RESEARCH ARTICLE

Compatibility testing and rheological characterization in development of novel *in situ* guar gum-based ophthalmic dosage form

NG Nanjundaswamy, Fatima Sanjeri Dasankoppa[1]

Department of Pharmaceutics, Government College of Pharmacy, Rajiv Gandhi University of Health Sciences, Bangalore, [1]Pharmaceutics, Karnataka Lingayat Education Society's College of Pharmacy, Vidya Nagar, Hubli, India

Guar gum is derived from the seeds of *Cyamopsis tetragonolobus*. Guar has certain drawbacks such as uncontrolled rate of hydration, fall in viscosity on storage, susceptibility to microbial degradation, and turbidity in aqueous dispersion. Many of these drawbacks can be overcome by using guar derivatives. Guar derivatives upon contact with water hydrate to form hydrogels for controlled-release mechanism and show stimuli-responsive changes in their structural network, and hence, the drug release. The present investigation aims at screening guar derivative (hydroxyl propyl guar) during preformulation stage by spectral (FTIR spectroscopy), thermal (differential scanning calorimetry (DSC)), isothermal (HPLC technique), and rheological characterization for the development of stable *in situ* ophthalmic dosage using linezolid as the model drug.

Key words: *Behaviour index (K), consistency index (n), hydroxy propyl guar, ICH Guidelines, power law model*

INTRODUCTION

Guar gum is known for its viscosity contribution in pharmaceutical formulations and also for ion-induced gelation effect.[1] It has certain drawbacks such as uncontrolled rate of hydration fall in viscosity upon storage, susceptibility to microbial degradation and turbidity in aqueous dispersion. These drawbacks are overcome by derivatization of guar to hydroxy alkyl derivatives.[2] One such derivative namely hydroxy propyl guar (HPG) is used in the present investigation for ion-induced gelation effect.[3] Linezolid is a synthetic antibacterial agent of a new class of antibiotics, the oxazolidinones which has clinical utility *in vitro* in the treatment of infections caused mainly by aerobic gram positive bacteria and certain gram negative bacteria and anaerobic bacteria.[4] Linezolid binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the formation of a functional 70S initiation complex, which is an essential component of the bacterial translation process.[5] Assessment of the potential compatibility between the active pharmaceutical ingredient and different excipients is an essential part of the preformulation study prior to the final formulation of a dosage form especially when novel excipients are intended to be used in the formulations. To predict the shelf life of the dosage form, one should know the stability aspects of the active ingredient in presence of other components of the formulation.[6,7] The study investigates the compatibility of antibiotic linezolid at accelerated conditions according to ICH guidelines (at 40°C (±2°C) /75% RH for 6 months)[6] with HPG, carbopol 940P, sodium alginate, benzalkonium chloride, and boric acid in the preformulation stage to develop a stable *in situ* guar gum derivative-based ophthalmic dosage form. Thermal analysis (DSC), FTIR (spectral), and HPLC technique (isothermal) are used in the study to detect any possible interaction and to establish stability and compatibility of the drug at accelerated stability testing conditions.[7]

In situ ophthalmic gels are expected to provide prolonged corneal contact time, reduced precorneal drug loss, and convenience of administration in comparison to eye drops, suspension, or ointments.[8] To fulfill the above criteria, viscoelastic property or

Address for correspondence:
Mrs. Fatima Dasankoppa,
Department of Pharmaceutics,
KLES College of Pharmacy, Vidya Nagar, Hubli- 31, India.
E-mail: sanjeri@yahoo.co.uk

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rheology plays an important role in *in situ* gel formulation.[9] Therefore, the present study also aims at rheological characterization, stability aspects of the formulations, and the effect of sterilization(moist heat) and storage on the variations of viscosity of *in situ* gels by calculating consistency index (K) and flow behaviour index (n values) using power law model.[9,10]

MATERIALS AND METHODS

Materials

Linezolid (99.94% drug purity, Cipla Limited, Vikroli, Mumbai), hydroxypropyl guar (Encore polymers, Mumbai), sodium alginate, Carbopol 940P, benzalkonium chloride (Microlabs, Bangalore) were all obtained as gift samples. The solvents used for HPLC were procured form S.D. Fine chemicals and were of AR grade.

