.47
9.	F8	67.47	75.56

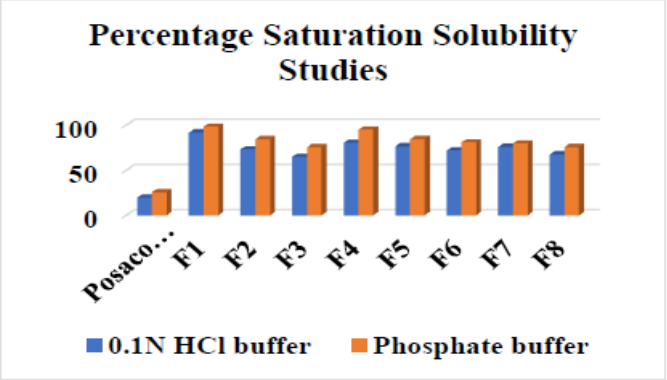


Figure 25: Saturation solubility studies of pure drug and nanoparticle formulations.

IN-VITRO DRUG RELEASE PROFILE

The most important feature of nanoparticle is increase in the dissolution velocity, not only because of increase in surface area but also because of increasing saturation solubility. Posaconazole is poorly aqueous soluble drug. Its solubility is pH dependant increasing with 0.1N HCl (pH 1.2) and phosphate buffer (pH 7.4) was selected for dissolution studies to stimulate gastric condition and follows the greater discrimination of our processing effects. In order to assess the goal of improving the dissolution rate of posaconazole loaded nanoparticle was achieved. *In-vitro* dissolution profile plot by percentage drug release vs. time profile of posaconazole and their nanoparticle formulation were determined in 0.1N HCl and phosphate buffer under the sink condition.

In-vitro drug release data from the nanoparticle were carried out for 2 hours and graphically represented as percentage drug release versus time profile (Figure 29 and 30).

The dissolution rate of pure drug is very low. Only 41.50 % of the drug was released in 0.1 N HCl and 22.64 % of the drug were released in phosphate buffer at the end of 2 hours. On the contrary, nanoparticle dissolution rate is increased more than the pure drug. This could be due to the increased surface area of the drug and possible better contact between the nanoparticle and dissolution medium.

The percentage drug release of nanoparticle F1 to F8 in 0.1 N HCl buffer medium (table.14) and F1 to F8 in phosphate buffer medium (table.15) drug was released at the end the end of 2 hours by increasing the surface area of drug also increasing the saturation solubility and dissolution velocity as well as increasing the dissolution rate.

Based on the above data F4 shows maximum *in-vitro* release in 0.1 HCl and phosphate buffer. From this study, conclude that addition of polymer, increasing the solubility as well as increasing the drug release and increasing the polymer concentration drug, may produce the sustained drug release.

Table 14: Comparative *in-vitro* dissolution profile of posaconazole and nanoparticle formulation 0.1N HCl buffer (pH 1.2).

S. No	Time in Hours	Time in Minutes			
		30	60	90	120
1.	Posaconazole	13.29 ± 0.46	21.75 ± 0.37	32.66 ± 0.27	41.50 ± 0.18
2.	F1	21.18 ± 0.32	40.07 ± 0.21	68.60 ± 0.32	90.51 ± 0.08
3.	F2	21.18 ± 0.32	46.05 ± 0.01	70.71 ± 0.24	92.48 ± 0.13
4.	F3	26.72 ± 0.32	39.38 ± 0.08	52.76 ± 0.18	79.71 ± 0.07
5.	F4	28.59 ± 0.14	49.65 ± 0.01	62.47 ± 0.07	93.73 ± 0.03
6.	F5	25.48 ± 0.05	41.50 ± 0.18	59.37 ± 0.12	79.62 ± 0.25
7.	F6	21.18 ± 0.32	31.07 ± 0.29	47.27 ± 0.13	72.37 ± 0.05
8.	F7	27.35 ± 0.21	43.05 ± 0.08	67.38 ± 0.48	82.43 ± 0.09
9.	F8	23.64 ± 0.17	32.66 ± 0.27	53.95 ±0.14	72.29 ± 0.22

Mean of three observations ± SD.

