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(RESEARCH ARTICLE)

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Formulation and evaluation of voriconazole loaded ophthalmic in situ gel using a natural polymer

Prerana Shantinath Husukale [1,*], Indrajeet Damodar Gonjari [1] and Nikita Harekrishna Gurav [2]

[1] *Department of Pharmaceutics, Government college of pharmacy, Karad, Maharashtra, India.*
[2] *Department of Pharmaceutics, Dr. Shivajirao Kadam College of Pharmacy, Kasbe Digraj, Sangli, Maharashtra, India.*

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Abstract

The eyes are one of the body's most significant and intricate organs, able to capture visual images and send them as signals via the optic nerve to the brain. The ocular transport of the medicine has been one of the challenging tasks for drug researchers because of the amazing development of the eye, which stifles the part of the prescription molecules into the perfect spot. The external visual course is the most often used method of medicine administration for treating visual diseases. Drugs used intraocularly that are topically controlled have very little visual bioavailability. A significant amount of medication is lost as a result of dose structure spilling brought on by tear turnover and nasolacrimal seepage weakening. Therefore, 1–10% of the medicine reaches the cornea. Voriconazole is the drug used in the treatment of fungal keratitis. Various polymers are screened out & among them, K-Carrageenan & Xanthan gum were used for the preparation of various formulations. Drug loaded with voriconazole was optimized using DOE experimental design with concentration of K- Carrageenan (X1), concentration of Xanthan gum(X2) as a dependent variable while Viscosity (Y1), Percent drug release(Y2) as a dependable variable. All the formulated batches were characterized for clarity, pH, drug content, gelling capacity, viscosity, in vitro drug release, accelerated stability study. An optimized batch was evaluated & showed there was no significant difference between them. The stability study suggested the formulation did not show any significant changes in drug content, viscosity, pH, gelling capacity & percent drug release. Conclusion-An ion sensitive ophthalmic in situ gel of antifungal agent using natural polymer will be serves as an alternative dosage form to reduce frequent dosing & safe.

Keywords: In situ gel; Voriconazole; Ophthalmic drug delivery; Natural polymer; K-Carrageenan; Xanthan gum

1. Introduction

The preferred form of visual chemotherapy is typically topical medication use due to its simplicity and security. Traditional medicine delivery methods and novel drug delivery strategies are the two groups that make up the visual medication delivery strategies. For the treatment of either external visual illnesses like conjunctivitis, blepharitis, and keratitis sicca or intraocular problems like glaucoma, proliferative vitreoretinopathy, extraordinary retinal decay, and retinitis, medications are frequently administered directly to the external layer of the eye as eye drops. However, a large portion of the medication is immediately eliminated from the visual surface and only a small portion is consumed into the eye because of the conjunctiva's fundamental retention and strong guard frameworks of the eye (like lachrymal emission and the flicker reflex). This results in unfortunate bioavailability of the medication for the eye.

Permeability barriers for ocular drug delivery system: The permeable membrane protect against medication entry into the eye by lachrymal fluid. Trans's corneal prescription can only penetrate so far due to the cornea's dense epithelium. The cornea is a more convenient route for administering lipophilic medications. Due to these strong interactions, the

* Corresponding author: Prerana Shantinath Husukale.

corneal epithelium serves as a rate-limiting border for the retention of hydrophilic medicines. The pH, thickness, cradles, and constitution modifiers all affect the cornea's capacity to retain medication. The conjunctiva is another barrier that influences pervasion because of its intricate structure and tight junctions. The thickness of the pores and perforations in the conjunctival epithelium are twice as thick as those in the corneal epithelium, with an average of 15 to multiple times more perforations.

Visual bioavailability: Most ordinarily involved course of medication conveyance in the treatment of visual illnesses is the skin visual course. Topically regulated intraocular drugs have extremely low visual bioavailability. A lot of medication is lost due to nasolacrimal seepage weakening with tear liquid and dose structure spillage because of tear turnover. Thus, around 1-10% of the medication arrives at the cornea.

1.1. Factors impacting intraocular bioavailability:

- Dilution with tears: When the measurement structure is imparted into the eye, it might become weakened with tear liquid, diminishing how much medication arriving at the cornea.
- The medication's energy in the eye's circular drive.
- Corneal obstructions.
- Corneal dynamic ionic vehicle.
- Interaction of the medication with the proteins found in the lacrimal liquid.

Every framework enjoys its own benefits and downsides. Decision of a specific hydrogel relies upon its inherent properties & conceived remedial use. Future utilization of biodegradable & water solvent polymers for the in-situ gel plans can make them more satisfactory and magnificent medication conveyance systems. To increment the visual bioavailability of medication we really want to increment hold season of medication in ophthalmic. Polymeric in-situ gel framework is thick polymer-based fluid that show sol-gel stage progress on the visual surface because of progress in unambiguous physicochemical boundary. As eye are extremely crucial organ treatment to eye contamination or illness is very troublesome. So, this work will be ready to conquer these kinds of issues.