Methods

Standardization of HPLC method for analysis of linezolid

HPLC measurements were conducted using HPLC- SPD-10A series Shimadzu, Japan, the system being controlled by Chemstation A.09.01 software for chromatographic analysis. The column used was Luna column $5UC_{18}$ (2)100A (250x4.6 size) having a surface area of 400±30 m^2/g and particle size of 5.00±0.30 μm. The flow rate was 1 ml/min and UV detection was carried out at 254 nm.[4]

A quantity of Linezolid equivalent to 100 mg was weighed accurately into a 100 ml volumetric flask and dissolved in a small quantity of mobile phase (The mobile phase used was previously filtered through 0.45μ, Supor membrane, N_{66}, nylon and degassed in ultrasonic bath). The volume was made up to the 100 ml mark with the mobile phase to get a concentration of 1000 μg/ml and was labeled as stock solution. The stock solution was diluted with mobile phase which is a mixture of ammonium acetate buffer and methanol in 60:40 ratios to get dilutions in concentration ranging between 20-140 μg/ml. The samples were subjected to inter-day evaluation to check the reproducibility of the results. The results were obtained in triplicate. Mean peak area versus concentration (μg/ml) was plotted and best fit was determined based on the results of linear regression, standard deviation, and coefficient of variation.

Drug polymer compatibility studies

Various blends of linezolid with HPG, carbopol 940P, sodium alginate, boric acid, benzalkonium chloride, were prepared in a ratio of 1:1, and stored in screw capped amber colored glass bottles; all the bottles were covered with black canvas and kept in stability chamber (Thermo lab scientific equipments Pvt. LTD., India, Model TH 90 S consisting of two chambers) set to 40°C (±2°C) /75% RH for six months as shown in Table 1. The various combinations (8s and 9s) were used to check the compatibility of linezolid with that of hydroxy propyl guar, carbopol 940P and sodium alginate, boric acid, benzalkonium chloride to find out any possible interactions in preformulation stage by spectral, thermal, and isothermal techniques. Sample no 8s and 9s were subjected to stability testing according to ICH guidelines.[10] The sample was withdrawn at time intervals of 1, 3, and 6 months, and the drug content was estimated by HPLC technique.[4]

FTIR spectroscopy

FTIR studies were carried out using FTIR Spectrophotometer-Thermo, USA. Model –Nicolet IR 200 employing KBr disc method. Infrared Spectroscopic analysis was carried out individually and in combination as shown in the Table 1. The prepared discs were scanned in the wavelength range of 500 to 4000 cm^{-1} to obtain IR spectra's. Functional peaks of linezolid were compared with that of the mixture samples (8s and 9s) for possible interactions.[6,11]

Differential scanning calorimetry studies

Differential scanning calorimetry (DSC) studies were performed using Shimadzu Model DSC 60, DSC was carried out by purging with argon at 80 ml/min. Samples, 40 μl, were placed in hermetically sealed aluminum pans. Heat supplied was in range of 25-250°C/min. The endothermic peak(s) were recorded for the individual samples and in combination as shown in Table 1. The DSC thermograms obtained were checked for possible interactions.[6,11]

Estimation of drug content in samples subjected to accelerated stability testing.[6,7]

The sample no 8s and 9s were subjected to drug estimation by HPLC technique at a periodic interval of 1, 3, and 6 months. A quantity of the blend containing (100 mg) containing approximately 50 mg of the drug was accurately weighed into a volumetric flask. A small volume of acetonitrile:methanol: water (4:4:2) was added to extract linezolid from the mixture. The volume was made up to 250 ml. The above contents were filtered using 0.45-μ syringe filter. From the above solution,

Table 1: Details of samples and blends subjected to accelerated stability testing