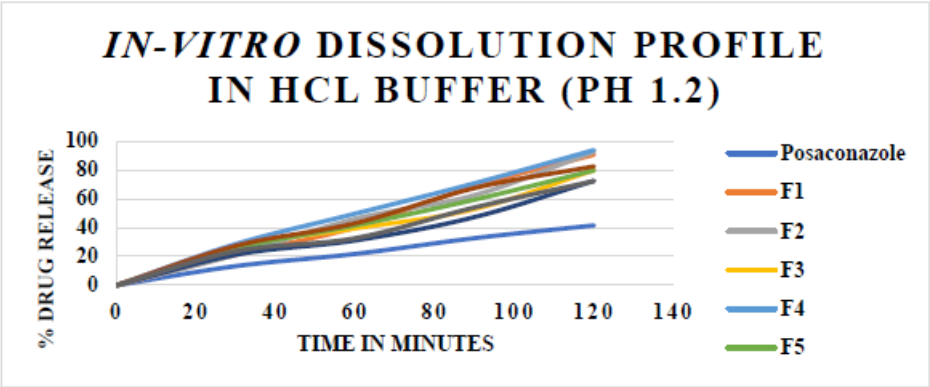


Figure 29: Comparative *in-vitro* dissolution profile of posaconazole and nanoparticle formulation 0.1N HCl buffer (pH 1.2).

Table 15: Comparative *in-vitro* dissolution profile of posaconazole and nanoparticle formulation in phosphate buffer (pH 7.2).

S. No	Time in Hours	Time in Minutes			
		30	60	90	120
1.	Posaconazole	1.56 ± 0.03	5.33 ± 0.07	8.78 ± 0.14	22.64 ± 0.39
2.	F1	35.12 ± 0.07	47.43 ± 0.19	54.70 ± 0.34	62.60 ± 0.38
3.	F2	29.47 ± 0.02	35.15 ± 0.08	45.27 ± 0.23	67.40 ± 0.41
4.	F3	22.26 ± 0.05	27.93 ± 0.09	35.17 ± 0.11	48.43 ± 0.26
5.	F4	34.15 ± 0.21	68.25 ± 0.52	78.25 ± 0.91	95.79 ± 0.26
6.	F5	22.25 ± 0.06	44.21 ± 0.15	66.52 ± 0.09	88.06 ± 0.35
7.	F6	15.27 ± 0.09	30.67 ± 0.08	45.56 ± 0.06	60.67 ± 0.24
8.	F7	21.54 ± 0.07	42.84 ± 0.08	65.56 ± 0.14	76.56 ± 0.15
9.	F8	26.25 ± 0.02	50.25 ± 0.25	74.56 ± 0.45	90.25 ± 0.28

Mean of three observation ± SD.

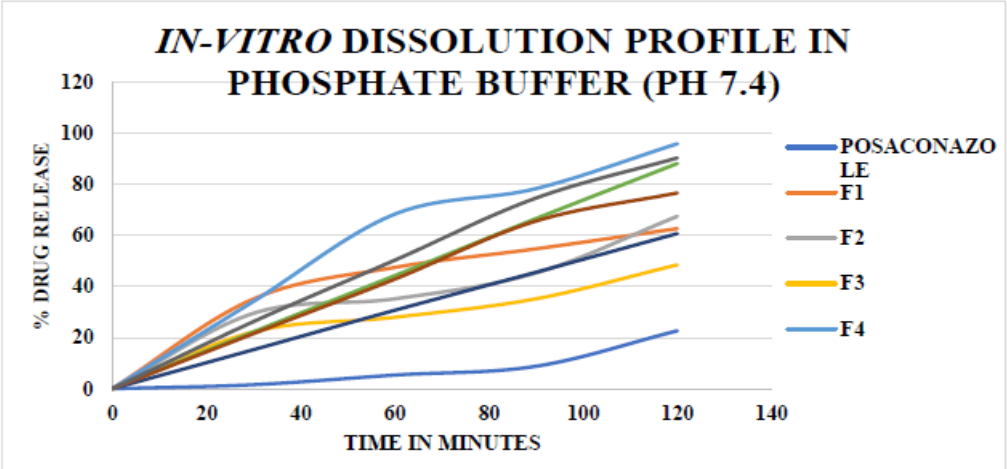


Figure 30: Comparative *in-vitro* dissolution profile of posaconazole and nanoparticle formulation in phosphate buffer (pH 7.2).

