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# Formulation and Evaluation of Voriconazole Loaded Nanosponges for Topical Delivery

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ABSTRACT

In this research, Voriconazole was first formed into a gel form, and then nanosponges were made using the solvent evaporation approach. By combining PVA into a co-polymer as well as HP-cyclodextrin and even HPMC K4M as rate-retarding polymers, the formulations for Nanosponges were produced. The compatibility of the medicine with formulation ingredients has been evaluated using Fourier Transform Infra-Red (FTIR) spectroscopy. We examined the surface morphology, yield, and drug entrapment effectiveness of the Nanosponges. SEM analysis was used to investigate the Nanosponges' shape and surface morphology. Nanosponges were discovered to be porous and spherical by scanning electron microscopy. SEM images showed that the Nanosponges were spherical in all configurations; however, at larger ratios, drug crystals were seen across the nanosponge surface. Improvement within the drug/polymer ratio (1:1 to 1:3), which takes place in ascending sequence due to the rise in polymer concentration, however after a certain level of concentration, it was noted that when the drug/polymer ratio rose, the particle size declined. All formulations' average particle sizes fall between 316.4 and 454.8 nanometers. The drug release of the optimised formulation was found to be 99.42%, while the drug content of other formulations ranged from 82.8 to 97.2% and their entrapment efficiencies from 86.24 to 96.88%. The optimised gel formulation's stability studies show that the formulated gel was stable up to 90 days.

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## INTRODUCTION

In order to alter and regulate the releasing behaviour of the medications, there has been a lot of focus in recent years on the creation of innovative nanosponge base drug delivery systems [1]. It is possible to change the therapeutic index and duration of a drug's activity by incorporating the system into a carrier. The frequent inclusion of vitamins and -hydroxy acids in topical treatments, which have apparent and observable advantages - particularly in ageing or photodamaged skin - has encouraged consumers' growing interest in skin care and skin treatment products [2]. Despite being

very helpful, these substances can occasionally cause irritation, which is often felt as burning, stinging, or redness and is more common in people having delicate skin. The formulators attempted to address this issue using one of the two techniques after realising the issue. They sacrificed efficacy in order to lower the concentration of these substances. Additionally, the vehicle has been altered to improve the product's skin compatibility or emolliency. Small, spherical, porous delivery devices called nanosponges are made of porous polymeric materials [3]. These are used to passively target cosmetic compounds to the skin, which has significant advantages like lowering the overall dose, keeping the dosage form on the skin, as well as preventing systemic absorption [4]. These nanosponges can be successfully added to topical systems for longer release as well as skin retention, which lowers the variability in drug absorption, toxicity, as well as improves compliance among patients by extending dose intervals. Drug irritability can be greatly reduced by nanosponges without compromising their effectiveness. The diameter of the nanosponge varies from 250 nm to 1 m [5].

## METHODOLOGY

### Pre-formulation studies:

Certain fundamental physical and chemical characteristics of the drug molecule alone as well as coupled with excipients must be established prior to the construction of the nanosponge dosage form. Preformulation is the name given to this initial learning period. The pre-formulation process' main goal is to produce data that will aid the formulator in creating stable, bioavailable dosage forms that might be mass-produced [6] .

The objectives of pre-formulation studies are:

To establish the drug substance's compatibility with various excipients and to analytically assess the drug substance and identify its necessary qualities.

### Spectroscopic study:

### Identification of pure drug:

### Solubility studies:

Voriconazole's solubility was tested in a variety of solvents, including distilled water, 0.1 N HCL, buffers with a pH of 6.8, and organic solvents such ethanol and methanol. Studies on drug solubility involved putting an excessive amount of the drug in various beakers with the solvents. The mixes were shaken continuously for 24 hours. What man's filter paper grade no. 41 was used to filter the solutions. On the basis of spectrophotometry, the filtered solutions were examined [7] .

### Physicochemical parameters:

The substance was described as being a white to off-white crystalline powder with no taste or odour, according to descriptive language.

