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NOVEL LONG OCULAR RETENTIVE FORMULATION DEVELOPMENT OF MICONAZOLE OPHTHALMIC SUSPENSION WITH HELP OF POLYMER PLATFORM SYSTEM

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ABSTRACT

Instilled ophthalmic formulations may not be completely available for eliciting therapeutic action because of various reasons such as rapid tear drainage, blinking of eye, lower residence time of ophthalmic formulation in eye and lower cul-de sac volume. The objective of present work was to develop long retentive miconazole ophthalmic suspension based on polymer platform system of carbopol 974 P and xanthan gum which was pre-identified by means of experimental design study. Carbopol 974 P and xanthan gum were used as gelling agent. The developed formulations were characterized for homogeneity, pH, particle size, viscosity, osmolality, rheology study, mucoadhesive strength, contact angle, assay of miconazole and benzalkonium chloride, degradation product, in vitro drug release, eye irritation test and pharmacodynamic efficacy study. A stable long retentive miconazole ophthalmic formulation was developed based on principles of quality by design and as per industrial standards.

KEYWORDS: Polymer, ocular long retentive, miconazole, ophthalmic suspension.

1. INTRODUCTION

Instilled ophthalmic formulations may not be completely available for eliciting therapeutic action because of various reasons such as rapid tear drainage, blinking of eye, lower residence time of ophthalmic formulation in eye and lower cul-de sac volume.[2,5] There are different methodologies available to prolong the drug release in eye however these types of formulations require specialized manufacturing equipment and scalability has always

remained a challenge. Hence prolonging the eye residence time with use of polymer becomes the most cost effective method. Researcher usually selects 2-3 polymers & performs the studies to identify the synergistic impact. It is merely difficult to study all the polymers at once in single study for identification of synergistic effect between various polymers. Difficulty in industry or academics lies in evaluation of various polymers at once which is time consuming. This kind of study has its own limitation of number of experimental trials to be conducted.

Formulation adhesiveness/retention in the eye is the function of viscosity being directly proportional; it plays a major role to extend the drug release by increasing the contact time in eye with help of muco-adhesive forces or by polymer inter-penetrated network (IPN). Choices of selection of polymeric ingredient were based on their individual viscosities. Significant synergies were considered for those combinations which have higher viscosities compared to their individual viscosities at lower concentrations. These systems would result in more viscous solution which remains in the eye for a longer period of time and thus enhances the extended release of the medicament.

The identified polymer system can be incorporated in different drugs to have better mucoadhesive properties. Syngerstic polymer ratio is already been identified for polymer system with experimental design previously published in "Identification of Polymer Synergy with Help of DOE" in International Journal of Emerging Technologies in Engineering Research (IJETER) Volume 6, Issue 1, January (2018).[7] This polymer system can be incorporated with different drugs in identified synergistic ratio with different concentration to achieve the desired product quality attributes.

There is very less work done in area of antifungal ophthalmic segment, hence antifungal drug miconazole was selected for formulation development.

2.0 MATERIALS AND METHODS

2.1 Materials

Miconazole was sourced from FDC limited. Monobasic sodium phosphate dihydrate, dibasic sodium phosphate dihydrate, sodium hydroxide, hydrochloric acid were procured from Merck. Propylene glycol was sourced from Dow chemicals. Carbopol 974 P NF was sourced from Lubrizol. Xanthan gum (xantural 75) was procured from CP Kelco. Benzalkonium chloride was procured from novonordisk pharmatech.

2.2 Methods

Manufacturing composition detail is summarized in table 1.

Table 1: Formulation composition of miconazole.

S.no.	Ingredients	%w/v
1	Miconazole	1
2	Benzalkonium chloride	0.025
3	Carbopol 974 P NF	0.125
4	Xanthan gum (xantural 75)	0.375
5	Monobasic sodium phosphate dihydrate	0.1
6	Dibasic sodium phosphate dihydrate	0.05
7	Propylene glycol	1.92
8	Sodium hydroxide	q.s.
9	Water for injection	q.s.

q.s. quantity sufficient

In 25% of total batch quantity of water for injection carbopol 974 P was added slowly under stirring to form a homogenous dispersion. This dispersion was autoclaved at 121 degree centigrade for 15 minutes. In 30% of total batch quantity of water for injection ethylene oxide sterilized xanthan gum was added slowly under stirring to form a homogenous dispersion. Carbopol 974P solution added to xanthan gum solution under stirring.

In 10% of total batch quantity of water for injection monobasic sodium phosphate & dibasic sodium phosphate were added. In 5% of total batch quantity of water for injection benzalkonium chloride was dissolved and added to buffer phase. Propylene glycol was added to buffer phase. Buffer phase solution was filtered using 0.22 micron polyethersulfone filter. Ethylene oxide sterilized miconazole was added to sterile buffer phase mixture and mixed for 15 minutes and further homogenized using rotar stator homogenizer. Drug phase was added to polymer phase and mixed for 30 minutes. Finished product pH was adjusted to 6 to7 with 0.22 micron polyethersulfone filtered 1 N sodium hydroxide solution. Final volume was made up using water for injection and suspension was stirred for 30 minutes. To understand the impact of pH on degradation product extreme pH ranges samples were also manufactured and stability studies were conducted. To understand the impact of sterilization of container closure system optimum pH formulation was packed in gamma and ethylene oxide sterilized low density polyethylene bottles with high density cap closure and stability studies were conducted.