Selection of best nanoparticle formulation

All eight posaconazole nanoparticle (F1 – F8) formulation was successfully prepared by the emulsification method and it was evaluated. From the all posaconazole nanoparticle formulations, F4 formulation was selected as best formulation based on the report and observed from physical evaluation of posaconazole nanoparticle. This F4 nanoparticle was selected for the further morphological evaluation, thermal analysis, *in-vitro* kinetic behavior studies, stability studies. This F4 formulation incorporated into the carbopal 940 hydrogel stabilized by TPGS for the application of fungal infections and gel furthermore it undergoes evaluation parameters of gel formulation.

SURFACE MORPHOLOGY BY SCANNING ELECTRON MICROSCOPY (SEM)

The successfully prepared nanoparticles formulation was examined by scanning electron microscopy to study the internal and external surface morphological changes in formulated nanoparticles. The SEM image of pure posaconazole shown in figure.22 (A-Posaconazole) that consisted large size crystals, indicating its posaconazole is crystalline nature. The SEM image of all formulation shown in figure.26 (B- F4). The nanoparticle formulation shape and surface morphology were different among the pure drug posaconazole; small sized globular shaped particle, which indicates the surface area of posaconazole nanoparticle formulations; it was revealed a smooth texture of amorphous form of nanoparticle from the crystalline nature of pure drug.

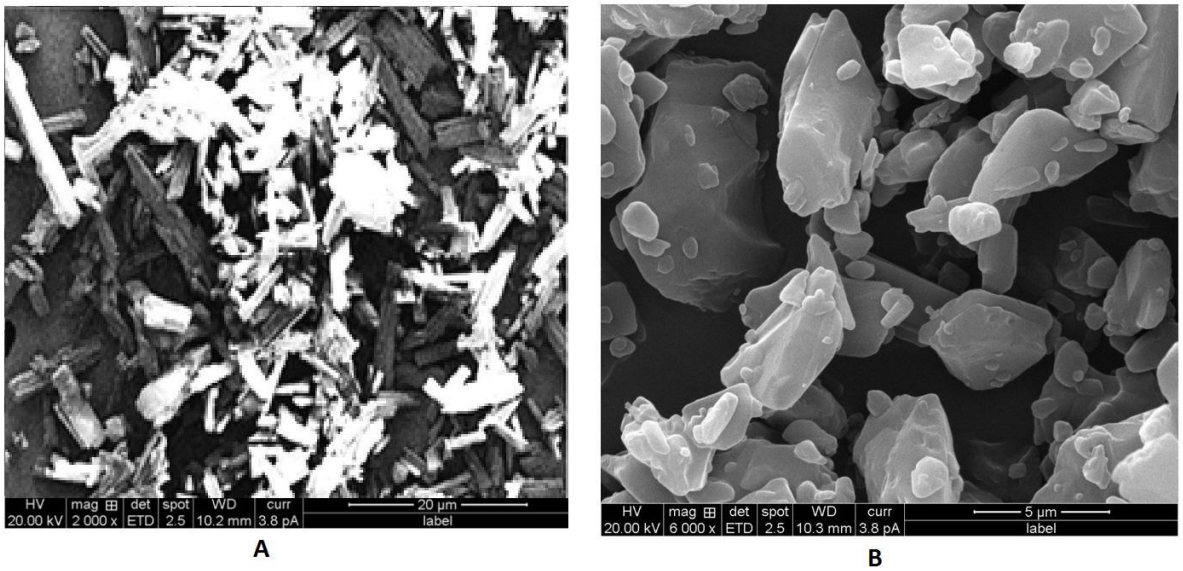


Figure 26: SEM image of posaconazole and posaconazole nanoparticle F4 formulation.

A-SEM image of pure drug posaconazole; B-SEM image of nanoparticle F4 formulation

THERMAL PROPERTY BY DIFFERNETIAL SCANNING CALORIMETRY(DSC)

In differential scanning calorimetry studies used to estimate the thermal properties of posaconazole and their nanoparticle formulations (shown in figure.28). The pure drug posaconazole exhibited a sharp endothermic melting point at 171 ºC indicating the crystalline nature of the drug. The result found for posaconazole endorses those found in the literature. It could be seen that the melting point found in the analysis of DSC is similar to the melting range obtained by the capillary method for posaconazole.

