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NOVEL IN SITU GEL TO PROVIDE SUSTAIN RELEASE DRUG DELIVERY FOR OCULAR FUNGAL KERATITIS

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ABSTRACT: Ocular deliveries possess a challenging pharmaceutical approach due to poor absorption index through the corneal appendages and washing away of the drug through tears and lachrymal secretion. The ocular appendages lead to provide lesser bioavailability of conventional dosage forms; hence, frequent dosing is advised to get the optimum effect of the medicine. Therefore, in-situ gel offers a promising solution to provide a promising approach to achieve greater residence time and bioavailability of natamycin for ocular fungal infections. In the present study, the in-situ gel was prepared using Carbopol and HPMC, which upon introduction to the ocular cavity, were converted to gel. The prepared solution is kept at the pH of 5.0, which upon instilled into the ocular cavity to get converted to gel. The formulation is further assessed for parameters like viscosity, pH, gelling capacity, drug content, *in-vitro* drug release profile, sterility testing and antifungal activity of the same. The results of the *in-vitro* drug release have been proven for sustain release of the formulation as well as gelling capacity is the predictor of the in-situ gel formation of the system. Hence, it can be utilized for further studies and to be marketed for fungal keratosis of the eye.

INTRODUCTION: AS per the data and statistics provided by the World Health Organization (WHO) corneal diseases are the major cause of vision loss and blindness, second only to cataracts. Fungal keratitis of the cornea is the main cause of corneal blindness; hence it is more virulent as compared to bacterial keratitis. Filamentous fungi, such as Fusarium and Aspergillus and yeast-like fungi, such as Candida, are most associated with keratitis [1, 2]. Natamycin is first-line topical therapy of the fungal keratitis of the ocular region. Natamycin is available in a 5% suspension as an ophthalmic preparation [3]. The formulation needs to improve for poor bioavailability since the suspension cannot adhere to the cornea for a longer period [5].

Additionally, natamycin has been reported to pass the corneal appendage due to the presence of epithelium in the eye, so the conventional dosage form must be administered up to six times daily. Natamycin being the polyene macrolide antimycotic produced by certain strains of the

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actinomycetes Streptomyces natalensis and other closely related Streptomyces species. Its mechanism of action appears to be through the binding of the molecule to the sterol moiety of the fungal cell membrane. The polyenesterol complex alters the permeability of the membrane to produce depletion of essential cellular constituents. Natamycin is ineffective towards *in-vitro* gram-positive or gram-negative bacteria and is found to be predominantly fungicidal [4]. The ocular delivery possesses the challenge in various aspects; hence it has more complex anatomical features and barriers that decrease the bioavailability of the drug at the ocular site [7, 8]. The conventional eye drops almost 90% of market stake have major issues in bioavailability of the dosage form being <5 % of the applied dose. This is attributed to various elimination mechanisms that account for its decreased absorption at application [9].

These are tear turnover, nasolacrimal drainage, protein binding, systemic absorption, enzymatic degradation, and complex penetration barriers (Corneal Barrier, Blood Aqueous Barrier (BAB), and Blood Retinal Barrier (BRB) one of the main downsides of ocular drug delivery is attaining peak concentration of drug at the anticipated site of action in the eye. Several ophthalmic dosage forms such as ointments, eye drop solutions, gels and ocular inserts have been investigated in order to persist the ocular residence time of drugs after the topical application to the eye. These formulations have resulted into increased corneal time and greater bioavailability of the drug.