3.0 Sterilization method for miconazole

Sterility is a key issue in manufacture and use of ophthalmic products. Microbial content or bioburden of the raw materials, in-process intermediates, and drug substance or active product ingredient are potential sources of contamination and require incoming testing of ingredients. Major source of microbial load could be due to polymers & drug, being high in concentration in the formulation.[4] The most used methods of achieving a sterile product are moist heat sterilization, dry heat sterilization, gas sterilization, sterilization by ionizing radiation, sterilization by filtration, and aseptic processing.[1]

Due to low melting point of miconazole[4], autoclaving & dry heat sterilization technique was not evaluated. Miconazole was sterilized by gamma radiation & ethylene oxide (ETO).

4.0 Characterization of miconazole ophthalmic suspension

4.1 Differential scanning calorimetry studies

Thermogram of the miconazole powder and polymer mixture formulation were obtained from (TA instruments [differential scanning calorimetry] universal V4. 5A. DSC curves of pure samples were compared to that obtained from 1:0.125:0.375 mixture of the miconazole: carbopol 974: xanthan gum. Miconazole and physical mixture along with polymer powder were sealed in an aluminum crucible and heated at the rate of 10°C/minutes up to 400°C. The exact peak temperature and melting point and heat of fusion were automatically calculated. It was assumed that the thermal properties (melting point, change in enthalpy, etc.) of blends were the sum of the individual components if the components are compatible with each other. An absence, a significant shift in the melting of the components or appearance of a new exo/endothermic peak and/or variation in the corresponding enthalpies of reaction in the physical mixture indicates incompatibility. However, slight changes in peak shape height and width are expected due to possible differences in the mixture geometry.

4.2 Physicochemical characterization

Appearance of formulation was checked by visual observation under light for homogeneity. pH was checked using digital pH meter (Metler Toledo.) and viscosity was determined using Brookfield's viscometer (LVDV II^+ PRO model) in small volume adapter using S31 spindle at 5 rpm, Osmolality was measured on undiluted samples using an Osmometer- Model 3250 of Advanced Instruments, Inc. This instrument uses the principle of measuring osmolality precisely by measuring the difference in freezing point depression due to presence of solutes in the test product and in solvent alone.

4.3 Rheology studies

To understand the formulated product structural bulk behavior under stress, rheology studies were evaluated using Anton Paar rheometer (Rheocompass model) with cone and plate geometry. The samples of the formulations were carefully applied to the lower plate to minimize sample shearing and were allowed to equilibrate for 3 minutes prior to analysis. To simulate the formulation behavior with eye blinking rate viscosity with application of shear rate was done. Storage modulus G' which represents the cohesive property, longer or extended retentive formulation and Loss modulus G" which represents adhesive property with substrate in this case eye was studied. Amplitude sweep was studied to understand the deformation behavior of samples in the non-destructive deformation range and to determine the upper limit of this range in term of yield stress. Yield stress is measure of eye residence time. After the yield stress point with increasing deformation, the inner structure gets softer and starts to flow or breaks down in a brittle way. Viscoelastic region of the product was identified.

Frequency sweep was studied to understand the time-dependent product structural behavior of a sample in the non-destructive deformation range. The oscillation frequency was increased from 0 to 100 radian/sec while amplitude was kept constant.

4.4 Mucoadhesive strength

The mucoadhesive force between the sample probe and the formulation was assessed in a detachment test using a TA-XT plus texture analyzer (Stable Micro Systems, Surrey, UK). Ophthalmic suspension was kept into sample holder and the analytical probe was lowered to begin the test. The probe moved at a constant speed (0.1 $mm \cdot s^{-1}$) on the surface of the formulation. The probe and the formulation were kept in contact for 60 seconds, and 5 g force was applied during this interval. After 60 seconds, the probe was drawn upward (0.1 mm·s−1) until the contact between the surfaces was broken. For comparison purpose the miconazole ophthalmic formulation devoid of polymer system (immediate release formulation) was used. The Texture Exponent 32 software (Stable Micro Systems, Surrey, UK) was used to determine the force required for the detachment (F_{adh}) and the work of adhesion (W_{adh}) (the area under the force/distance curve). Triplicates reading were taken to understand the variability.

4.5 Contact angle

Contact angle is measurement of spreading and wetting ability of the formulation. Formulation is non- wetting and non-spreading if the contact angle is greater than 90^{o}, and formulation will be clinically ineffective in that case. For comparison purpose miconazole ophthalmic suspension along with only placebo formulation comprising of polymer platform was evaluated using goniometer.

4.6 Zeta potential

Zeta potential is a measure of the magnitude of the electrostatic or charge repulsion/attraction between particles and is one of the fundamental parameters known to affect stability. Its measurement brings detailed insight into the causes of dispersion, aggregation or flocculation. Zeta potential was evaluated using Zetasizer Ver. 7.12.

4.7 Particle size analysis

Particle size is important criteria for ophthalmic formulation. Generally acceptance criteria for ophthalmic suspension formulation to have particle size below 15 micron. Formulation particle size was analysed by motic microscopy.