Fungal keratitis is a significant reason for vision misfortune in emerging nations. As of now, contagious keratitis stays a baffling demonstrative test and a troublesome administration issue for ophthalmologists. Early conclusion of fungal keratitis and its treatment is significant in forestalling difficulties and loss of vision. Second generation triazole, voriconazole is a one of, wide range antifungal agent, successful against Aspergillus spp. also, Fusarium spp. In preclinical prospective study, Hariprasad et. al in an update on VCZ in ophthalmology demonstrated that systemic VCZ achieved good penetration into the aqueous and fluid humor of the human eye.so it is the base behind the selection of antifungal agent VCZ for the work. Selection of K- carrageenan for this with the reason followed as biodegradable; less or no toxic characteristic; for use in pharmaceuticals as an excipient (natural polymer) like this polymer, they are gone through modification such as crosslinking, derivative formation, polymer-polymer crosslinking. Carrageenan is used in a variety of dosage forms, including suspensions (wet and reconstitute), emulsions, gels, creams, lotions, eye drops, suppositories, tablets, and capsules. In suspension formulations, usually only the carrageenan and carrageenan fractions are used and provides viscosity to the liquid. Carrageenan has been shown to mask the chalkiness of antacid suspensions when used as a suspending agent in these preparations. When used in concentrations of 0.1–0.5%, carrageenan gives stable emulsions. Carrageenan is used in hand lotions and creams to provide slip and improved ‘rub out’. In the case of topical gels, a combination of i, k-, and carrageenan’s produces a spreadable gel with acceptable tactile sensation, resulting in drug release that is more likely to follow diffusion kinetics. Xanthan gum used in small amount to modify the viscosity of polymeric constituted system of in situ gel.

The ion activated in situ gel formulation method incorporation for this study to alternate the use the of other methods including temperature triggered and pH triggered & most important is it is easily adaptable to the properties of eye component in ophthalmic fluid environment.

In situ-based based gels are structures that shows transformation sol-to- gel at the site of administration. When delivered becomes liquid and experience a sol to gel transformation caused by external factors such as temperature, pH, ion shift, and magnetic field or in the biological environment. It was first recognized in the middle of the 1980s. In situ gel-framing frameworks are low consistency arrangements that undergo work progress in the conjunctival circular drive to shape viscoelastic gels because of conformational alterations in the polymer due to physiological environment. Given that an inert gel or respond is delivered by the eye's liquid portion in the interim between an implant's placement in the eye and the formation of a firm gel, the rate at which an in-situ gel develops is crucial.

2. Material and Method

Materials: Voriconazole was obtained from Micro Lab Ltd. Bengaluru; K- carrageenan (low Viscosity grade) and Xanthan gum gift samples obtained from Marine Hydrocolloids, Kochi; other excipients used were of analytical grade.

2.1. Formulation and optimization of in- situ gel

The polymeric solution was made by dispersing the required amount of K- carrageenan as a ion activated polymer and xanthan gum as a viscosity modifier in water with a magnetic stirrer with slight heating until the polymers completely dissolved. To the above prepared solution, the required amount of Voriconazole was added with continuously stirring until it thoroughly mixed.

Benzalkonium chloride as a preservative was added to the resulting solution, pH of the solution was checked & Phosphate buffer 7.4 was used to adjust the pH of the solution to 7.4. The prepared formulation filled in vial and closed with closures, covered with aluminum foil and sterilized by using autoclave.[8][9]

Table 1 Selection of variable

Level	Variable	X_1(concentration of K- Carrageenan) %w/v	X_2 (Concentration of Xanthan Gum) % w/v
Low	-1	0.2	0.01
Medium	0	0.4	0.02
High	+1	0.6	0.03

Table 2 Formulation table of in situ gel

Sr. No	Name of Ingredients	L1	L2	L3	L4	l5	L6	L7	L8	L9
1	Voriconazole	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
2	K- Carrageenan	0.2	0.2	0.2	0.4	0.4	0.4	0.6	0.6	0.6
3	Xanthum Gum	0.01	0.02	0.03	0.01	0.02	0.03	0.01	0.02	0.03
4	Benzalkonium Chloride	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
5	Distilled water	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml

2.2. Preformulation study

2.2.1. Overall Properties

The sample of Voriconazole was studied for organoleptic characteristics such as color, odor and appearance. [1], [2], [3]

2.2.2. Liquefaction Point

Liquefaction point of the drug was measured by using melting point apparatus.

2.2.3. Solubility

In distilled water, Phosphate buffer pH7.4 & Simulated Tear Fluid solution, the drug's saturation solubility was measured. The excess amount of drug was taken in a solubility tube containing 10 ml of each solvent. The tubes are shaken for 24hrs on a mechanical shaker to aid in solubilization and then allowed to rest for 2hrs for the sake of equilibrium. Whatman filter paper is used to filter the solution. At 256 nm, the filtered solution was spectrophotometrically examined. [2],[3][22]

2.2.4. Determination of λ max of Voriconazole

Standard solution of Voriconazole was prepared by dissolving 100mg drug in 100 ml of solvent (1000 µg/ml). 1ml from this stock (100µg/ml) was further diluted up to 10 ml to produce 10 µg/ml solutions. The resulting solution (10µg/ml) was scanned over range of 200-400nm on UV-Vis Spectrophotometer. [1],[2],[3],[4],[5]