Sample no.	Composition (s)
1	Linezolid
2	Hydroxy propyl guar
3	Carbopol 940P
4	Sodium Alginate
5	Boric acid
6	Benzalkonium chloride
7	Linezolid: HPG, (1:1) mixture
8s	Linezolid: HPG + sodium alginate + carbopol 940P (1:1) mixture, after accelerated stability testing at 40°C (±2°C) /75% RH
9s	Linezolid: HPG+ sodium alginate + carbopol 940P +boric acid+ Benzalkonium Chloride+ (1:1) mixture after accelerated stability testing at 40°C (±2°C) /75% R

s-indicates the samples subjected to accelerated stability condition of 40°C (±2°C) /75% RH for six months

5 ml was diluted to 10 ml with mobile phase and subjected to drug content analysis by HPLC technique.[8] The calculations were made by the aid of standard calibration equation.

Formulation design

Various blends of HPG, sodium alginate, and carbopol 940P dispersions were prepared in purified water (distilled water subjected to moist heat sterilization and stored at a temperature of 80°C and used within 24 hours after sterilization). The gum and the polymers were allowed to swell overnight. Agents for adjustment of osmolality and preservative were added. Then it was mixed properly and pH was adjusted to 7.4 with 0.1 N NaOH/ 0.1N HCL and volume were made up with purified water as shown in Table 2.

In situ gelling ability

The gelling ability of the formulation was assessed by placing a drop of dispersion in a vial containing 2 ml of artificial tear fluid (ATF freshly prepared) maintained at a temperature of 37±2°C in a thermostatic water bath.[9,12] The time taken for formation of the gel and dissolution of the gel was recorded.

Rheological characterization

Effect of sterilization on the viscosity

The formulations were subjected to wet heat sterilization by means of an autoclave with a sterilization cycle of 20 min at 121°C at 15 psig to assess the rigours of the sterilization on variations in viscosity.

The viscosity measurements were done using Brookfield viscometer DV-2 model. The *in situ* gel formulations were placed in the sampler tube (100 ml capacity). The samples were analyzed both at room temperature at 25°C (Before gelation) and at thermostated temperature of 37°C±0.5°C (After gelation) by circulating water at 37°C to the viscometer adaptor prior to each measurement.[9,12]

The angular velocity of the spindle was 30 rpm and the viscosity of the formulations was measured. To evidence the variations in the consistency following sterilization and parameter % viscosity variation (difference in viscosity values before and after sterilization and after addition of simulated tear fluid in the ratio of 1:4), the viscosity values were recorded before and after sterilization at 30 rpm using spindle no TR11 with rest time of 3minutes.

The present report is based on the rheological characterization of the HPG based *in situ* ophthalmic gels. Viscosity of non-Newtonian fluids, which change with changing rate of shear, is characterized by more than one parameter and is represented by the power law model.[13,14]

$$\mu a = K\,(1/n)nx\,(4\pi N)^{n-1}$$

or

$$\ln(\mu a) = (n-1)\ln 4\pi N + \ln(K) - n\ln(n)$$

where, μa is the apparent viscosity (Poise),
N the spindle speed (RPS),
K is the consistency index (p s^n)
n is the flow behavior index, dimensionless.

The values of $\ln(\mu a)$ and $\ln(4\pi N)$ were fitted to obtain a linear relationship; and from the slope and intercept of the best fit line, the flow behavior index "n" and consistency coefficient "K" were determined.

Effect of ageing on viscosity

The sterile formulations were stored at 40°C/75% RH for 1 month and 25°C/60% RH for 1 month and three months. At the end of each period, the formulations were subjected to viscosity measurements as previously described. The rheological data obtained was analyzed by fitting the data to the power law model as explained above to calculate the flow behavior index "n" and consistency coefficient "K".[13,14]

RESULTS AND DISCUSSIONS

The linearity of Linezolid was found to be in concentration of 20 to140 μg/ml with a correlation coefficient of 0.9980. The average linear regression equation was represented by Y=3407x+3966, where X=concentration in μg/ml (ppm) and Y=Peak area. The retention time was found to be 10.88 minutes with a standard deviation of 0.172. The results are shown in Figure 1, which is a typical chromatogram for 40 μg/ml. Hence, it can be concluded from the study that the above method is precise, accurate, and reproducible and can be used for drug estimation [Figures 1 and 2].