### Determination of absorption maximum ($\lambda_{max}$):

The term "max" refers to the wavelength at which light is absorbed the most. Every substance has this "max," which is both characteristic of and helpful in identifying the substance. It's crucial to determine the substance's maximum absorption rate for precise analytical analysis. Since most medications are aromatic or include double bonds, they absorb radiation in the UV area (190-390 nm). 10mg were weighed precisely. Separately, voriconazole was dissolved in 10 ml of clean volumetric flask in methanol. The same substance was diluted to a volume of 10 ml to produce stock solution-I with a concentration of 1000 g/ml. Pipette 1ml of the stock solution I into a 10ml volumetric flask. Using methanol buffer, the volume was increased to 10 ml to generate stock solution II with a concentration of 100 g/ml. 1 ml was pipette-out of stock solution II into a 10 ml volumetric flask. Using methanol buffer, the volume was increased to 10 ml in order to achieve a concentration of 10 g/ml. In order to reach the absorption maximum (-max), A UV-visible double beam spectrophotometer was then used to scan this solution between 200 and 400 nm [8] .

### Construction of calibration curve:

Voriconazole, accurately weighed at 10 mg, was dissolved in 10 ml of clean volumetric flask. A 6.8 ph buffer was used to dilute the fluid to 10 ml, yielding a concentration of 1000 g/ml. To get a concentration of 100 g/ml, 1 ml of this standard solution was pipette out into a 10 ml volumetric flask and the volume was topped off with methanol. Aliquots of 0.2, 0.4, 0.6, 0.8, 1.0, and 1.2 ml from the aforementioned stock solution were transferred to separate 10 ml volumetric flasks, and the solution was diluted to 10 ml with methanol buffer to achieve concentrations of 2, 4, 6, 8, 10, and 12 g/ml, respectively. At 247 nm, the absorbance of each solution was determined [9] .

### Drug excipient compatibility study:

Using Fourier Transform - Infra Red spectroscopy (FT-IR), the compatibility of the medicine and excipient was discovered. In order to ascertain whether there might be any FT-IR spectra were obtained from Bruker FT-IR Germany (Alpha T), and they were used to study the relationships between the pure drug and the excipients in the solid state. To make potassium bromide pellets with a KBr press, the

solid powder sample has been crushed using a mortar with 100 times the quantity of potassium bromide. The powder was subsequently inserted into a stainless steel die as well as compressed between polished steel anvils at a pressure of around 8t/in2. The wavelengths of the spectra were between 4000 and 400 cm-1 [Table 1 ] [10] .

**Method of Preparation of Nanosponges:**

By adopting the solvent evaporation process, nanosponges were created using various ratios of -cyclodextrin, HP -cyclodextrin, HPMC KM4 as a rate-retarder polymer, and co-polymers like polyvinyl alcohol. A specific amount of PVA in 100 ml of an aqueous continuous phase that had been created using a magnetic stirrer was slowly added to a disperse phase made up of Voriconazole (1 gm) and the necessary amount of PVA dissolved in 10 ml of solvent (ethanol). On a magnetic stirrer, the reaction mixture was agitated at 1000 rpm for three hours. The created nanosponges were collected by filtering them through Whatman filter paper and allowed to dry for two hours at 50°C in the oven. In order to guarantee that any remaining solvent was removed, the dried nanosponges were kept in vacuum desiccators [11] .

**Evaluation parameters of Nanosponges:**

The Nanosponges was evaluated for various parameters:-

Entrapment efficiency

Scanning electron microscopy

Particles size and shape

**Entrapment efficiency**

The 100mg Voriconazole weight equivalent nanosponge was dissolved in 10ml of distilled water for analysis. Ten millilitres of the transparent layer of the medication after it has been dissolved is taken.

After that, a UV spectrophotometric technique at 247 nm (U.V Spectrophotometer, Systronics) was used to determine how much medication was present in the water phase. With a different nanoparticulate sample, the experiment was repeated.

The concentration of the medication in the clear supernatant layer was determined using the UV-spectrophotometric technique after centrifuging the suspension at 500 rpm for five minutes. The calibration curve is used to determine the drug's concentration [12] .

By deducting the quantity of drug in the nanoparticle suspension divided by the amount of drug in the aqueous phase, a percentage of drug inside the particles was estimated. The following equation was used to calculate the drug's entrapment efficiency (%) .

$$\%\ of\ Drug\ entrapment\ = \\ (Mass\ of\ drug\ in\ nanosponge/ \\ Mass\ of\ drug\ used\ in\ formulation) \\ \times 100$$

**Scanning electron microscopy**

Scanning electron microscopy is used to examine the morphological characteristics of prepared nanospongess at various magnifications.

**Particle size and shape**

Malvern Zetasizer ZS was used to measure the average particle size and shape of the synthesised nanospongess utilising water as the dispersions medium [13] . To determine the size of the particles, the sample were scanned [Figure 1 ].