2.2.5. Preparation of standard curve

Voriconazole was weighed accurately (10mg) transferred into 10 ml standard volumetric flask. It dissolved with Phosphate buffer (7.4 pH), Simulated Tear Fluid and distilled water respectively in each at separate manner. Made up to the volume with same (solution A). Accurately pipette out 1ml of solution A into a 10 ml standard volumetric flask and made upto the 10 ml volume using same solvent to get a concentration of 1000 µg/ml (solution B). Accurately pipette out 0.5 ml, 1.0 ml, 1.5 ml, 2.0 ml, 2.5 ml, 3.0 ml of solution B into six separate 10 ml standard flask & made up to the volume target a concentration of 5,10,15,20,25,30 µg/ml (solution C). One of the above solution was scanned in UV range using blank & wavelength of maximum absorption was found to be about 256nm. The absorption of solution at different concentration were measured at 256 nm. Calibration curve was plotted between absorbance vs concentration. [1][5],[6]

2.2.6. FT-IR Analysis

The representative sample of Voriconazole was mixed with IR grade KBr and triturated to obtain uniform blend. This blend was dried for 10 min and then subjected to Fourier transform infrared spectroscopy (FT-IR) scan in range of 400-4000cm^{-1}.[3],[5]

2.2.7. Compatibility Test

To supply a consistent, effective, desirable, and secure item, the physicochemical comparability between Voriconazole and the other excipient should be outlined. FT-IR spectrophotometer was used to acquire the IR spectra of the pharmaceutical polymer and polymer combination in order to evaluate the reliability & relevance of the medication in the definition.[7],[9]

2.3. Factorial Design and Optimization

Experimental design was used to statistically optimize the formulation factors & their effects on the selected responses.

A 3^2 [3 level, 2 factor] factorial design was adopted to systematically study the combine influence of the effect of independent variables such as the concentration of K- carrageenan (X1), concentration of Xanthan gum (X2) on the dependable variables like Viscosity (Y1), Percent Drug release(Y2). In this design, two factors were evaluated each at three level –lower, medium, higher, coded as -1,0, +1 respectively. A design comprising of 9 experimental runs with one central points for the evaluation of batch to batch variations.

2.4. Characterization of in situ gel

2.4.1. Clarity

The way to test the clarity of each compartment is to examine it in dazzling light while looking for eye reflections and contrasting it with a dark and white base.[5],[10]

2.4.2. pH

Drug solubility and stability in ocular formulations are both impacted by pH. When administered, there shouldn't be any irritation for the patient and the formulation should be stable at that pH. Digital pH meters are used to measure it.[5],[10],[11]

2.4.3. Drug Content

Dose uniformity depends upon the uniform distribution of an active ingredient. The drug content was determined by diluting 1 ml of the formulation to 10 ml with distilled water. Aliquot of 1 ml withdrawn and further diluted to 10ml. Voriconazole concentration was determined at 256 nm by using UV-Vis spectrophotometer. [5]

2.4.4. Gelling Capacity

Gelling limit of not entirely settled by putting a drop (20µl) of the plan in a vial containing 2 ml of newly prepared simulated tear liquid and time taken for its gelling is noted.[10],[15]

- (+) Gelation following not many moment and scatter quickly.
- (++) Gelation right away and stay for not many hours.
- (+++) Gelation right away and stay for broadened hours.

2.4.5. Viscosity

A Brookfield viscometer with RV spindle 63 was used to conduct the in situ gel viscosity measurements. The formulation whose viscosity was to be determined was introduced to the beaker, where it was let 30 minutes to settle at a temperature of 250°C plus or minus 1°C before the measurement was made with care taken to prevent the spindle from touching the jar's bottom, it was lowered perpendicularly into the middle of the sample and rotated for 10 minutes at a speed of 50 rpm. The reading for viscosity was taken. [12],[13],[14]

2.4.6. In vitro Drug Release

In vitro release study of in-situ gel solution was carried out in simulated tear fluid at 50 rpm. Simulated tear fluid (composition- Sodium Chloride 0.68gm, sodium bicarbonate 0.22gm, calcium chloride dehydrate 0.008gm, potassium chloride 0.14gm & distilled water to 100 ml) was used as the medium for in vitro release study. The temperature was maintained at 32^0c± 0.5c to mimic eye temperature.[16] After that 2ml of formulation was placed in the donor compartment. At predetermined time intervals, samples (1ml) of receiving solution were withdrawn and replaced with the same volume of fresh release medium. The drug release from each sample was determined by using UV-Vis Spectrophotometer.[17]

2.4.7. Isotonicity Evaluation

Isotonicity is an important ophthalmic characteristic. To avoid tissue damage or eye irritation, Isotonicity must be maintained. The shape of normal RBC in normal saline solution and shape of RBC in test sample (the streamlined formulations were mixed with a few drops of blood) are compared by using calibrated microscope. For calibration of microscope stage micrometer scale & eyepiece micrometer scale were used.