However, posaconazole nanoparticle showed broad melting peak indicating the absence of crystalline nature. No characteristic melting peak of posaconazole was observed in the DSC curve of posaconazole loaded nanoparticle were molecularly dispersed in an amorphous form. There was no important difference between the components during heating. From thermogram it was concluded that the drug and polymers do not interact with each other.

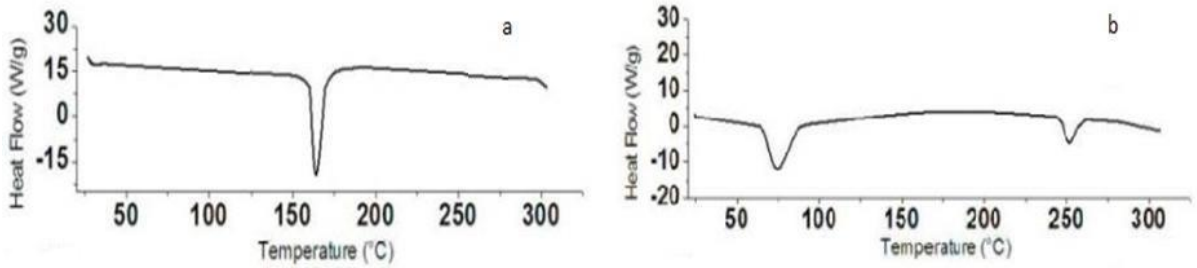


Figure 28: DSC thermogram of posaconazole and posaconazole nanoparticle F4 formulation.

a-DSC thermogram of pure drug posaconazole; b-DSC thermogram of posaconazole nanoparticle F4 formulation.

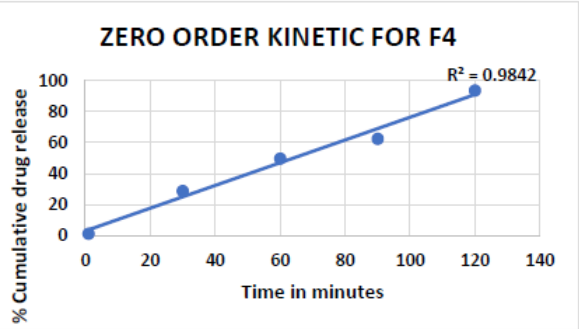
***IN-VITRO* DRUG RELEASE KINETIC BEHAVIOR**

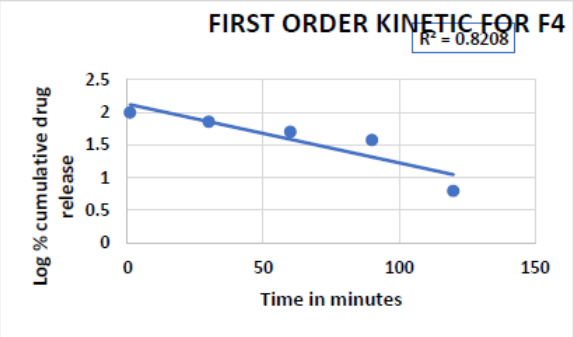
F4 formulation in 0.1N HCl buffer

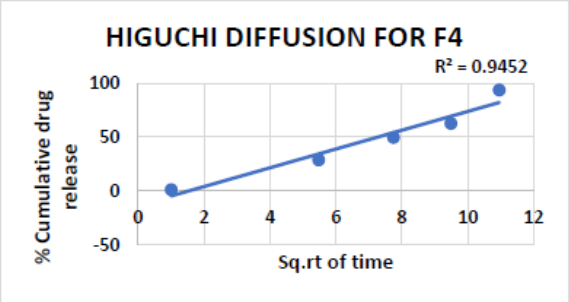
The drug release kinetic profile of F4 formulation r^2 value was analyzed as per zero order, first order, Higuchi and Korsmeyer peppa's kinetic models and it was found in the range 0.9842, 0.8208, 0.9952 and 0.9475 respectively. F4 formulation was best fitted in Higuchi's diffusion and followed by zero order kinetic model. F4 formulation drug release may follow the diffusible controlled drug release.