**Formulation of Nanosponge loaded gel:**

To achieve smooth dispersion, the polymer was first agitated at 600 rpm for two hours while being soaked in water for the gel for two hours. To balance the pH, triethanolamine (2% v/v) was added. Thus, the previously manufactured, optimised nanosponge was added, and the aqueous dispersion was given an ethanolic solution of the permeation enhancer, propylene glycol [Table 2 ]. Table 4 displays the composition of nanosponge gels [14] .

**Visual Appearance and Clarity:-**

Under fluorescent lighting, on a white and black background, visual appearance and clarity were checked for the presence of any particle matter [15] .

**pH:**

After all the materials had been added, a pH metre was used to determine the pH of the created in-situ gelling system [16] .

**Drug Content uniformity:**

Utilising a spectrophotometric technique, drug content homogeneity of generated in-situ gelling systems was assessed.

Pipetting 1 ml of each optimised formulation and diluting it up to 100 ml with Simulated Tear Fluid (pH 6.8) was used to assay these formulations. The mixtures were agitated for two to three minutes until a clear gel solution was obtained.

The solution was filtered using Millipore membrane filtrate (0.45um), and a UV-Visible spectrophotometer was used to detect the absorbance at 247 nm [17].

**In-Vitro Gelation:-**

The ability of formulations containing various ratios of poloxamer and HPMC to gel was assessed. It was carried out by adding a drop of polymeric solution to vials containing 1 ml of freshly made and equilibrated Simulated Tear Fluid and visually timing how long it took for the gel to form and disintegrate [18] .

**Rheological Studies:-**

By taking into account the formulation's viscosity, it is crucial to calculate the drug's residence duration in the eye. At physiological temperature, the prepared solutions were allowed to gel before the viscosity was measured using a Brookfield viscometer (Brookfield DV+Pro, Brookfield Engineering Laboratories, Middleboro, MA, USA).

**In vitro Drug Release studies of nanosponge gel formulations:**

Using the dialysis membrane method, in vitro assessment experiments of topical gel were carried out. The membrane was submerged in 0.1NHCl for 12 hours, then 6.8pH phosphate buffer was added to the receptor compartment. A test substance equal to 100mg was equally placed to the membrane's surface. To prevent air bubbles from getting trapped under the prepared membrane, the cell was carefully mounted with the membrane in place. The entire assembly was kept at 37°C for 12 hours while stirring was done at a continuous 600 rpm. At 1-hour intervals, aliquots of the drug sample (4 mL) were obtained and replaced with an equal volume of freshly made buffer [63]. Three duplicates of each experiment were carried out. The UV spectrophotometer was used to analyse the drugs at 247 nm [19] .

**Modelling of Dissolution Profile:**

To explain the release kinetics of voriconazole from the matrix tablets in the current investigation, data from the in vitro release were fitted to several equations and kinetic models.

The kinetic models employed were the Higuchi release, Zero Order Equation, First Order, and Korsmeyer-Peppas models.

Kinetic Research: Models in mathematics:

To interpret the release rate of the drug from matrix systems for the optimised formulation, various release kinetic equations (zero-order, first-order, Higuchi's equation, and Korsmeyer-Peppas equation) were used [20] .

Calculated was the best match with the highest correlation (r2).

**Zero-order model:**

The equation can be used to illustrate medicine absorption from dose forms that gradually release the medication but do not break down.

$Qt = Q0 + K0t$

**First Order Model:**

In general, release behaviour follows the first order equation below:

$\text{Log } C = \text{Log } C_o - kt/2.303$

**Higuchi model:**

The Higuchi model is generally stated by the following equation.

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

Where, $K_H$ is the Higuchi dissolution constant.

**Korsmeyer-Peppas model**

First, to determine the mechanism of drug release, 60% of the drug release data were fitted into the Korsmeyer-Peppas model.

$Mt / M\infty = Kt^n$

Only the part of the release curve where Mt / M 0.6 should be considered to determine the exponent of n.

Log cumulative percentage drug release vs log time was used to illustrate data from in vitro drug release investigations to analyse the release kinetics [Table 3 ].

**Stability studies:**

In order to ascertain the physical and chemical stabilities, the optimised formulation was stored for stability testing for a period of three months at ambient (30 2°C), refrigerator (4 2°C), as well as accelerated (40 2°C, 75%RH) conditions.

The formulation was assessed aesthetically, for drug release after 30, 60, and 90 days, and for entrapment effectiveness.

## RESULTS AND DISCUSSIONS

**Voriconazole Characterization:**

**Physical Properties:**

Studying the physicochemical characteristics of the bulk drug is important in order to manufacture the medicinal ingredient into a dosage form.