2.4.8. Accelerated Stability Study

To ascertain the physical stability of the formulation under accelerated storage circumstances, an ICH-recommended stability study for in-situ gel formulation is conducted. A suitable amount of the formulation placed in a vial was kept in a stability chamber for three months at an accelerated temperature and humidity level of 400°C/2°C/75%RH.The samples were taken out and measured for significant physiochemical characteristics such as gelling capacity, pH, viscosity, and in vitro drug release at different time intervals such as 0, 30, 60, and 90 days. The traditional Arrhenius plot was used to calculate how long the optimized formulation will last. [18]

3. Results

3.1. Pre formulation study

Table 1 Organoleptic properties of Voriconazole

Sr. No	Parameter	Reported	Observed	Conclusion
1	Appearance	Solid	Solid	Complies with standards
2	Colour	White to off white	White	
3	Odor	Odorless	Odorless	

Table 2 Liquefaction point of Voriconazole

Parameter	Reported	Observed	Conclusion
Liquefaction Point	129-134^0 c	130^0 c	Complies with Standard

Table 3 ƛmax determination of Voriconazole

Sr. No	Solvent	Reported	Observed	Conclusion
1	PBS 7.4	256	256	The ƛ max. of the experimental Voriconazole drug complies with Standard
2	STF	256	256	
3	Water	256	256	

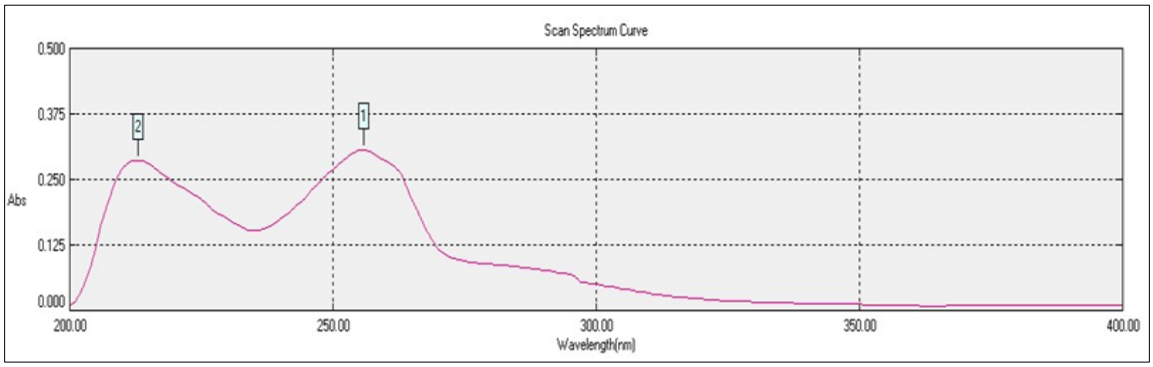

Figure 1 U.V. Spectra of Voriconazole in PBS7.4

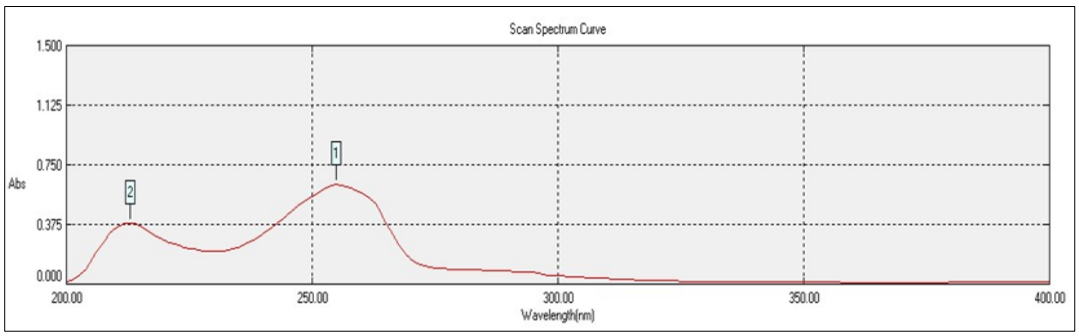

Figure 2 U.V. Spectra of Voriconazole in STF

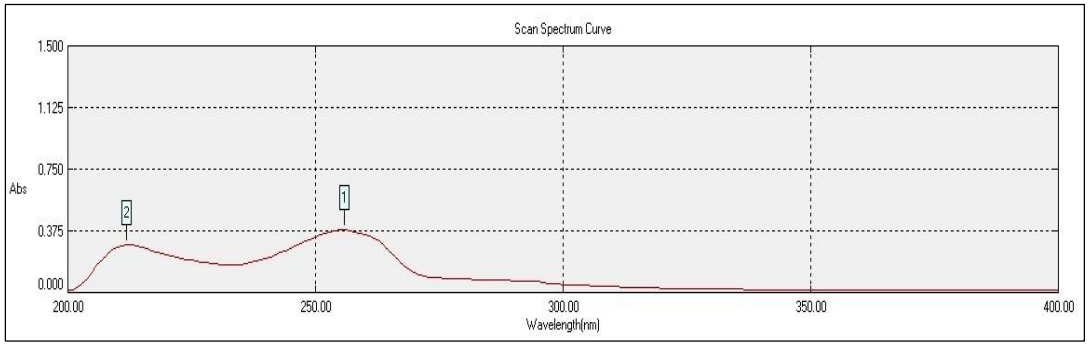

Figure 3 U.V. Spectra of Voriconazole in water

Table 4 Calibration curve in Water

Sr. No.	Conc. (µg/ml)		Absorbance		Mean	Std. deviation
1	0.5	0.102	0.104	0.102	0.10266667	0.001154701
2	1	0.209	0.209	0.207	0.20833333	0.001154701
3	1.5	0.303	0.3	0.302	0.30166667	0.001527525
4	2	0.366	0.365	0.367	0.366	0.001
5	2.5	0.41	0.4	0.42	0.41	0.01
6	3	0.578	0.578	0.576	0.57733333	0.001154701