However, various limitations of such innovations like blurred vision and poor patient compliance resulted from ointments and inserts, respectively; they have not been fully acknowledged. Furthermore, drugs that are administered systemically to employ their action in the ophthalmic system are less likely to bind to the ocular tissues. In addition, Intravitreal injections and barriers in the periocular route pose another problem; hence it can prove to be discomforting for the patients as the same time [10]. The Development of formulations containing smart polymers to undergo a transition in contact with body cavities gives a better therapeutic effect [11]. They are in the solution phase before administration but gels under physiological conditions. The ocular bioavailability of the drugs can be improved by prolonging their residence time in the cul-de-sac and by increasing their corneal permeability Gelation occurs via the cross-linking of polymer chains that can be achieved by covalent bond formation (chemical cross-linking) or non-covalent bond formation (physical cross-linking) [12]. In situ gel-forming systems can be described as low viscosity solutions that undergo a phase transition in the conjunctival cul-de-sac to form viscoelastic gels due to conformational changes of polymers in response to the physiological environment. The rate of in situ gel formation is important because between instillation in the eye, and before a strong gel is formed, the fluid mechanics of the eye produces the solution or weak gel. Both natural, as well as synthetic polymers can be used for the fabrication of in situ gels [13].

The most commonly employed pH-sensitive polymer is carbopol; hence it can damage the surface of the eye due to its acidic pH in the solution form [14]. This problem was solved by partially by combining carbopol with HPMC, a viscous enhancing polymer, which resulted in pH-responsive polymer mixtures that were sol at pH 4 and gel at pH 7.4. A mixture of poly (methacrylic acid) and poly (ethylene glycol) also has been used as a pH-sensitive system to achieve gelation15. Here in the present work, natamycin is incorporated into the polymer matrix of the system being formulated for in-situ gelation. Hence it can effectively prolong the drug release at the application site and improve the corneal bioavailability to treat the fungal infection.

MATERIALS AND METHOD:

Materials: The material used for the preparation of the in-situ gel was obtained from various sources. Natamycin as the drug was procured from Sigma Aldrich, Bangalore. The other excipients such as Carbopol 940, HPMC K4M, HPMC-E50LV, Sodium Chloride, Benzalkonium Chloride, Sodium Hydroxide was purchased from ACS chemicals.

Analytical Method for Natamycin: Accurately weighed 5 mg natamycin was dissolved in 100 ml of 0.1% methanolic glacial acetic acid to get the stock solution of 50 gμ/ml. From this stock solution 20 ml was withdrawn and further diluted to 100 ml with 0.1% methanolic glacial acetic acid to obtain a

concentration of 10 µg/ml. From this stock solution, aliquots of 1, 2, 3, 4, 5, 6, 7, 8 & 9 ml were withdrawn and further diluted to 10 ml with 0.1% methanolic glacial acetic acid to obtain a concentrations range of 1 to 9 µg/ml. The absorbance of the solutions was measured at 304 nm by using a UV-Visible spectrophotometer.

Drug Polymer Compatibility Studies by FT-IR: There is always a possibility of drug-excipients interaction in any formulation due to their intimate contact. The Infra-Red spectra of natamycin and polymers (Carbopol 940, HPMC K4M) and physical mixture of drug and polymer were obtained on Fourier Transform Infrared Spectrophotometer in order to detect the existence of interaction between drug and polymer. The procedure consisted of dispersing a sample (drug alone, polymers alone, and mixture of drug and polymers) in KBr to prepare 10% of mixture and ground generally in mortar-pestle with KBr before being compressed into pellets. This pellet was placed in a light path, and spectrum was recorded at a resolution of 2 cm^{-1} over a frequency range of 4000 to 400 cm^{-1}. The background spectrum of KBr was used as blank for determination.

Method of Preparation of In-Situ Gel: Different concentrations of polymers were used to prepare ophthalmic solutions as per the composition shown in **Table 1.** Required quantity of sodium chloride was dissolved in 75 ml of distilled water, HPMC E-50LV or HPMCK4M was added to the above solution and stirred slowly with a magnetic stirrer, care was taken that no lumps of HPMC was formed during stirring. Carbopol 940 was sprinkled over this solution and allowed to hydrate overnight. A preservative, Benzalkonium chloride, was then added to it. The solution was again stirred with a magnetic stirrer after [24]. From this solution, 15 ml was withdrawn and used for further preparation. Natamycin was added in distilled water and sonicated for 15 min. Now, the drug solution was added to the Carbopol-HPMC solution under constant stirring until a uniform solution was obtained. The pH of the formulation was obtained 5.5 using 0.1N NaOH. Distilled water was then added to make up the volume to 20 ml [16].