4.8 Miconazole assay

Sample was prepared by weighing formulation equivalent to 40 mg of miconazole, in to a 100 ml volumetric flask. 70 ml prefiltered and degassed methanol was added, flask mixed for 5-6 minutes and sonicated for 1-2 minutes to ensure the formulation is completely dissolved. Further diluted the sample with prefiltered and degassed methanol to 100 ml volume and mixed. Sample was filtered through a 0.45 micron glass microfiber filter or PVDF filter. Initial 3-4 ml filtrate was discarded and transferred in to HPLC vial. Standard was prepared by weighing 40 mg miconazole working standard and further addition of prefiltered degassed methanol to 100 ml volumetric flask.

Mobile phase, stationary phase and chromatographic conditions were selected based on drug product profile and available literature information. Further stability indicating HPLC method was developed.

Chromatographic conditions

Column : Kromasil C4, 150 mmX4.0mm, 5 µm

Detector: UV 235 nm

Column temperature: 30^0C

Sampler temperature: 10^0C

Injection rate : 10 µL

Flow rate : 1.2 ml/minute

Run time : 20 minute

Retention time : About 10.6 minute

4.9 Benzalkonium chloride (BKC) assay

Standard was prepared by weighing about 50 mg of BKC in to 100 ml volumetric flask. Acetonitrile was added to make up the volume and mixed. 5.0 ml of this sample was further diluted to 100 ml with acetonitrile, filtered though 0.45 micron syringe glass filter. Sample was prepared as of similar standard concentration. Mobile phase, stationary phase and chromatographic conditions were selected based on available literature information. Further stability indicating HPLC method was developed with UV detector.

4.10 Degradation product

Same chromatographic conditions as of assay were used for estimation of degradation product however further composition of mobile phase and run time extended to ensure adequate separation of peak of interest.

4.11 In-vitro drug release

Dissolution method was customized by using 2 g sample in sample holder covered with 450 micron membrane and dispersed in 200 ml of simulated tear fluid with 0.5% SLS, paddle 75 rpm. Assay method was adopted for drug release. Concentration of standard and samples were modified accordingly.

4.12 Antimicrobial efficacy studies

Antimicrobial preservative testing at lower concentration of preservative i.e. 90% of label claim is tested, as there is a drop in levels of benzalkonium chloride to around 90% of the label claim at the end of 6 months accelerated stability at 40ºC/25% RH, hence worst case study was performed.

4.13 Accelerated stability studies

Finished product formulation of pH (6.0, 6.5 and 7.0) was filled in low density polyethylene bottles with high density cap closure. Optimum pH formulation was packed in gamma and

ethylene oxide sterilized low density polyethylene bottles with high density cap closure to understand the impact on sterilization of container closure system. Samples were kept at stability studies as per internal conference of harmonization (ICH) guideline[8] for semipermeable container at 40 ± 2°C and 25 ± 5% RH and 25 ± 2°C and 40 ± 5% RH for 6 month.

4.14 Ocular irritation studies

Ocular irritation study was performed as per protocol number MET.IOP.IAEC.2017-18.PR-08 at MET institute of Nashik. New zealand white rabbits (three), each weighing about 2 to 3 kg were used for study. A dose of one drop of the test formulation was instilled in to right eye of each rabbit. The left eye served as control. The eyes of the rabbits were carefully examined, observed at 1 hr and 24 hours, 48 hours and 72 hours post application and the observations extended to determine the reversibility or irreversibility till the end of the observation period of 7 days. Score methodology was used for evaluation of cornea opacity, iris, conjunctivae redness, chemosis for eye lids and/or nictating membranes.[3]

4.15 Pharmacodynamic studies (In-vivo antifungal efficacy studies)

Antifungal efficacy study was performed in as per protocol number MVC/IAEC/ 10 /2019 at Bombay veterinary college, Mumbai. Wistar rat (six) of both genders, each weighing about 150-250 g was used for study. The animals were housed in individual cages, and the experiments were conducted in a sanitized room at a temperature maintained around 25 °C. Immunosupression in all test groups animals were induced by cyclophosphamide marketed preparation. The optimized dose of the drug used was 8 mg/kg bodyweight for 15 consequent days through oral route. The suppressed animals showed the signs of decrease body weight dullness and other motor responses. Fungal infection was induced by inoculating live culture of candida albicans species of 10^{-8} cfu/ml concentration. The initial marginal injury was done on eye lid membrane to hasten the infection. Further inflammation and all markers like mucous membranes, opacity of lens, etc were taken in to consideration before instillation of miconazole ophthalmic formulation. Another group of fungi induced infected animals (six) was kept as positive control. A dose of two drops of the test formulation was instilled in to eyes of each rat twice every day. The eyes of the rats were carefully examined, observed everyday post application and the observations extended till complete recovery of fungal infection had happened. Score methodology was used for evaluation of chemosis, eyelid membranes (hyperaemia), corneal membrane opacity, corneal reflex, blindness or vision

impairment. A score of 0 to 5 was used for all physiological observations except for corneal reflex scale of 5-0 were used, which indicates 5 scale is normal reflex action.