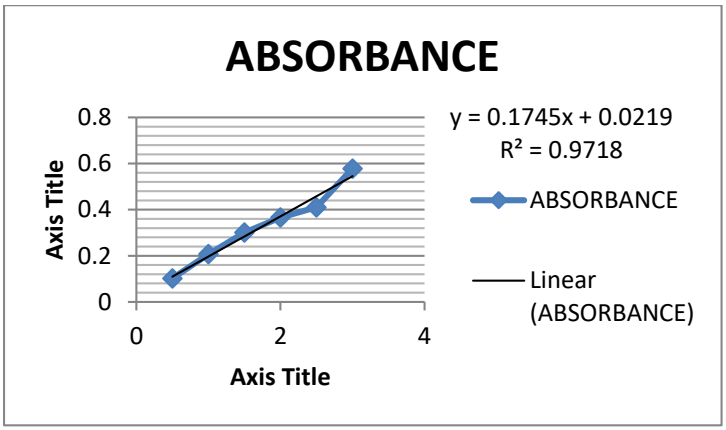

Figure 4 Calibration curve in Distilled water

Table 5 Regression coefficient and slope of Voriconazole in different solvents

Solvent	λ max	R^2	Equation of straight line
STF	256	0.87	y=0.1325x + 0.0103
PBS7.4	256	0.94	y=0.1894x-0.0081
Distilled water	256	0.97	y= 0.1745= 0.0219