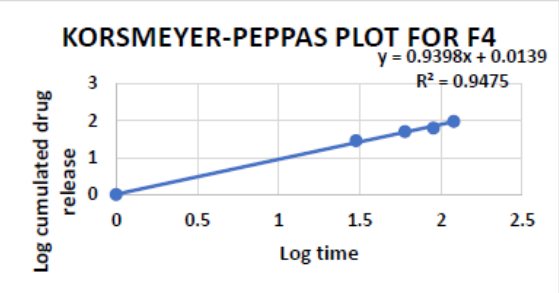
Table 16: *In-vitro* drug release kinetic profile of F4 formulation in acid buffer.

Time in minutes	Log time	Sq.rt of time	% Cumulative Drug release	% Cumulative drug remaining	Log % cumulative Drug release	Log percentage cumulative drug remaining
0	0	1	1	99	0	1.995635195
30	1.477121255	5.477225575	28.59	71.41	1.456214155	1.853759033
60	1.77815125	7.745966692	49.65	50.35	1.695919253	1.701999475
90	1.954242509	9.486832981	62.47	37.53	1.795671506	1.574378564
120	2.079181246	10.95445115	93.73	6.27	1.971878617	0.797267541







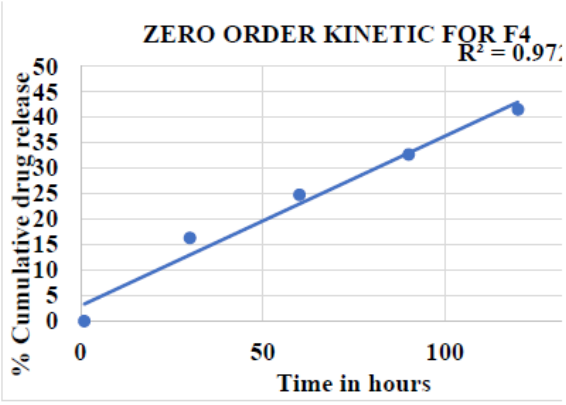


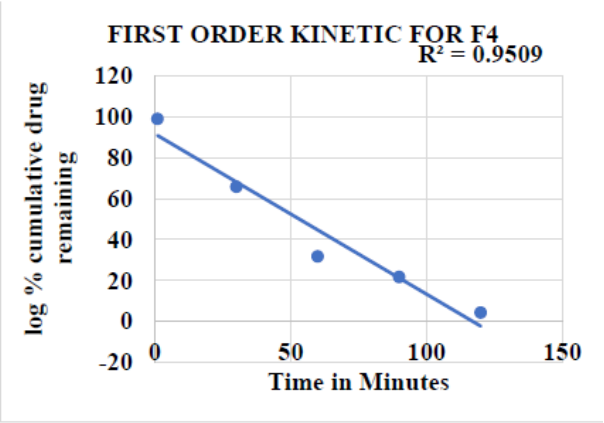
F4 formulation in Phosphate buffer

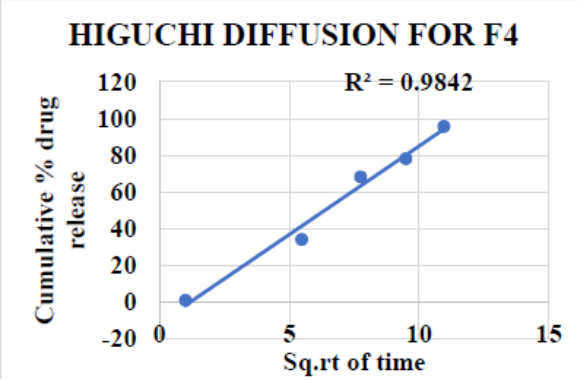
The drug release kinetic profile of F4 formulation r^2 value was analyzed as per zero order, first order, Higuchi and Korsmeyer peppa's kinetic models and it was found in the range 0.9728, 0.9509, 0.9867 and 0.9842 respectively. F4 formulation was best fitted in Higuchi's diffusion and followed by zero order kinetic model. F4 formulation drug release may follow the diffusible controlled drug release.