5.0 RESULTS AND DISCUSSION

5.1 Sterilization method for miconazole

Based on degradation data miconazole ethylene oxide sterilization was preferred over gamma sterilization for formulation development.

Table 2: Degradation data of different sterilization technique of miconazole.

Impurity	Limit	Miconazole un treated	Miconazole ethylene oxide sterilized	Miconazole gamma sterilized
Miconazole impurity I	NMT 0.15%	0.01	0.01	0.08
Miconazole impurity II	NMT 0.10%	ND	ND	ND
Miconazole impurity III	NMT 0.10%	ND	ND	ND
Miconazole impurity IV	NMT 0.15%	0.01	0.005	0.04
Miconazole impurity V	NMT 0.15%	ND	ND	ND
Any other unspecified impurity	NMT 0.10% of each	0.01	0.02	0.08
Total impurity	NMT 1.0 %	0.04	0.06	0.37

NMT: Not more than ND: Not detected

5.2 Differential scanning calorimetry studies

Miconazole was found to be compatible with identified polymer system. Figure 1 and figure 2 shows DSC scan of miconazole and DSC scan of miconazole and polymer mixture.

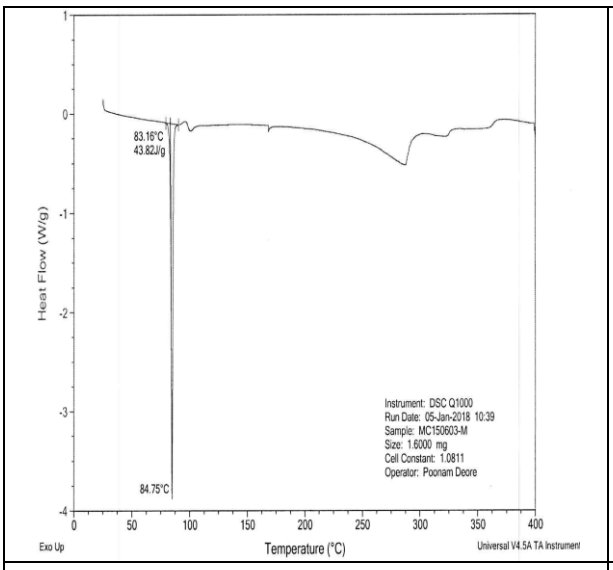

Fig 1: DSC scan of miconazole.

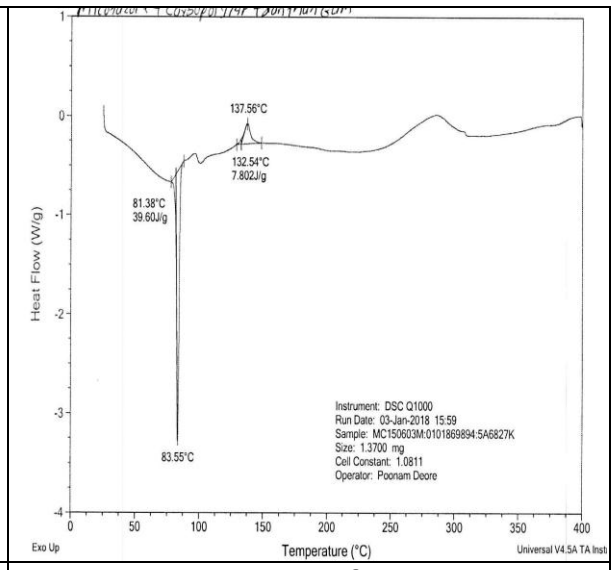

Fig 2: DSC scan of miconazole & polymer mixture.

5.3 Physicochemical characterization

White to off white homogenous suspension was formed. pH range of 6 to 7 was also studied in stability & there was no pH drop observed in stability. Also there was no significant drop in viscosity & osmolality observed in stability. There was no impact of container closure sterilization ethylene oxide (ETO) and gamma on physical parameters such as pH, viscosity and osmolality was observed. Figure 3 shows viscosity data of pH range and container closure sterilization.

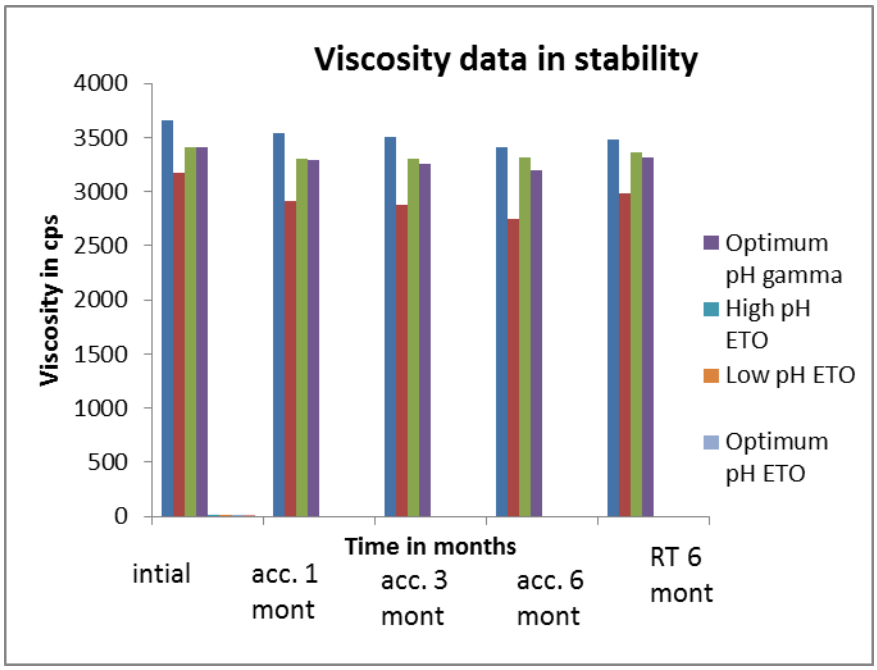

Fig 3: Viscosity data of pH range & container closure sterilization.