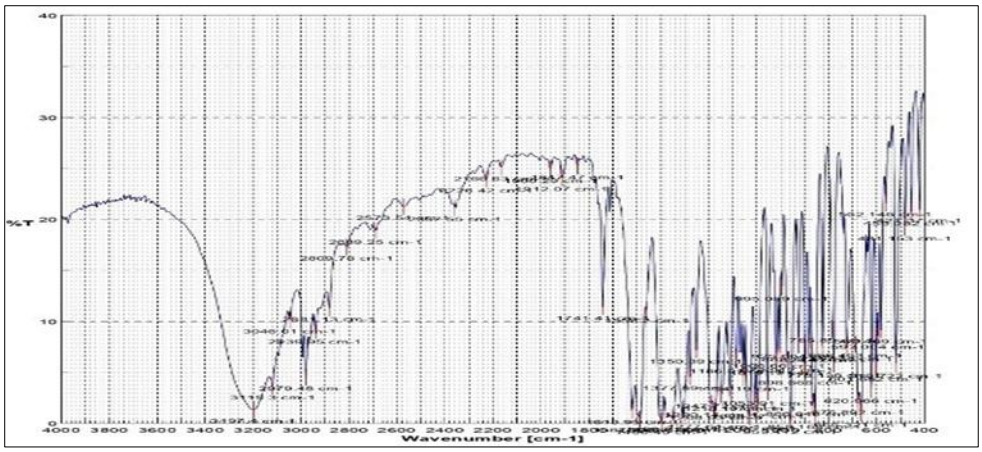

Figure 5 IR spectrum of Voriconazole

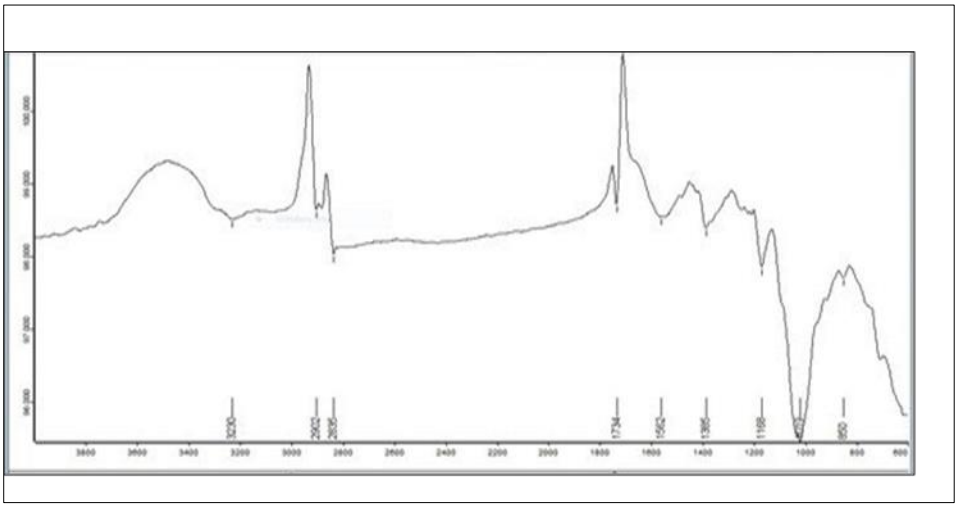

Figure 6 IR Spectra of Carrageenan + Xanthum gum

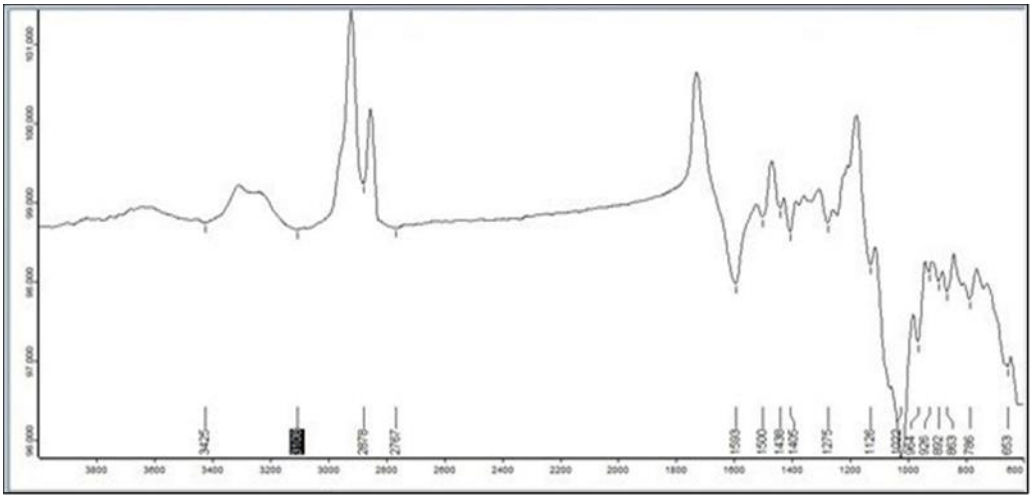

Figure 7 IR Spectra of Drug with other ingredients

The disappearance of an absorption bond & appearance of new bond in final IR-spectra; result interaction between API & excipients. The result of compatibility study using IR spectrometry reveals no difference in wavelength when compared to those obtained for their physical combination with polymer. These findings show that Voriconazole, polymers and other compounds had no interaction. As a result, they are compatible with one another.

3.2. Formulation study

3.2.1. Clarity & pH

The preparations were visually examined for appearance and clarity to check the presence of any particulate matter successfully. The ophthalmic preparations mostly having pH range 6.5 to 7.4 which is generally adjusted by using 0.1 NAOH or Phosphate buffer 7.4. All the prepared formulation batches show the pH within the range as tabled no.6.

3.2.2. Drug content

It specifies the percent of medicament uniformly distributed in the formulation. The optimum drug content for prepared formulation was discovered between 95.55 to 97.78% as shown in table no.6.

3.2.3. Gelling capacity

All the formulations were to be clear. The gelling capacities of prepared formulations are recorded as shown in table.

- + indicates phase transition within 60 sec and gel structure stable for 6 hrs.
- ++ indicates phase transition within 44 sec and gel structure stable for more than 6 hrs.
- +++ indicates phase transition within 30 sec and gel structure stable for long time

Table 6 Evaluation results obtained for In-situ gel formulation

Batch	Clarity	pH	Drug content	Gelling capacity	Viscosity	In vitro release
L1	clear	6.79	92.55	+	192.6	90.12
L2	clear	6.81	92.64	+	240.3	90.33
L3	clear	6.63	94.92	++	249.8	91.02
L4	clear	6.80	93.67	++	398.5	93.32
L5	clear	7.22	97.78	+++	420.0	93.38
L6	clear	7.24	97.75	+++	438.2	93.33
L7	clear	7.16	95.91	+++	459.3	93.28
L8	clear	7.27	92.85	+++	466.4	90.25
L9	clear	7.31	93.90	+++	472.2	86.18

3.2.4. Viscosity

The viscosity measurement was done by using Brookfield viscometer. As the concentration of polymeric component increases, the viscosity of formulation also goes on similar order.

On applying factorial design, Quadratic model was suggested by software for response-1

Factor coding is Coded. Sum of squares is Type III - Partial

The Model F-value of 391.11 implies the model is significant. There is only a 0.02% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, B, A^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve model.