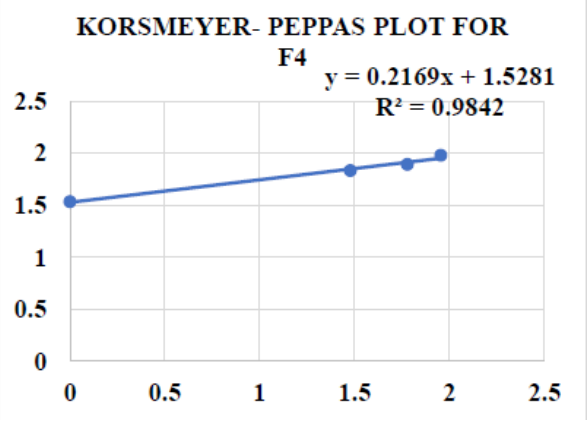
Table 19: *In-vitro* drug release kinetic profile of F4 formulation in phosphate buffer (pH 7.4).

Time in minutes	Log time	Sq.rt of time	% Cumulative Drug release	% Cumulative drug remaining	Log % cumulative Drug release	Log percentage cumulative drug remaining
0	0	1	1	99	0	1.995635195
30	1.477121255	5.477225575	34.15	65.85	1.533390708	1.818555779
60	1.77815125	7.745966692	68.25	31.75	1.834102656	1.50174373
90	1.954242509	9.486832981	78.25	21.75	1.893484346	1.337459261
120	2.079181246	10.95445115	95.79	4.21	1.981320173	0.624282096









The *in-vitro* drug release kinetic data obtained were fitted to kinetic models. Data were analyzed as per zero order, first order, Higuchi and Korsmeyer peppa'skinetic models. Based on the correlation coefficient values (r^2) obtained from different models shown in the table.22, F4 formulation having good linearity in both 0.1N HCl and phosphate buffer is

predicted by zero order release as a controlled release and it has followed by Higuchi's plot as a diffusion process based on Fick's law, square root of time dependent.

The mechanism of drug release of all formulations was found that diffusible controlled drug release formulation.

Table 22: Various kinetic profiles for nanoparticle F4 formulation.

0.1N HCl buffer (pH 1.2)						
S. No	Formulation	Zero (r^2)	First (r^2)	Higuchi (r^2)	Peppa's	
					n	r^2
1.	F4	0.9842	0.8208	0.9925	0.9398	0.9475

Phosphate buffer (pH 7.4)						
S. No	Formulation	Zero (r^2)	First (r^2)	Higuchi (r^2)	Peppa's	
					n	r^2
1.	F4	0.9728	0.9509	0.9867	0.2169	0.9842

Stability studies

The stability study was carried out for formulation F4 as per ICH guidelines at refrigerator temperature (4 ºC), room temperature (25 ºC) and accelerated temperature (40 ºC) for a period of 90 days. After 90 days the formulation was assayed for remaining percentage drug content and redispersibility. The results indicated that formulation shows drug content within the limits after 90 days, indicating better stability.

Table 23: Stability studies of F4 formulation.

S.No	Days	% R.D.C 4 ºC	% R.D.C 25 ºC	% R.D.C 40 ºC
1	0	100.00 ± 0.00	100.00 ± 0.00	100.00 ± 0.00
2	15	99.99 ± 0.022	99.98 ± 0.051	99.97 ± 0.011
3	30	99.98 ± 0.025	99.96 ± 0.016	99.95 ± 0.010
4	45	99.89 ± 0.063	99.86 ± 0.053	99.81 ± 0.005
5	60	99.79 ± 0.034	99.71 ± 0.093	99.64 ± 0.019
6	90	99.70 ± 0.011	99.61 ± 0.054	99.56 ± 0.033

R.D.C = Remaining drug content.