5.4 Rheology study

- Viscosity of formulation decreases with application of shear rate of 1000 sec-1 which indicates formulation showed pseudoplastic behavior.
- Storage modulus G' represents the stored deformation energy, higher extended release, elastic portion or solid state of viscoelastic behavior and loss modulus G" characterizes the deformation energy lost (dissipated) through internal friction when flowing. Viscoelastic solids with G' > G" have a higher storage modulus than loss modulus. This is due to links inside the material, for example chemical bonds or physical-chemical interactions. Storage modulus G’ which represents the elastic or cohesive property was found to be about 15.491 for formulation. Higher G’ modulus gives longer retention or extended release as well as good flow.

- G" loss modulus which represents the adhesive property with any other substrate in this case it would be eye cornea. G" was 4.03 for the formulation. An amplitude sweep test was performed to define the fluid linear viscoelastic region (LVER), the results showed that this region was at 100% shear strain for the formulation which indicates formulation has good structural behavior. Angular frequency of 0 to 100 rad/sec (radian/sec measurement of rotational speed) was applied to understand the product structural behavior. tan δ was less than 1 till an angular frequency of 1.36 rad/sec which shows gel kind nature & further it increased more than 1 which shows fluid like nature. Yield stress value studied over amplitude sweep which is measure of residence time of the formulation with other substrate in this it would be eye cornea was observed to 1.385 Pa for the formulation. Figure 4 and figure 5 shows frequency sweep study data. Figure 6 is Shear strain vs. storage modulus and loss modulus. Figure 7 is viscosity vs. shear rate graph.

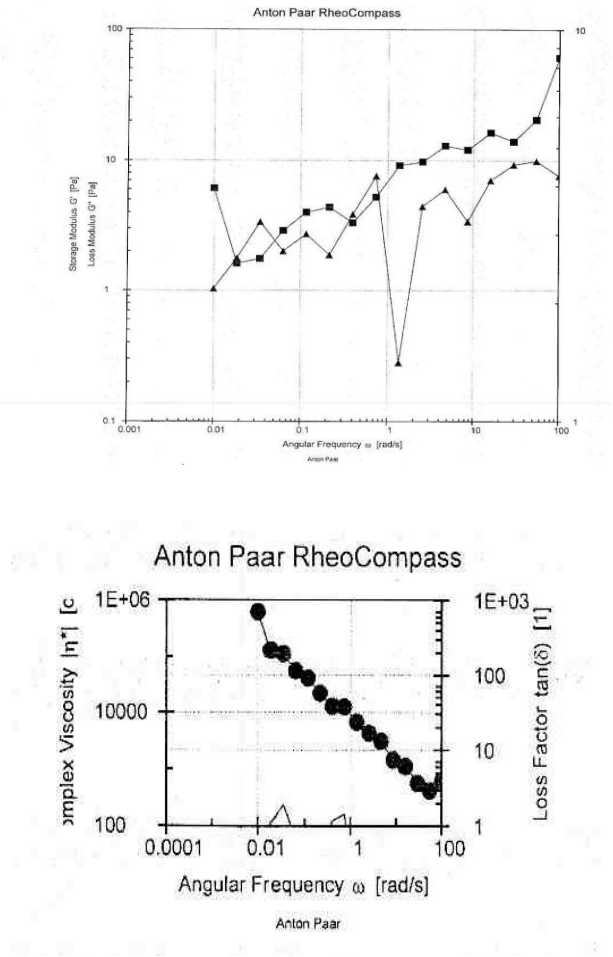

Fig. 4 & 5: Frequency sweep study data.

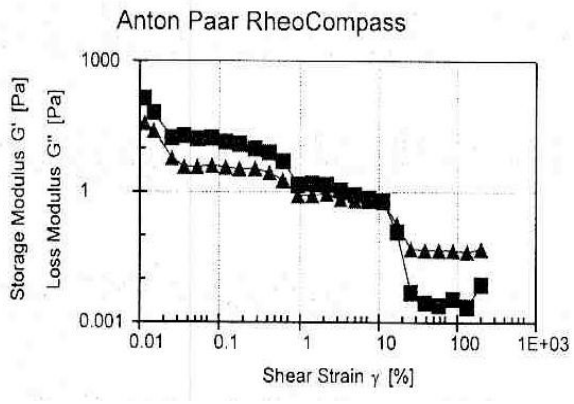

Fig. 6: Shear strain vs. storage modulus and loss modulus.