TABLE: 1FORMULATION OF IN-SITU GELS OF NATAMYCIN

S. no.	Batch No	Natamycin	Carbopol 940	HPMC-K4M	HPMC-E50LV	Sodium Chloride	Benzalkonium Chloride (ml)	Water (up to ml)
1	F1	5	0.5	0.5	-	0.9	0.01	20
2	F2	5	0.5	1.0	-	0.9	0.01	20
3	F3	5	0.5	1.5	-	0.9	0.01	20
4	F4	5	0.5	-	0.5	0.9	0.01	20
5	F5	5	0.5	-	1.0	0.9	0.01	20
6	F6	5	0.5	-	1.5	0.9	0.01	20
7	F7	5	0.25	0.5	-	0.9	0.01	20
8	F8	5	0.25	1.0	-	0.9	0.01	20
9	F9	5	0.25	1.5	-	0.9	0.01	20
10	F10	5	0.25	-	0.5	0.9	0.01	20
11	F11	5	0.25	-	1.0	0.9	0.01	20
12	F12	5	0.25	-	1.5	0.9	0.01	20
13	F13	5	0.7	-	-	0.9	0.01	20

Physical Characteristics of the Gel [17]: Colour, clarity of the formulation were determined by its physical appearance with visualization. Viscosity of the in-situ gel was measured by a Brookfield viscometer using a spindle No.64, and pH of the formulation was measured using a digital pH meter.

Gelling Capacity [17]: The gelling capacity of the prepared formulation was determined by placing a drop of the formulation in a vial containing 2.0 ml of freshly prepared simulated tear fluid *i.e.,* 7.4 pH and equilibrated at 350 °C and visually assessing the gel formation and noting the time for gelation and the time taken for the gel formed to dissolve. The composition of artificial tear fluid was sodium chloride 0.670 g, sodium bicarbonate 0.200 g, calcium chloride•2H2O 0.008 g, and purified water q.s. 100 g.

Drug Content [17]: The drug content of in situ gel was determined by taking a sample (1 ml) of in-situ gel in a 10ml volumetric flask and diluted with 0.1% methanolic glacial acetic acid. Then the absorbance was measured at max (304 nm) using

UV-spectrophotometer to calculate the percentage of drug content.

***In-vitro* Drug Release [18]:** The release of natamycin from formulations was assessed using a dialysis bag under sink condition for 7 h. Samples of formulation (1.0 mL) containing 50 mg natamycin were enclosed in dialysis bags (mw cut-off 13000-14000), were incubated in 200 mL of artificial tear fluid, pH 7.4 at 370 °C under mild agitation. In order to increase the solubility and maintain sink condition, 1.0% (v/v) tween 80 was added into the dissolution medium. Aliquots (5.0 mL) were collected at predetermined intervals and replaced with equal volume of artificial tear fluid to maintain sink conditions. The amount of the drug in the receiving solution was analyzed by UV spectrophotometer at 304 nm.

Sterility Testing: IP method (2010) was followed for the sterility testing of eye drops. Sterility testing was carried out by incubating formulations for not less than 14 days at 30 to 350 °C in the alternative thioglycolate medium to find the growth of bacteria and at 20 to 250 °C in the soybean-casein digest medium to find the growth of fungi in the formulations [10].

Antifungal Activity: Antifungal efficiency studies were carried out to ascertain the biological activity of sol-to-gel systems against fungus. This was determined in the agar diffusion medium employing "Disc diffusion technique". Sterile suspension of marketed Natamycin eye drops was used as a standard. A layer of nutrient agar (20 ml) seeded with the test microorganism was allowed to solidify in the petri-plate. Discs containing different concentrations of drug were placed on the solidified agar layer with the help of sterile forceps. After keeping petri-plates at room temperature for 4 hr., the plates were incubated at 37 °C for 24 h. The zone of inhibition (ZOI) was compared with that of the standard13.