A. Colour: white colour

B. Melting Point: 129-134°C

C. Solubility: Solubility of Voriconazole was conducted using various solvents, including distilled water, 0.1N HCL, as well as 6.8 pH buffers.

**Table 1: Formulation table of Voriconazole loaded nanosponges**

| S.NO | Excipients | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|---|
| 1 | Voriconazole (gm) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| 2 | PVA (gm) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| 3 | HPMC K 4M (gm) | 0.5 | 1.0 | 1.5 | – | – | – |
| 4 | HP $\beta$ cyclodextrin | – | – | – | 0.5 | 1.0 | 1.5 |
| 5 | Ethanol (ml) | 10 | 10 | 10 | 10 | 10 | 10 |
| 6 | Water | 100 | 100 | 100 | 100 | 100 | 100 |

**Table 2: Formulation of Nanosponge loaded gel**

| Ingredients | F7 | F8 | F9 |
|---|---|---|---|
| Optimize Nanosponge(mg) | 400 | 400 | 400 |
| Xanthan gum | 100 | | |
| Guar gum | | 100 | |
| Karaya gum | | | 100 |
| Propylene Glycol(ml) | 1 | 1 | 1 |
| Distilled Water(ml) | 5 | 5 | 5 |
| Triethanolamine(2%v/v)(ml) | 1 | 1 | 1 |

**Table 3: Drug transport mechanisms suggested based on 'n' value**

| S. No | Release exponent | Drug transport mechanism | Rate as a function of time |
|---|---|---|---|
| 1 | 0.5 | Fickian diffusion | $t^{-0.5}$ |
| 2 | 0.45 < n = 0.89 | Non -Fickian transport | $t^{n-1}$ |
| 3 | 0.89 | Case II transport | Zero order release |
| 4 | Higher than 0.89 | Super case II transport | $t^{n-1}$ |

**Table 4: Solubility of Voriconazole**

| S.No | Buffer | Solubility (mg/ml) |
|---|---|---|
| 01 | Water | 0.224 |
| 02 | Ethanol | 1.42 |
| 03 | Methanol | 0.926 |
| 04 | 0.1 N HCL | 0.458 |
| 05 | 6.8 pH buffer | 3.678 |

**Table 5: Calibration curve data of Voriconazole**

| Concentration | Absorbance |
|---|---|
| 0 | 0 |
| 2 | 0.154 |
| 4 | 0.311 |
| 6 | 0.472 |
| 8 | 0.628 |
| 10 | 0.792 |
| 12 | 0.956 |

**Table 6: Particle size of Nanosponges**

| S.NO | Formulation code | Particle size (nm) |
|---|---|---|
| 1 | F1 | 321.6 |
| 2 | F2 | 398.2 |
| 3 | F3 | 218.2 |
| 4 | F4 | 396.4 |
| 5 | F5 | 454.8 |
| 6 | F6 | 416.4 |

**Table 7: Drug content of Formulated Nanosponges**

| Formulation code | Mean % drug content |
|---|---|
| F1 | 88.22 |
| F2 | 94.60 |
| F3 | 97.12 |
| F4 | 92.64 |
| F5 | 97.08 |
| F6 | 90.82 |

**Table 8: Entrapment efficiency of Nanosponges**

| Formulation code | Entrapment efficiency % |
|---|---|
| F1 | 90.86 |
| F2 | 95.12 |
| F3 | 96.54 |
| F4 | 92.84 |
| F5 | 95.88 |
| F6 | 90.12 |

**Table 9: Visual appearance and clarity of all (F7-F9) formulations**

| Formula | Appearance | Clarity |
|---|---|---|
| F7 | Transparent | Clear |
| F8 | Transparent | Clear |
| F9 | Transparent | Clear |

**Table 10: pH measurements of all formulations (F7-F9)**

| Formula | pH |
|---|---|
| F7 | 6.6 |
| F8 | 6.8 |
| F9 | 6.9 |

**Table 11: Drug content of Formulated gels**

| Formulation Code | Drug content |
|---|---|
| F7 | $95.52 \pm 0.47$ |
| F8 | $96.31 \pm 0.56$ |
| F9 | $98.15 \pm 0.69$ |

**Table 12: Gelling capacity of all formulations (F7-F9)**

| Formulation | Gelling capacity at 25 °C | Gelling capacity at 37°C |
|---|---|---|
| F7 | — | + |
| F8 | —– | ++ |
| F9 | — | +++ |