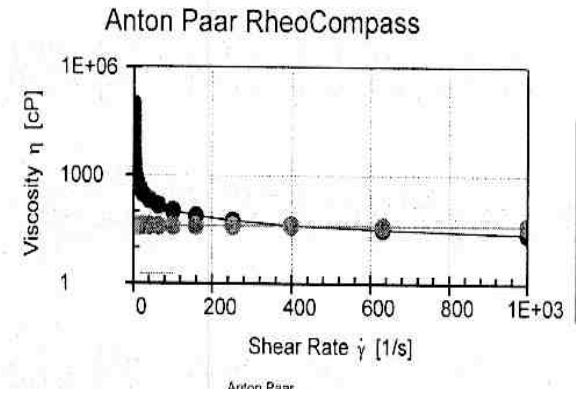

Fig. 7: Viscosity vs. shear rate graph.

5.5 Mucoadhesive strength

Mucoadhesive force i.e. force of adhesiveness (F_{adh}) and work of adhesion (W_{adh}) of miconazole long retentive formulation was found to be higher than immediate release formulation devoid of any polymers. This concludes that polymer system increased the mucoadhesive strength of developed miconazole ophthalmic suspension which would remain in eye for longer time. The F_{adh} value was 0.046 N and 0.011 N respectively for long retentive and immediate release formulation. The W_{adh} value was 0.431 N.sec and 0.196 N.sec respectively for long retentive and immediate release formulation. Figure 8 and figure 9 shows mucoadhesive force for long retentive and immediate release formulation.

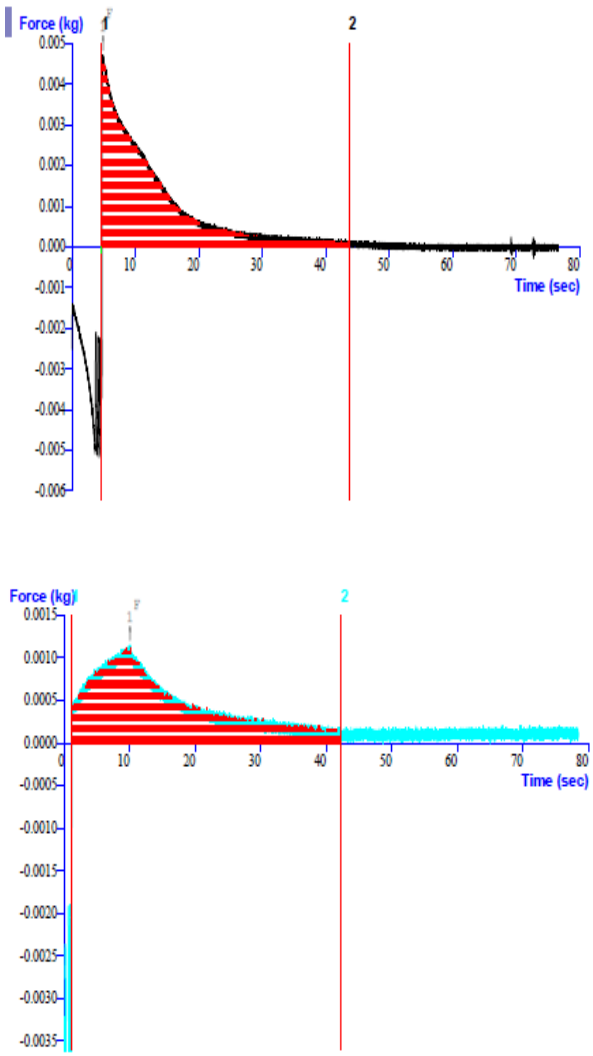

Fig. 8 and 9: Mucoadhesive force for long retentive and immediate release formulation.

5.6 Contact angle: Contact angle of miconazole ophthalmic suspension was found to be 67.342 whereas for only placebo polymer it was 56.403. Contact angle data proves that polymer platform as such also has good wetting and spreading properties & incorporation of hydrophobic drugs also doesn't alter much these properties.

5.7 Zeta potential: Zeta potential of miconazole ophthalmic suspension was - 42.5 mv shows the developed suspension is electrically stabilized and has good stability behavior against coagulation/flocculation.

5.8 Particle size analysis: Particle size data of pH range formulation and formulation packed in gamma and ETO sterilized container closure was below 10 micron. Table 3 shows particle size data in stability.

Table 3: Particle size data in stability.

Particle size data (d90) in micron					
Condition	**Months**	**High pH ETO**	**Low pH ETO**	**Optimum pH ETO**	**Optimum pH gamma**
Initial	0	6.93	6.72	6.82	6.77
40°C/25%RH	1	6.43	8.0	6.54	6.66
40°C/25%RH	3	7.32	7.69	7.21	6.87
40°C/25%RH	6	6.43	8.2	6.8	6.57
25°C/40%RH	6	6.53	8.43	6.7	6.88

5.9 Miconazole assay and impact of pH & sterilization of container closure system on assay

Across the pH range 6.0, 6.5 and 7.0 (low, optimum and high) the miconazole content was well within specification limit of 90.0 to 110.0% which indicates formulation remains stable across pH range of 6.0 to 7.0. Gamma sterilization of container closure has more deleterious effect on stability; miconazole content was beyond the acceptance limit as compared to that of ethylene oxide sterilization (ETO). ETO sterilization is better choice for container closure. Figure 10 shows miconazole assay in stability.