Physical mixtures samples 8s and 9s Table 1 were characterized by, FTIR spectral analysis for any physical as well as chemical alteration of the pure drug characteristics. The principal functional group of linezolid are amide N-H stretch and amide C=O stretch. Literature value ranges 3400 to 3200 cm^{-1} (for amide N-H stretch) and 1690-1660 cm^{-1} (for amide C=O stretch). The values as shown in Table 3 are concordant with the principal functional group wavelength. When exposed to accelerated storage conditions of 40°C/75% RH for 6 months, [Figures 3-5], there was no significant shift in the absorption peaks of the functional groups of linezolid, present in the physical mixture.

Table 2: Formulation design of *in situ* gelling system using HPG

Ingredients (%) w/v	Formulation code				
	H1-SA-CA	H2	H2-SA	H2-CA	H2-SA-CA
HPG	0.25	0.75	0.5	0.5	0.5
Sodium alginate	0.125	-	0.25	-	0.125
Carbopol 940P	0.125	-	-	0.25	0.125
Benzalkonium chloride	0.01	0.01	0.01	0.01	0.01
Boric acid	0.3	0.3	0.3	0.3	0.3
Purified water (q.s)	100	100	100	100	100

Thermogram of linezolid revealed a sharp peak at 176.47°C and a small blunt peak at 146.33°C [Figure 6]. The samples 8s and 9s were kept for accelerated stability testing. After 6 months period, the samples were analyzed by DSC thermal analysis. The thermogram TH8s and TH9s revealed a sharp endothermic peak of linezolid at 175-176°C (according to literature-Melting point of linezolid is 173-181°C) [Figures 7 and 8]. The other peaks obtained in the thermogram were concordant with that of endothermic peaks of individual gum/polymers/excipients as shown in Table 3.

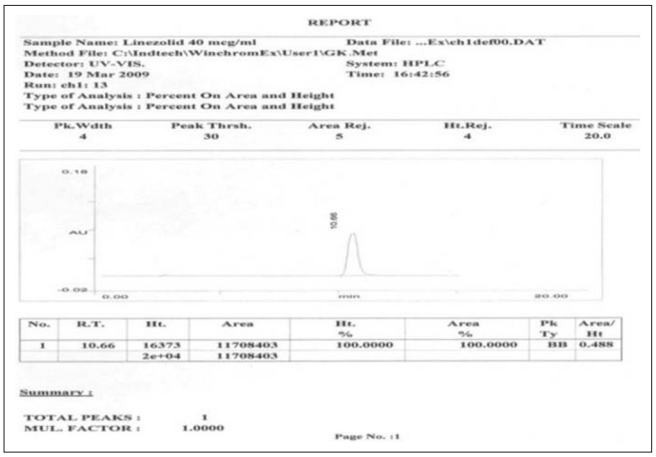

Figure 1: Typical chromatogram of linezolid at 40 µg /ml

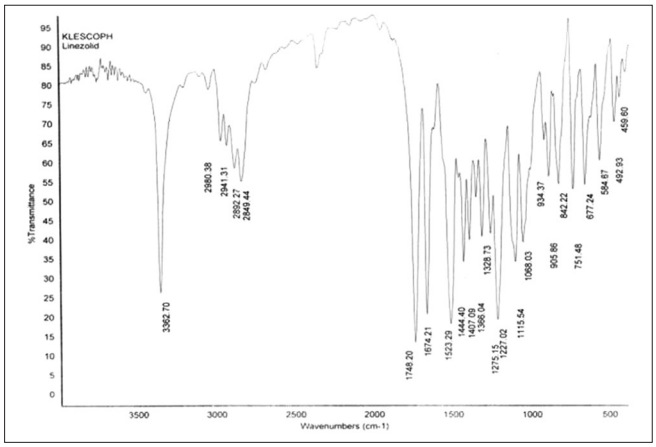

Figure 3: IR spectra of linezolid

The stressed sample 9s containing drug and all the excipients that are to be incorporated in the formulation were analyzed by HPLC technique. The HPLC chromatogram of sample 9s at before and after 1, 3, and 6 months revealed 99.14%, 91.46%, and 91.14% of the drug, respectively, even after being exposed to stress conditions [Figures 9-12 and Table 4].