+ Gelation dissipates quickly after 50–60 seconds; ++ Gelation occurs in 60 seconds and is stable for 3 hours; +++ Gelation occurs in 60 seconds and lasts for 6 hours

**Table 13: Viscosity Studies of Formulations**

| Angular Velocity (rpm) | F7 | F8 | F9 |
|---|---|---|---|
| 10 | 103.0 | 107.1 | 112.3 |
| 100 | 96.0 | 97.4 | 99.2 |

**Table 14: In vitro diffusion studies of Voriconazole Nanospongein corporated gel**

| Time (hrs) | F7 | F8 | F9 |
|---|---|---|---|
| 0 | 0 | 0 | 0 |
| 1 | 15.42 | 12.46 | 9.12 |
| 2 | 27.29 | 23.48 | 12.71 |
| 3 | 46.62 | 34.28 | 26.63 |
| 4 | 53.04 | 42.12 | 38.12 |
| 5 | 60.78 | 50.16 | 44.68 |
| 6 | 71.82 | 58.06 | 50.54 |
| 7 | 77.94 | 67.82 | 62.24 |
| 8 | 85.92 | 79.68 | 73.26 |
| 9 | 92.96 | 87.24 | 78.12 |
| 10 | 98.12 | 96.12 | 83.36 |
| 11 | | 99.56 | 89.90 |
| 12 | | | 94.14 |

**Table 15: Regression Values**

| S.NO | Zero order | First order | Higuchi | Peppas |
|---|---|---|---|---|
| Code | $R^2$ | $R^2$ | $R^2$ | $R^2$ |
| F9 | 0.988 | 0.929 | 0.935 | 0.844 |

**Table 16: Gelling capacity of all formulations (F9)**

| Formulation | Gelling capacity at 25 °C | Gelling capacity at 37°C |
|---|---|---|
| 30th day | +++ | +++ |
| 60th day | +++ | +++ |
| 90th day | +++ | +++ |

**Table 17: Drug content of Formulated gels**

| Formulation Code | Drug content |
|---|---|
| 30th day | $98.05 \pm 0.54$ |
| 60th day | $97.98 \pm 0.11$ |
| 90th day | $97.85 \pm 0.64$ |