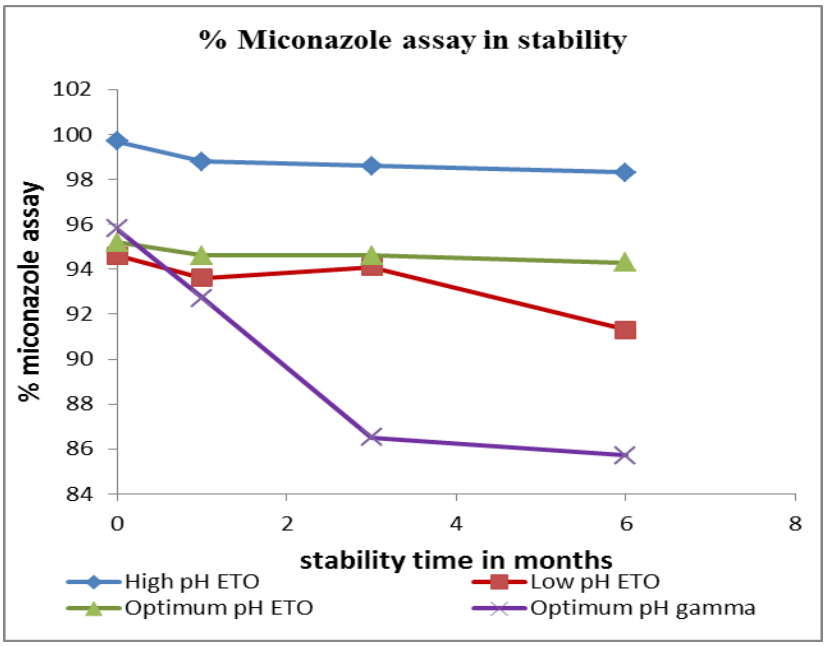

Fig. 10: Miconazole assay in stability.

5.10 Benzalkonium chloride assay and impact of pH & sterilization of container closure system on assay

Across the pH range 6.0, 6.5 and 7.0 (low, optimum and high) the benzalkonium chloride content was well within specification limit of 90.0 to 110.0% which indicates formulation

remains stable across pH range of 6.0 to 7.0. There was no impact of container closure sterilization on benzalkonium chloride assay was observed. Figure 11 shows benzalkonium chloride assay in stability.

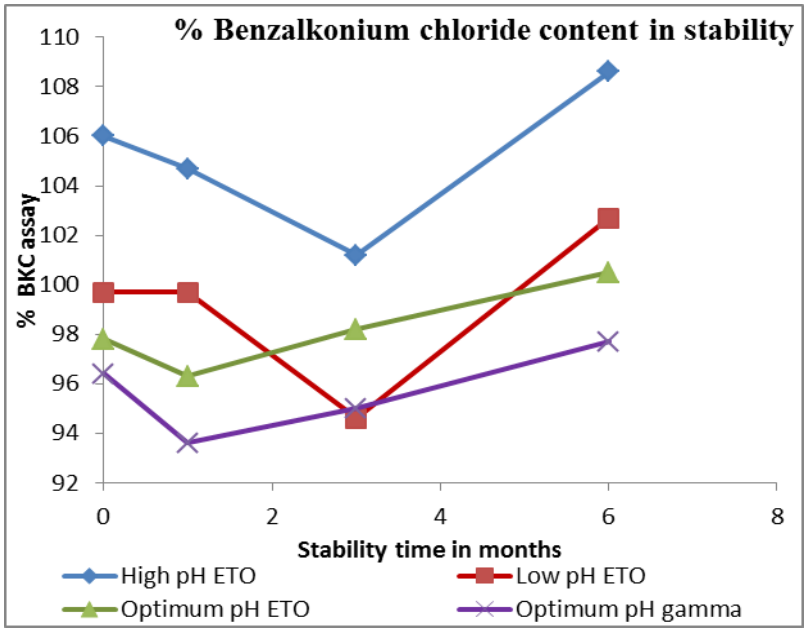

Fig. 11: Benzalkonium chloride assay in stability.

5.11 Degradation product

Gamma sterilization container closure system showed higher degradation product hence ethylene oxide sterilization is better choice. Degradation products were found to be similar across the pH range.

5.12 In vitro drug release study

Polymer system helped to extend the drug release. Extended release formulation showed about 90 percent drug release in 24 hours whereas immediate release formulation released in 1 hour. Figure 12 shows comparative drug release for extended release and immediate release formulation.