FTIR spectra are helpful to confirm the identity of the drug but due to presence of many ingredients in the sample mixture, it is difficult to predict the compatibility of the linezolid with other ingredients and excipients, whereas, DSC thermograms proved to be a valid tool for qualitative estimation where melting endotherms of the drug were

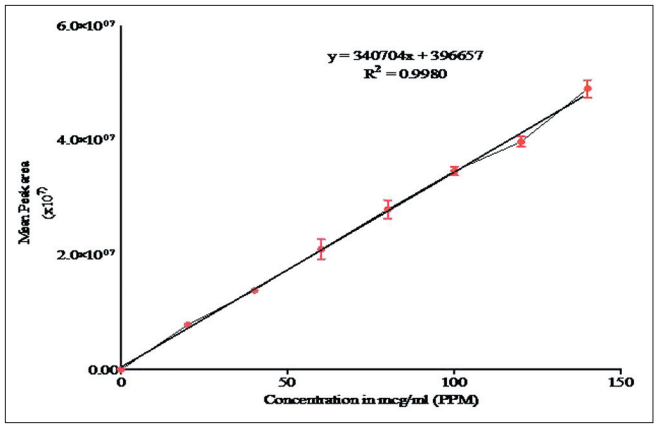

Figure 2: Calibration curve for estimation of linezolid by HPLC

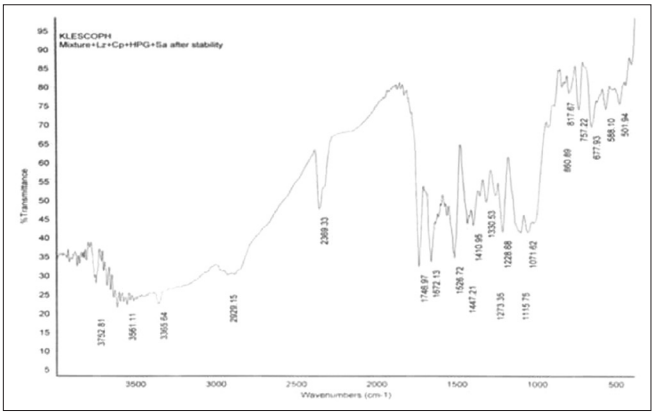

Figure 4: IR spectra of sample 8s after accelerated stability testing

Table 3: Comparison of functional group peaks and endothermic peak(s) of linezolid with that of samples subjected to accelerated stability testing by FTIR spectroscopy and DSC analysis.

Sample no.	FTIR spectra(s)	Peak Functional group wavelength [Wave length (cm^{-1})]		DSC thermogram(s)	Endotherm peak(s) (°C)
		Amide N-H stretch	Amide C=O stretch		
1	IR 1	3362.70	1674.21	TH 1	**176.47, 146.33**
8s	IR 8s	3365.64	1672.13	TH 8s	91.22, **145.97**, **176.91**, 120.05
9s	IR 9s	3359.98	1672.84	TH9s	49.30, 118.10, 158.31, **175.09**

*s- indicates the samples exposed for stability study at 40°C (±2°C) and 75% RH; Bold numbers indicates the endothermic peaks of Linezolid