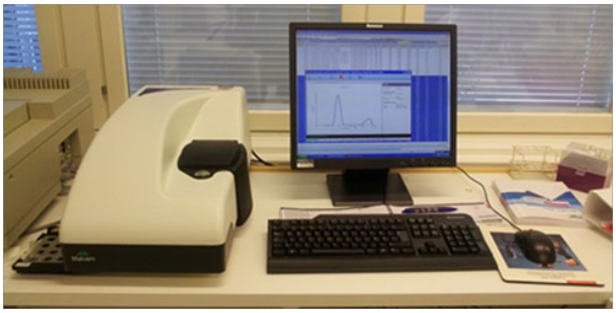

**Figure 1: Photography representation of Malvern zeta sizer used for finding particle size & zeta analysis**

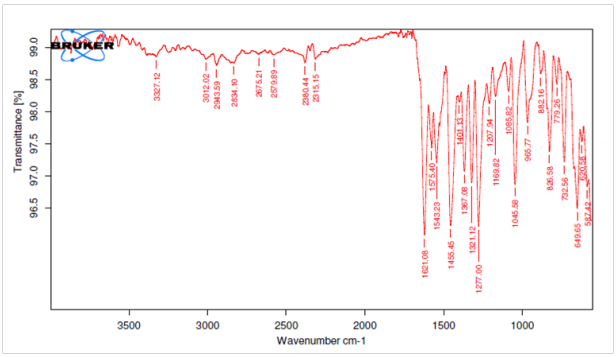


**Figure 2: FTIR Spectra of Pure Drug**

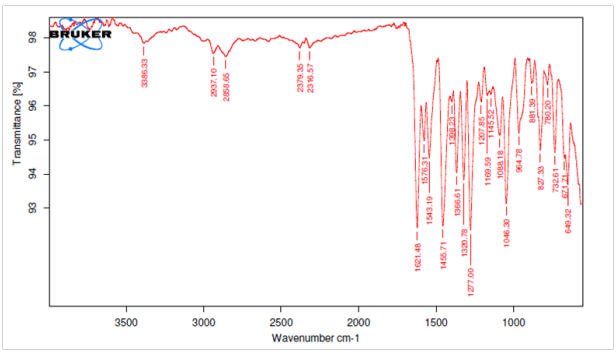


**Figure 3: FTIR Spectra of drug and excipients**

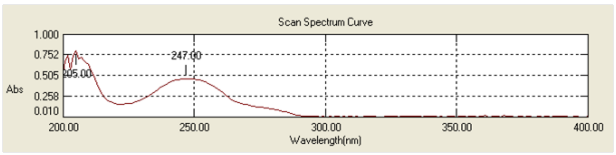


**Figure 4: λ-max in 6.8 phosphate buffer**

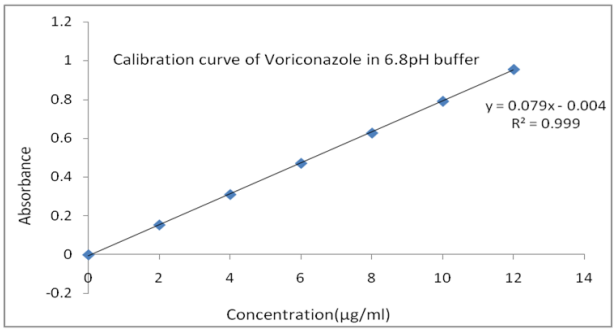


**Figure 5: Calibration Curve of Voriconazole in 6.8 pH phosphate buffer**

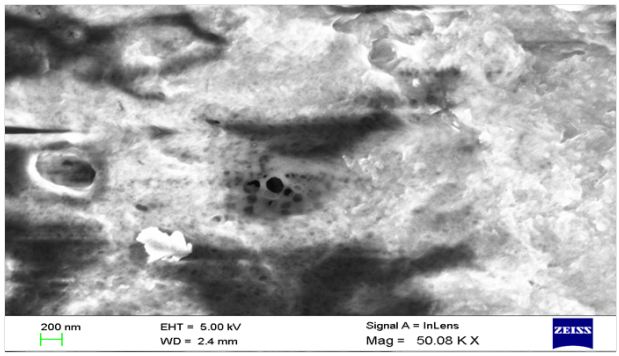


**Figure 6: Nanosponges structure optimized formulation (F3)**

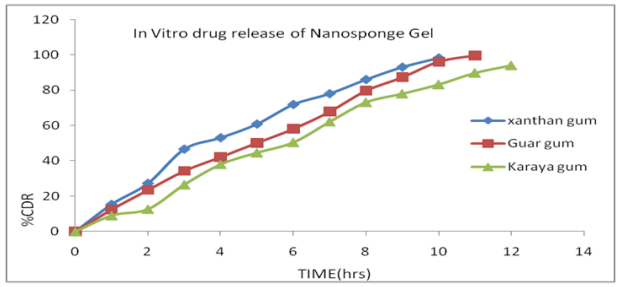


**Figure 7: Percentage of drug release graph F7-F9**

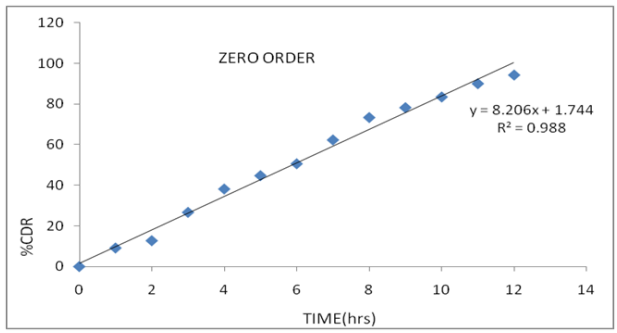


**Figure 8: Zero Order Plot for F9**

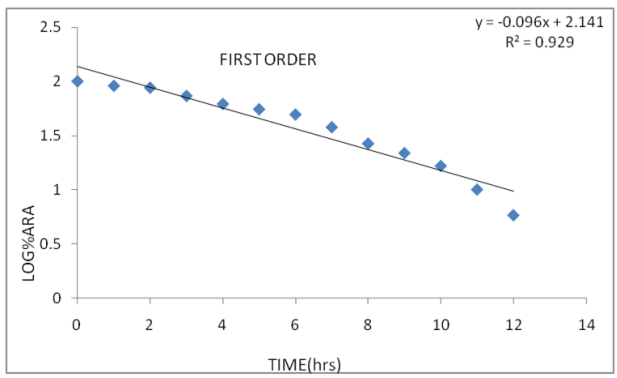


**Figure 9: First Order Plot for F9**

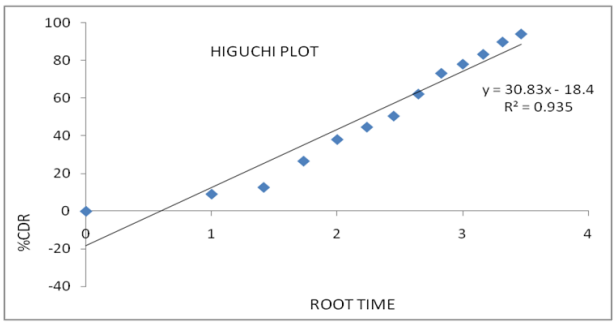


**Figure 10: Higuchi Plot for F9**

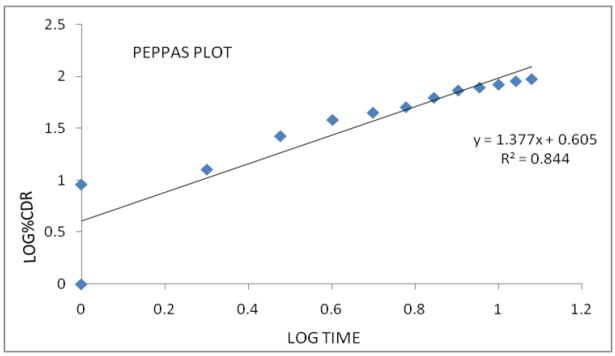


**Figure 11: Peppas Plot for F9**

## Discussion

According to the aforementioned solubility studies, 6.8 pH phosphate buffer has a higher solubility of the medication than the other buffers. More ethanol than methanol was found to be solubilized in organic solvents.

### Drug excipient compatibility:

By comparing the spectra of the FT-IR analysis of the pure drug with those of the various excipients employed in the formulation, the compatibility of the drug and excipient was established [Figures 2 and 3 ].

### Discusion:

### Spectral data:

The major functional groups are primary amine, nitro, and carbonyl group

Obtained peak in IR spectra are as follows.

### IR (KBr) $cm^{-1}$:

732.50-732.61(CH- bending), 1169 (C=C stretching), 1277 (C-O stretch in aromatic compound), 1456 (C-C "oop" in aromatic compound) 1543 (N-N stretching).The spectral data confirm the structure of the compound.

### Disscusion

It indicates that the excipients employed in the formulation were compatible with the medicine because it was intact and had not interacted with them. The medication is therefore in a free condition and can readily release from the polymeric network in its free form.

### Determination of absorption maximum ($\lambda$max)

For a precise quantitative evaluation of the drug dissolution rate, the Voriconazolemax was determined in a 6.8 pH phosphate buffer [Figure 4 ].