Accelerated Stability Studies: Short term accelerated stability study was carried out for the period of 45 days for the formulations. The samples were stored at different room temperature storage conditions, elevated temperatures such as 400 °C at 75% RH, and refrigerator (2 to 80 °C). Samples were withdrawn after a month and analyzed for visual appearance, clarity, pH, gelling capacity, and drug content.

RESULTS AND DISCUSSION:

Standard Calibration Curve of Natamycin: Natamycin exhibited its maximum absorbance at 304 nm and obeyed Beer's law in the range of conc. 3-7 µg/ml. Linear regression of absorbance on concentration gave equation y = 0.091 × - 0.022 with a correlation coefficient of 0.997. The calibration curve of natamycin in 0.1%methanolic glacial acetic acid showed in **Fig. 1.** was linear in the concentration range 3-7 µg/ml.

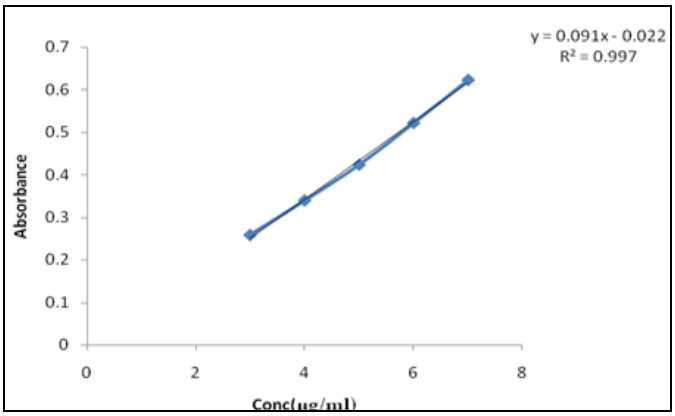

FIG. 1: CALIBRATION CURVE OF NATAMYCIN USING 0.1% METHANOLIC GLACIAL ACETIC ACID

Drug Polymer Compatibility Studies (FTIR): The Natamycin and polymer mixture is evaluated for the physical compatibility of the formulation. Previously scanned drug peaks and polymer mixture peaks are being compared with the final formulation peaks. FT-IR studies show no significant interaction between drug and polymers; hence, all the drug and polymer peaks are seen clearly, and no interaction can be seen in **Fig. 2.**

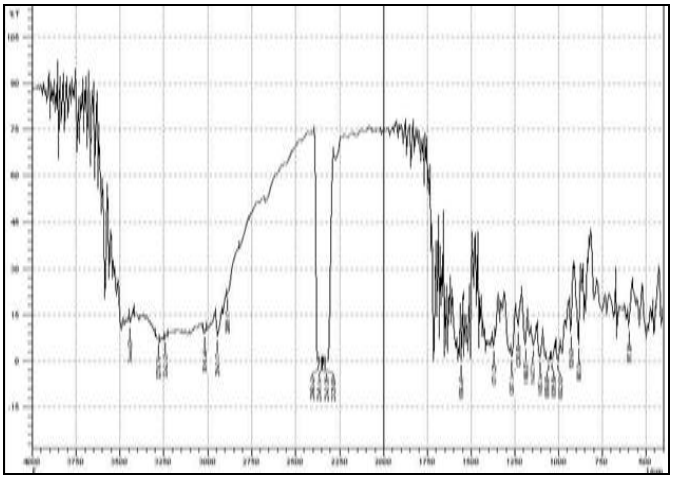

FIG. 2: FT-IR SPECTRA OF FORMULATION

Evaluation of the Dosage Form: Physical properties are as per the requirements and rheological study of the formulations exhibited decrease in viscosity on the increase in shear rate because of the pseudoplastic behaviour of the formulations. Moreover, these formulations' pseudoplastic property may favor sustaining the release of drug in the conjunctival sac of the eye and without blinking difficulty for undergoing shear thinning. The highest drug content was observed in batch no F12.