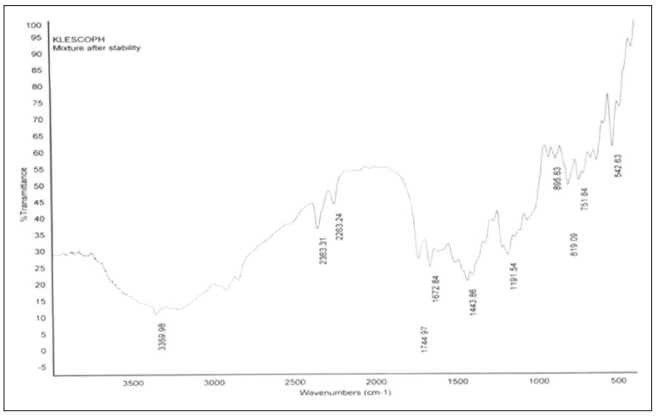

Figure 5: IR spectra of sample 9s after accelerated stability testing

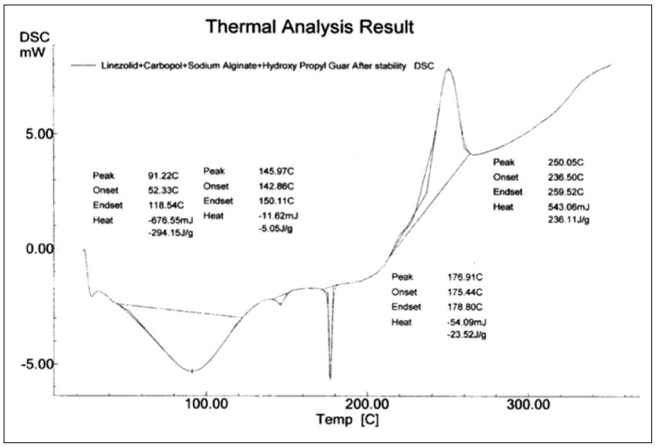

Figure 7: Thermogram of sample 8s after accelerated stability testing

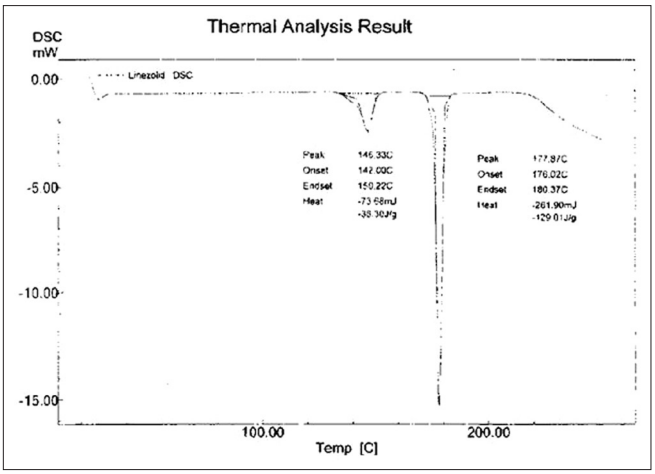

Figure 6: Thermogram of linezolid

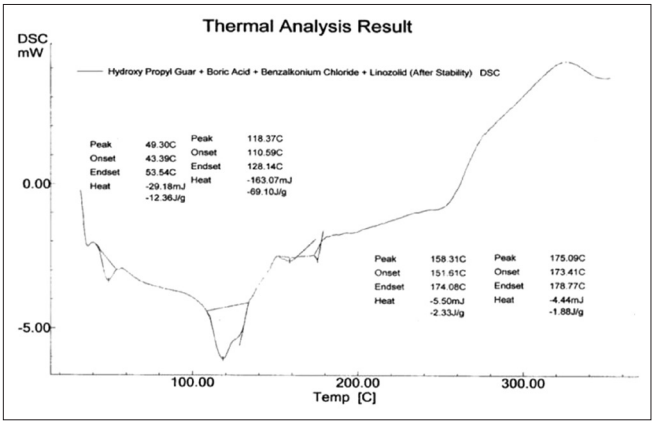

Figure 8: Thermogram of sample 9s after accelerated stability testing

well preserved as evident from the thermograms TH8s and TH9s. Thus, linezolid is compatible with all the ingredients intended to be used in the formulation and DSC being a sensitive, rapid, and convenient tool for screening various excipients in the preformulation stage. Reproducible HPLC data revealed the stability of the drug even after exposure at stressed temperature and humidity conditions. Therefore, to assess the compatibility of the drug in dosage designing, a combination of thermal, spectral, and isothermal techniques is a useful tool for qualitative and quantitative analysis during preformulation stage.