### Discussion

As indicated in [Figure 4] the maximum absorbance of voriconazole in pH 6.8 buffer was discovered to be 247 nm.

Therefore, 247nm was chosen as the wavelength for the drug analysis in the dissolution media.

### Calibration curve

In 6.8 phosphate buffer, a linearity of 2–12 g/ml was discovered. As the regression value approached 1, it became clear that the procedure followed Beer-Lambert's law [Table 5 , Figure 5 ].

### Particle size analysis of Nanosponges:

By using optical microscopy to measure the nanosponges' particle sizes, it was discovered that their sizes were uniform. The average particle size of all formulations ranged from 316.4 nm to 454.8 nm and increases with increasing polymer concentration, however It was discovered that as the ratio of medication to polymer increased after a certain concentration, the particle size decreased. This may be because there was substantially less polymer available per nanosponge when the medication to polymer ratio was high. High drug-polymer ratios likely result in less polymer being present around the drug, a thinner polymer wall, and smaller nanosponges. The results of the particle size analysis show that The ratio of the polymer to medication concentration affects the formulation's particle size [Table 6 ].

### Morphology determination by scanning electron microscopy (SEM):

The morphology of the produced nanosponges utilising scanning electron microscopy (SEM), was investigated. SEM may be used to determine the shape and dimensions of microscopic specimens with particles that are as tiny as 10 to 12 grams. An electron beam scanned the sample in a predetermined pattern inside a chamber that had been evacuated.

A multitude of When the electron beam interacts with the object, physical phenomena result and when they are noticed, they are utilised to create images and reveal fundamental details regarding the specimens. The nanosponges were seen to be homo-

geneous, spherical, and free of any drug crystals on the surface.

The size of spherical nanosponges in terms of surface area and surface area per unit weight are influenced by the shape of the nanosponges.

The dissolution rate that exists in the dissolution environment may be impacted by the irregular shape of the particles [Figure 6].