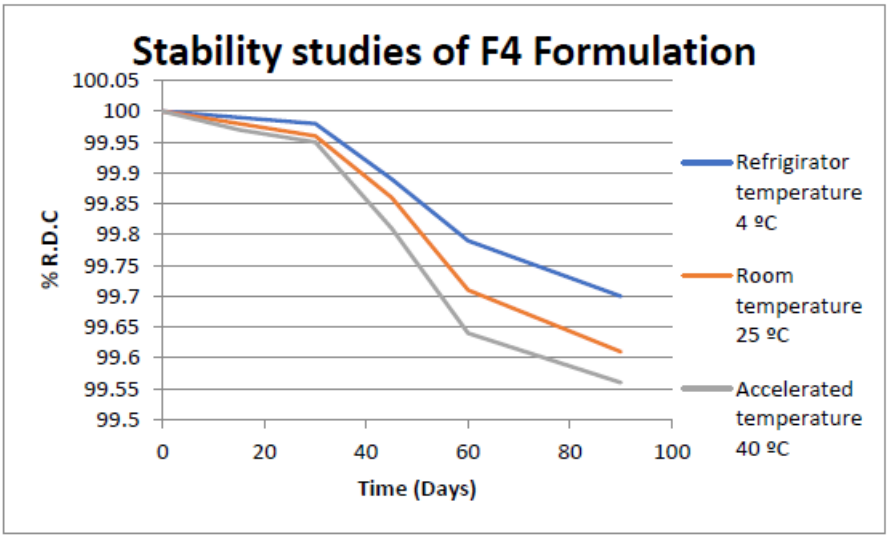


Figure 31: Stability studies of F4 formulation.

EVALUATION OF NANOPARTICLE INCORPORATED GEL

The nanogel was successfully prepared by nanoparticle formulation 1 incorporated into 1 % of carbopol gel. Polymeric hydrogel containing 1% carbopol showed highest viscosity and homogenous in nature.

Figure 32: Various gel formulations.

Physical appearance of gel

The prepared various gel formulations were clear, white colour, transparent, smooth and homogenous appearance with high viscosity. No particles present in the all-gel formulations.

pH measurements

The pH of various gel formulations was determined by using digital pH meter as follows, the pH of various gel formulations matches with the pH of the skin.

Homogeneity

All gel formulation was tested for homogeneity by visual inspection after the gels have set in the container. Gels were tested for their appearance and presence of any aggregates.

Spreadability

Spreadability test was carried out for all gel formulations. Spreadability of formulation was decrease with the increasing the concentration of the polymer. The spreadability is very much important as show the behavior of gel comes out from the tube.

Swelling index

Swelling index test was carried out for all gel formulations. From these data was found, topical gel prepared from carbopol polymer has greater percentage swelling index in all gel formulations.

Table 24: Physical properties of gel formulations.

S.No	Formulations	pH	Homogeneity	Spreadability	% Swelling index	Viscosity (cp)
1.	Gel I	5.4	Good	5.4	88.48	31972
2.	Gel II	5.5	Good	5.6	89.07	33561
3.	Gel III	5.7	Good	5.4	94.56	34129

***In-vitro* permeability/ skin permeation study**

The *in*-vitro permeability study was carried out using Franz diffusion cell. After 2 hour diffusion, 83.61% (Gel I), 90.33% (Gel II), 86.83% (Gel III) and 95.95% (Gel IV) of the drug was diffused from the gel formulations. It can be clearly seen that the permeation of the drug from the gel formulation IV is much faster than the other formulation. The enhanced diffusion may be explained in terms of the huge specific surface area of the gel formulation droplets and improved permeation of the posaconazole because of the presence of the stabilizer such as TPGS. The order of drug diffused from various formulations was found to be decrease in the following order G1 > G2 > G3.

Table 25: *In-vitro* permeability study of various gel.

S.No	Time in minutes	Percentage drug release		
		Gel I	Gel II	Gel III
1.	20	04.03	17.12	19.04
2.	40	08.06	31.33	35.14
3.	60	12.15	43.62	53.32
4	80	16.26	54.98	73.48
5.	100	18.43	79.65	85.72
6.	120	20.61	90.33	95.95

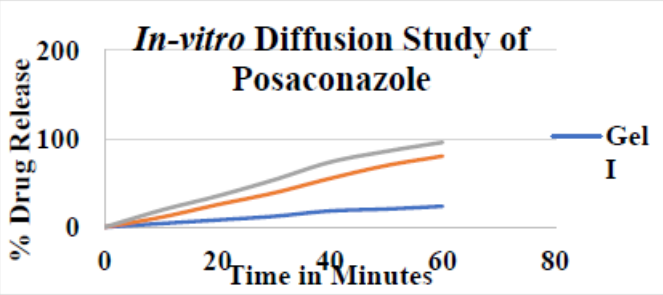


Figure 33: *In-vitro* permeability studies of various gel formulations.

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