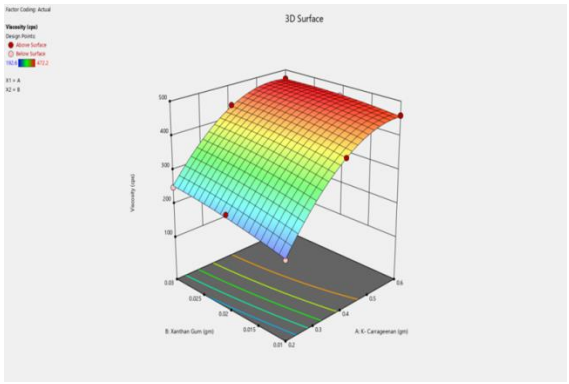

Figure 8 3D surface graph of viscosity

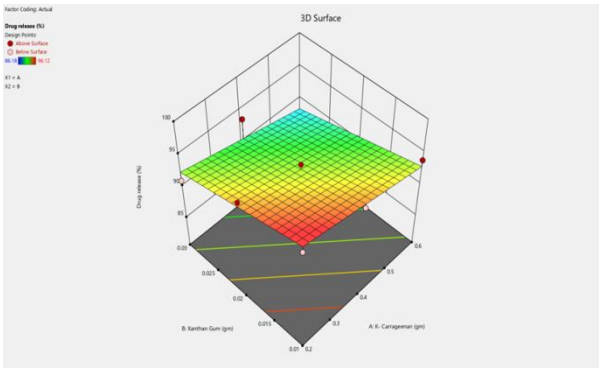

Figure 9 3D surface graph of In vitro drug release

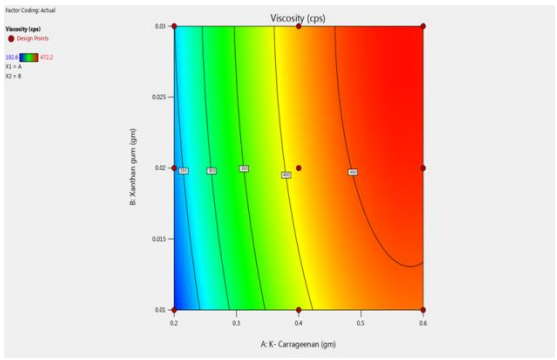

Figure10 Contour plot of viscosity

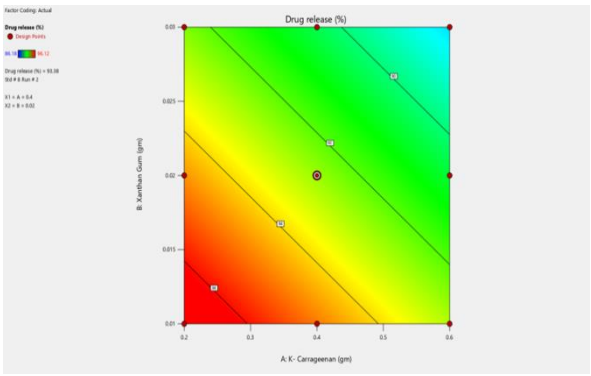

Figure 11 Contour plot of In vitro release

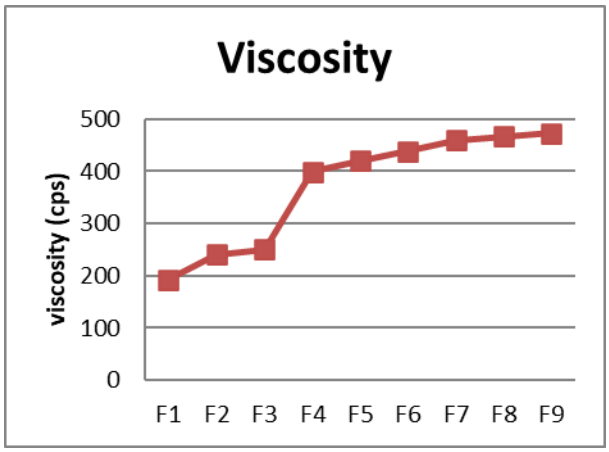

Figure 12 Graph of viscosity of formulation batches

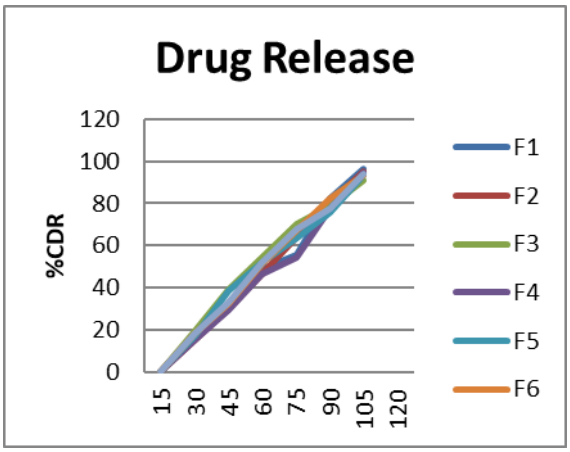

Figure 13 Graph of In vitro releasease of formulation batches

3.2.5. In vitro drug release

The In vitro drug release study was done by using Franz diffusion cell apparatus. The % cumulative drug releases of all batches were found within the range of 86.18-93.38%.

As the concentration of components in the formulation was increases with batch to batch, after some batches the release happens in decreasing order by the effect of increased viscosity.

On applying factorial design, linear model was suggested by software for response.

Factor coding is Coded. Sum of squares is Type III – Partial.