**Drug content**

The drug content ranged from 82.8 to 97.2% for the Nanosponges (F1-F6) that were developed [Table 7 ].

**Discussion:**

Formulation F1 had an 88.2% drug content, Formulation F2 had a 94.60% drug content, Formulation F3 had a 97.12% drug content, Formulation F4 had a 92.64% drug content, Formulation F5 had a 97.08% drug content, and Formulation F6 had a 90.82% drug content.

**Entrapment efficiency:**

It is computed to determine the effectiveness of any process, which aids in choosing the best method of production.

Following formulation preparation, the Practical Yield was determined by comparing the amount of Nanosponges recovered from each preparation to the total starting material (Theoretical yield).

It can be computed using the formula below [Table 8 ].

$$Entrapment \quad efficiency = (Practical \ yield/Theoretical \ yield \ (drug + polymer)) \times 100$$

**Discussion**

The entrapment efficiency of formulation F1 was found to be 90.86%, that of formulation F2 to be 95.12%, that of formulation F3 to be 96.54%, that of formulation F4 to be 92.84%, that of formulation F5 to be 95.88%, and that of formulation F6 to be 90.12%. F3 exhibits a high entrapment efficiency of 96.54% among all the formulations.

**Visual Appearance and Clarity:**

All of the formulations (F7-F9) were clear and transparent in appearance, and both at room temperature and when refrigerated, the formulations were liquid [Table 9 ].

**pH Measurement**

The formulations all have appropriate pH values between 6.6 and 6.9, which is suitable for ocular administration [Table 10 ].

**Drug Content Uniformity**

The prepared gels' medication content was discovered to be adequate, ranging from 95.52 to 98.15 % [Table 11 ].

**Gelling Capacity**

When tested, every composition displayed immediate gelation contact with buffer. However the nature of the gel formed depended on the concentration of the polymer used [Table 12 ].

**Rheological Studies: -**

A Brookfield DV 3 The viscosity of the sample was assessed using a programmable rheometer, formulations by changing the angular velocities or the shear rate. Formulations F7 through F9 had viscosities that ranged from 96.0 to 112.3 cps at 100 rpm. Viscosity dropped as the rotational velocity rose, showing no thixotropic characteristic [Table 13 ].

**Discussion**

The nanosponge formulation containing Karaya gum released the most amount of the drug, but xanthan gum and guar gum did not exhibit sustained drug release, according to the aforementioned invitro experiments. The karaya gum-containing formulation F9 was therefore regarded as the ideal formulation. For the F9 formulation, drug release kinetics were carried out [Table 14, Figure 7 ].

**Regression values of F9**

For Zero order, First order, Higuchi, and Korsmeyer Peppas, the optimised formulation F9 has coefficient of determination (R2) values of 0.988, 0.929, 0.935, and 0.844, respectively. Data was fitted into the Korsmeyer Peppas equation, which demonstrated linearity with the Higuchi plot's regression line slope, which reflects the rate of drug release through the mode of diffusion, the n value of 1.377 for an optimised formulation, to further confirm the diffusion mechanism. Thus, the Super case transport mechanism is indicated by the n number. As a result, the Higuchi model provided the greatest fit for the release kinetics of the optimised formulation, which demonstrated zero order drug release with a super case transport mechanism [Figures 8, 9, 10 and 11 and Tables 15 and 16 ].

**Drug Content Uniformity:**

According to stability experiments of Nanosponges loaded gel utilising karaya gum, the drug concentration and gelling capacities were determined to be satisfactory because there was little change in either at the time of formulation or 90 days later [Table 17 ].

## CONCLUSION

The optimized formulation F9 has good gelling property with pH of 6.9, and drug content of 98.15% and coefficient of determination (R2) values for zero order, first order, higuchi, and korsmeyer peppas of 0.970, 0.731, 0.966, and 0.768, respectively. Data was fitted into the Korsmeyer Peppas equation, which demonstrated linearity with the Higuchi plot's regression line's slope, which represents the rate of drug release through the mode of diffusion, the n value of 1.377 for an optimised formulation, to further confirm the diffusion mechanism. Thus, the super case transport method is indicated by the n value. As a result, the Higuchi model provided the greatest fit for the release kinetics of the optimised formulation, which demonstrated zero order drug release with a super case II transport mechanism. The stability studies revealed that the formulated Nanosponge gel uncovered to be stable for the period of 90days.

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## Conflict of Interest

The authors attest that they have no conflict of interest in this study.

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