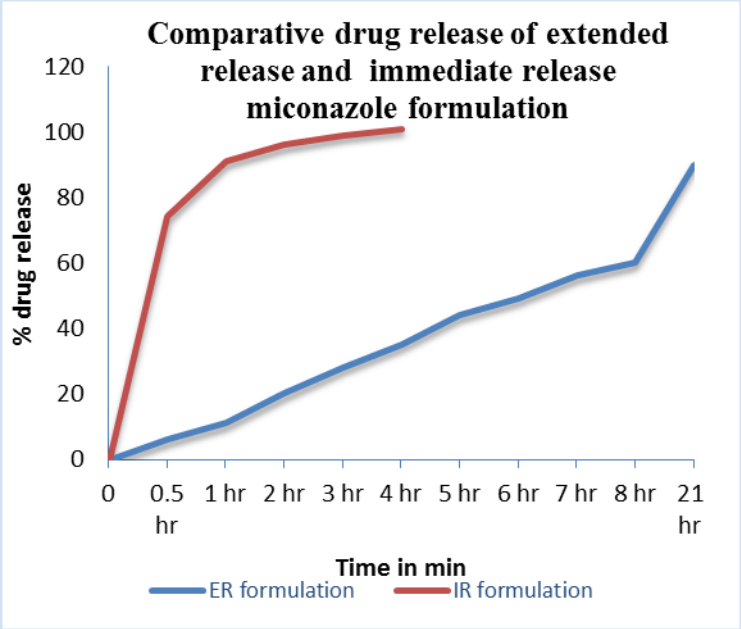

Fig. 12: Comparative drug release for extended release and immediate release formulation.

5.13 Antimicrobial efficacy studies

The results of AET test 90% benzalkonium chloride concentration is summarized below: Table 4 shows summary results of Antimicrobial effectiveness test at lower concentration of benzalkonium chloride (90% of label claim).

Table 4: Summary results of Antimicrobial effectiveness test at lower concentration of benzalkonium chloride (90% of label claim).

Name of microbial culture Bacteria	**Log reduction in viable count from initial calculated viable count at '0' hour**		**Log of viable count at 28 days**	**USP compliance**
	After 7 days (Limit: NLT 1)	**After 14 days (Limit: NLT 3)**	**Limit: No increase from 14 days**	
Escherichia coli ATCC 8739	5.62	5.62	No increase	Complies
Pseudomonas aeruginosa ATCC 9027	5.64	5.64	No increase	Complies
Staphylococcus aureus ATCC 6538	3.80	5.65	No increase	Complies
Yeasts and Molds	**Log of viable count at 7 days**	**Log of viable count at 14 days**	**Log of viable count at 28 days**	**USP compliance**
Limit	**No increase form '0'hr**	**No increase form '0'hr**	**No increase form '0'hr**	
Candida albicans ATCC 10231	No increase	No increase	No increase	Complies
Aspergillus brasiliensis ATCC 16404	No increase	No increase	No increase	Complies

Preservative efficacy data was well within the USP acceptance criteria for all the specified bacteria and yeasts and fungi. Thus benzalkonium chloride in the formulation acts effectively as a preservative.

5.14 Ocular irritation studies

Ocular irritation study data proved that developed formulation is non-irritant to rabbit eyes.

5.15 In-vivo antifungal efficacy studies

The test formulations were administered in to the infected eye twice a day of animals for 15 consecutive days. 80% animals showed recovery in one week time in test formulations and rest of the animals were treated for complete 15 days for healing the remnants of infections. Improvements in the clinical parameters post instillation suggesting the propensity of the prepared systems to sustain drug release with a minimal loss due to drainage. Gross examination of the ocular tissues showed that the formulations caused no undue irritation and no leakage of the developed polymer based formulation was observed from any part of the eye.

Score data for positive control & test formulation is presented in table number 5. Stastical analysis for positive control and test formulation was done using t test for all physiological parameters and differences were found to be statistically significantly at $p < 0.05$.

Table 5: Score study data.

Parameters		**Chemosis**	**Eyelid membranes (hyperaemia)**	**Corneal membrane opacity**	**Corneal reflex**	**Blindness vison impaired/not impaired**
Animal number						
Positive control	1	5	5	5	2	VM
	2	4	4	5	1	VM
	3	5	5	4	2	VM
	4	5	5	4	1	VM
	5	2	5	5	2	VM
	6	5	4	5	2	VM
Average		**4.33**	**4.67**	**4.67**	**1.67**	-
Test formulation	1	2	2	3	4	NI
	2	2	3	2	3	NI
	3	3	2	2	3	VM
	4	3	3	1	4	NI
	5	2	3	1	4	NI
	6	2	2	1	5	VM
Average		**2.33**	**2.50**	**1.67**	**3.83**	-
p value		**Less than 0.05**				-
VM : vision impaired NI : Vision not impaired						

6.0 CONCLUSION

A stable long retentive miconazole ophthalmic suspension was developed using polymer system identified by principles of quality by design which will reduce the adverse effects associated with frequent dosing. Unlike other long acting ophthalmic formulation this formulation developed by simple manufacturing process without use of any sophisticated equipment. Developed formulation can be directly scale up for bigger scale. Being ophthalmic formulation sterilization method is key parameters and suitable sterilization method for formulation, drug and container closure system was identified to mitigate risks. The product is stable up to 6 months at accelerated conditions in low density polyethylene bottles. Thus, a proposed shelf life of 24 months can be assigned to the product without the need for any special storage conditions. Pharmacodynamic in-vivo antifungal efficacy and ocular irritation study proved that the developed formulation is non-irritant to eyes and efficacious against most pathogenic fungi candida albicans species. Twice a day administration coupled with its ability to provide sustained release could probably result in less frequent administration, thus enhancing patient compliance.

7.0 Disclosures

The author reports no conflict of interest in this work. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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