Formulations were designed by varying the composition of HPG, sodium alginate, and carbopol 940P. The formulations were tested for their gelling ability. All the formulations exhibited good gelling ability in simulated tear fluid after sterilization, which is important requirement for *in situ* gels. Results are shown in Table 5. The stability of the formulations was tested by subjecting them to sterilization (moist heat) and storage at 25°C for 1 and 3 months and 40°C for 1 month and effect on viscosity was assessed by calculating % viscosity variation, consistency index (K) and flow behaviour index (n) using power law model.

Table 4: Drug content of sample 9s stored at 40°C/75% RH for 1, 3, and 6 months

Stability test period	Peak area	% Drug content
1 month	34177341±8021	99.14
3 months	31559720±5309	91.46
6 months	31448718±7519	91.14

n = 3

H1-SA-CA, H2 and H2-CA exhibited decrease in viscosity (15 to 29%), while H2-SA, H2-SA-CA showed increase in the viscosity (3 to 6%) upon sterilization. H1-SA-CA, H2 and H2-CA did not retain the physical stability upon sterilization. H2-SA and H2-SA-CA formulations exhibited increase in viscosity (8%) on storage at 25°C for 3 months and slight decrease in viscosity at 40°C for 1 month (4 to 6%); as shown in Table 5, these formulations retained the viscosity even at elevated temperature.

By application of power law model it was evident that H1-SA-CA, H2 and H2-CA exhibited increase in flow behavior index and decrease in consistency index after sterilization, storage at 25°C for 1 month and 3 months and at 40^{0}C for 1 month. H2-SA and H2-SA-CA exhibited decrease in flow behavior index and increase in consistency index, which

Table 5: Viscosity values (poise units) before sterilization, gelling capacity and % viscosity deviation values after sterilization, after 1 month, 3 months of storage at 25°C and 1 month storage at 40°C .(evaluated at 30 RPM)

Formulation code	Gelling capacity	Viscosity values after gelation (poise)		% Viscosity variation (mean values ±SD, *n* = 3)		
		Before sterilization	After sterilization	After sterilization *t*=0	3 months T=25°C	1 month T=40°C
H1-SA-CA	+++	18.49±3.28	15.60±1.5	-15.87±0.155	-3.98±0.030	-6.00±0.001
H2	+++	45.92±1.24	35.74±1.9	-22.14±0.453	-3.96±0.012	-4.04±0.012
H2-CA	+++	43.38±0.86	30.73±1.2	-29.06±0.089	-4.00±0.01	-15.00±0.001
H2-SA	+++	40.66±1.24	43.19±1.8	6.051±0.081	6.97±0.023	-2.02±0.033
H2-SA-CA	++++	77.08±1.1	79.62±1.6	3.19±0.194	8.93±0.001	2.01±0.012

++++ - Indicates thick gel is formed soon after addition and remains upto extended period of time; +++ - Indicates gels soon after addition and remains upto 8 hrs