TABLE: 2: EVALUATION OF IN-SITU GELS

Batch	Colour	Clarity	pH	Gelling Time(seconds)	Drug Content ± S.D (%)	Viscosity (cps)
F1	Light yellow	Cloudy	5.5	2	90.10 ± 0.770	500
F2	Light yellow	Cloudy	5.5	2	90.54 ± 0.551	500
F3	Light yellow	Cloudy	5.5	2	90.32 ± 0.675	500
F4	Light yellow	Cloudy	5.5	2	92.30 ± 0.802	500
F5	Light yellow	Cloudy	5.5	2	91.86 ± 0.598	500
F6	Light yellow	Cloudy	5.5	2	93.40 ± 0.636	500
F7	Light yellow	Cloudy	5.5	2	93.84 ± 0.489	500
F8	Light yellow	Cloudy	5.5	2	90.98 ± 0.875	500
F9	Light yellow	Cloudy	5.5	2	94.50 ± 0.412	500
F10	Light yellow	Cloudy	5.5	2	93.62 ± 0.654	500
F11	Light yellow	Cloudy	5.5	2	92.30 ± 0.325	500
F12	Light yellow	Cloudy	5.5	2	94.06 ± 0.139	500

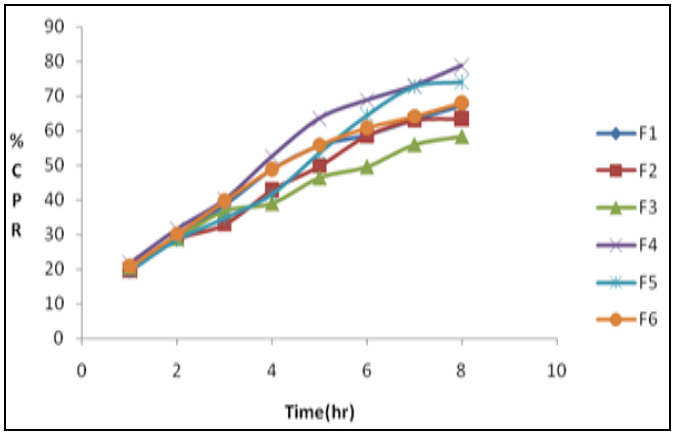

FIG. 3: RUG RELEASE STUDY OF BATCH F1 TO F6

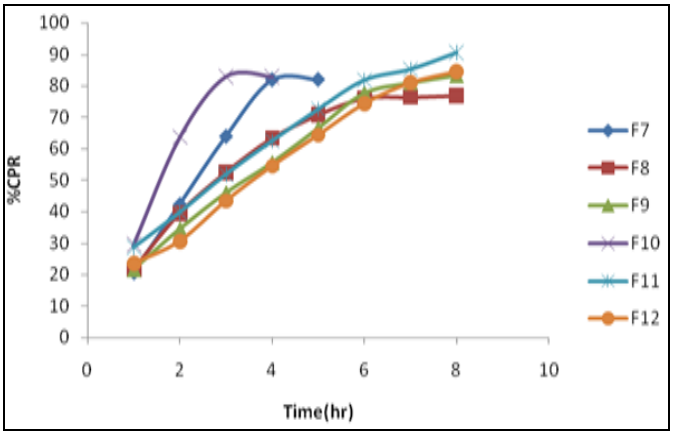

FIG. 4: DRUG RELEASE STUDY OF BATCH F7 TO F12

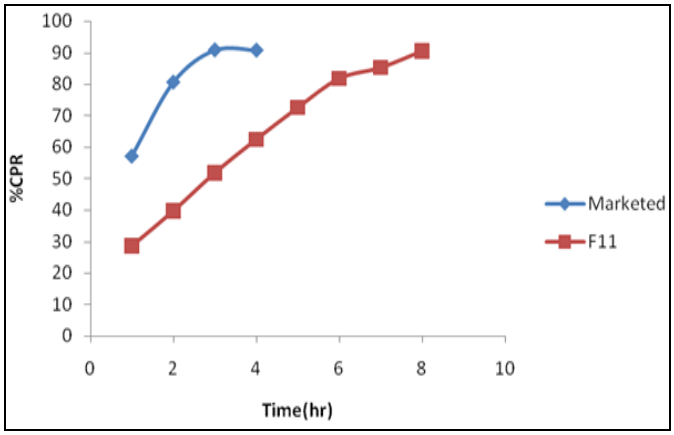

FIG. 5: DRUG RELEASE STUDY OF BATCH F11 AND MARKETED FORMULATION

***In-vitro* Drug Release [19]:** The release profiles of the formulations were indicative that the formulation F-11 showed a better sustaining effect amongst all formulations. This may be due to the optimum concentration of carbopol 940 (0.25%) along with HPMC E50LV (1.0%) in the formulation F-11. The *in-vitro* release study was conducted using Phosphate buffer pH 7; the

diffusion studies show better release of the formulated product. The *in-vitro* release profile of F-11 was then compared with the marketed formulation of natamycin. The release studies found that the drug release was about 57.23% and 28.48% for marketed product and F11 respectively after 1 h. And at the end of two hours, the drug release was 80.68% and 39.63% for marketed product and F-11, respectively. The comparative release was shown in **FIG. 3, 4, 5.** Results indicated that the drug release was significantly prolonged by using the in situ gelling system due to the addition of the polymers carbopol 940 and HPMC (E50LV). The high viscosity plays an important role in controlling the release of drugs from the formulations. When the polymer concentration increases, drug release decreases, and when polymer concentration decreases, drug release from the formulation increases.

Sterility Test: The formulation F-11 passed the test for sterility as there was no appearance of turbidity and hence no evidence of microbial growth when incubated for not less than 14 days at 30-350 °C in case of alternative thioglycolate medium and at 20-250 °C in the case of soybean casein digest medium. Autoclaving could be considered AS A suitable method for sterilization of this product.