The Model F-value of 8.79 implies the model is significant. There is only a 1.65% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve model

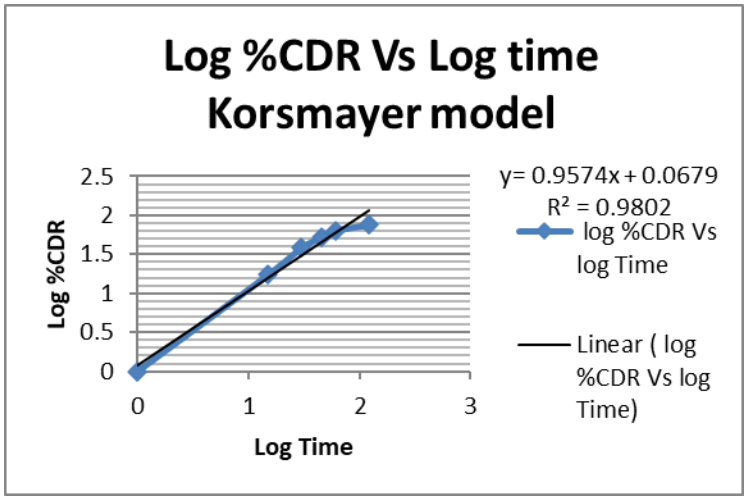

Figure 14 Korsmayer peppas Model

Table 7 Drug release kinetics

kinetic model	R^2	n
Zero order	0.9289	
1st order	0.9686	
Higuchi	0.9447	
Korsmeyer Peppas	0.9802	n= 0.9

3.2.6. Isotonicity Study

It ought to be noticeable in the table, which portrays view of an isotonic control arrangement as NaCl 0.9%, As a result, the arrangements could be described as isotonic. Isotonic arrangements keep up with the trustworthiness of RBCs. Normal human RBCs have a biconcave shape, their diameter is about 7-8 µm, and their thickness is about 2.5 µm. In the wake of noticing utilizing a microscope, the outcomes showed that readiness given an ordinary RBCs that comparative outcome with isotonic control arrangement.

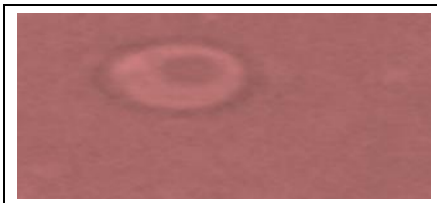

Figure 15 Microscopic view of isotonic control [0.9% NaCl]

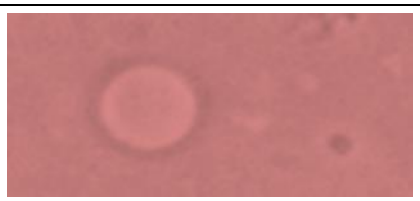

Figure16 Microscopic view of Test

3.2.7. Accelerated Stability Study

No indication of aggregation /precipitation or pH change was observed over a period of 90 days. This fact results revealed that the formulation were stable after such time.

Table 8 Accelerated stability study

Time (Month)	Temperature %RH	Appearance	Parameters			
			% drug content	pH	Gelling capacity	% drug release
1	40±1^{0}c /75%±5%	No change	95.91	7.2	+++	93.37
2		No change	95.91	7.2	+++	93.35
3		No change	95.91	7.2	+++	93.30

4. Discussion

The melting point was determined using the capillary method & was found 1300c so it was indicated the powder sample of Voriconazole is in pure state as per monograph in USP. The melting point was found to be in range, shown in table

Based on the results obtained, it is found that the proposed method of analysis is accurate, reproducible, economical & employed for to check quality control of sample in formulation.

FT-IR study of Voriconazole shows absorption peaks as shown in table, these peaks are of specific functional groups. The wavelengths of respective functional groups are closely matches with the IR- spectra of sample which reveals the sample is voriconazole

According to solubility chart given in IP, the solubility of Voriconazole was found as above soluble in STF and PBS7.4 and in distilled water. Voriconazole has low aqueous solubility which indicates that it is comes under class II of BCS classification system; but according to scientific discussion paper for Vfend from EMEA and rjptonline.org articles tells that 0.4 to 2.7 mg /ml solubility of VCZ in water & it is used for preparation of formulation.

The melting point was determined using the capillary method & it was indicated the powder sample of Polymer is in pure state as per standard. The melting point was found to be within the range, shown in table.

FT-IR study of polymers used shows absorption peaks as shown in table, these peaks are of specific functional groups. The wavelengths of respective functional groups are closely matches with the IR- spectra of sample which confirms the samples are of K- carrageenan & Xanthan gum.

The disappearance of an absorption bond & appearance of new bond in final IR-spectra; result interaction between API & excipients. The result of compatibility study using IR spectrometry reveals no difference in wavelength when compared to those obtained for their physical combination with polymer. These findings show that Voriconazole, polymers and other compounds had no interaction. As a result, they are compatible with one another.

5. Conclusion

The prepared ion triggered in situ gel is evaluated for all the desired parameter like efficacy and safety. Accelerated stability studies show that no change in the drug content. If the Pre-clinical and clinical studies of this work will be carried out in defined way and if passes all the respective criteria‘s of marketed preparation then it is the good alternative for other marketed preparations. Developed formulation successfully overcome drawbacks of the conventional eye drops with fine approach to improve bioavailability, and thus the therapeutic activity. The ease of administration by this formulation will be coupled with its ability to provide sustained release and this could results in less frequent administration, and enhanced patient compliance.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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