Antifungal Activity: The results of the antifungal efficacy tests were shown in **Table 3.** The study indicated that natamycin retained its antifungal efficacy even after being formulated as an in situ gelling system. The antifungal activity of natamycin in situ gel formulation may be due to a fairly rapid initial release of drug into the viscous solution formed by dissolution of gel, followed by formation of a drug reservoir that permits the drug to be released to the target site relatively slowly.

TABLE: 3: RESULTS OF ANTIFUNGAL STUDY

Concentration (µg/ml)	Standard ZOI (mm)	Test (F11) ZOI (mm)	Percent efficacy
Candida albicans			
5	13	12	92
50	22	20	91
500	25	23	92
Aspergillus fumigates			
5	7	7	100
50	16	10	63
500	30	24	80

TABLE: 4: RESULTS OF STABILITY STUDY

Evaluation Parameters	After One Month Time Period(F11) Storage Condition		
	2° To 8 °C	Room Temperature	At 40 °C
Appearance	Light Yellow	Light Yellow	Light Yellow
Ph	5.6	5.3	5.2
Gelling Capacity	+++	+++	+++
Drug Content	92.20%	92.69%	91.00%

CONCLUSION: The present work optimized the in-situ gel for ocular delivery of natamycin using a combination of in-situ gelling systems of natamycin and evaluated for various parameters to provide the scientific result for overcoming the most serious challenge of the formulation is capable of providing sustained release of the drug. The pre-formulation data for the drug-polymer compatibility was found to be satisfactory to further optimization of the formulation. The optimized polymer ratio for highest *in-vitro* release of the drug is 0.25:1 of Carbopol 940: HPMCE50LV. This formulation has been studied further for sterility testing and compared with marketed formulation for sustained release for up to 8 h of the formulation using phosphate buffer medium. The *in-vitro* antifungal activity of the formulation was found to be effective satisfactory while using Aspergillus fumigates, Candida albicans species. It is indicative of better fungal activity for a longer period of time. The present investigation directs the formulation of antifungal eye drops, which requires frequent dosing; hence it can be overcome by in-situ gelling technique. To provide the further base to this research, *in-vivo* studies can be designed as well as to provide a better scale up for the production; other statical methods can be employed to provide the accurate and effective dosage for industry application.

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