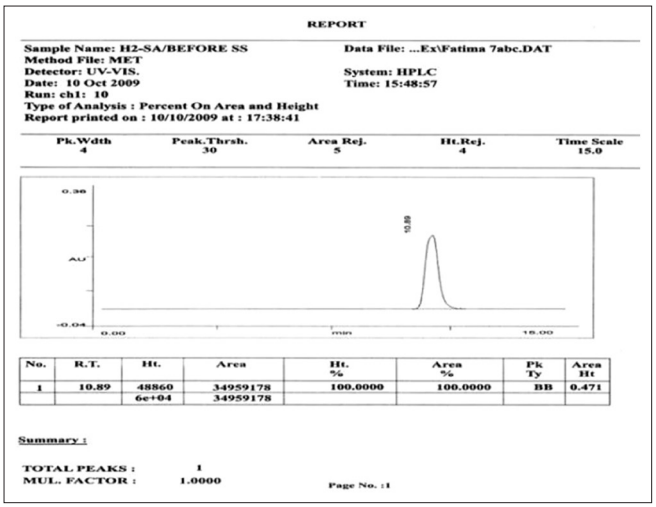

Figure 9: HPLC spectra of 9s before accelerated stability testing

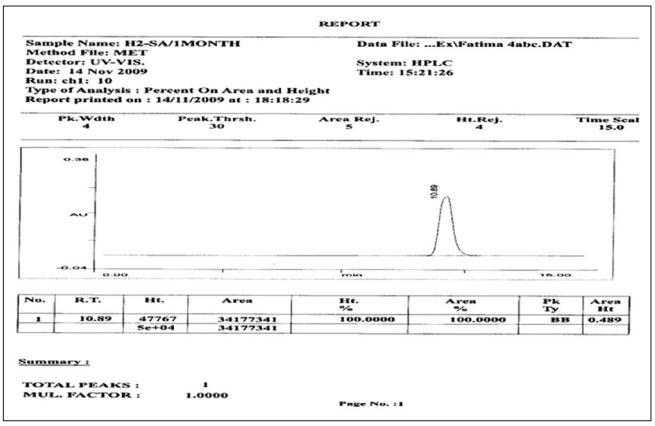

Figure 10: HPLC spectra of 9s after 1 month exposure to accelerated stability testing

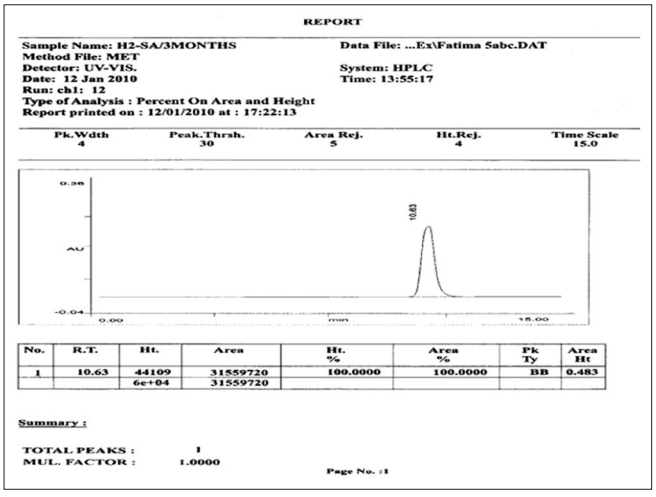

Figure 11: HPLC spectra of 9s after 3 months exposure to accelerated stability testing

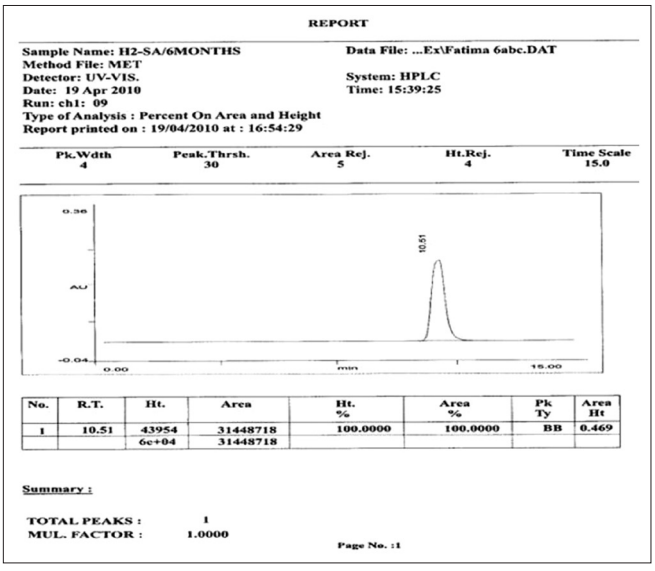

Figure 12: HPLC spectra of 9s after 6 months exposure to accelerated stability testing

reveals increase in the viscosity of the formulation on storage even at elevated temperature. H1-SA-CA, H2 and H2-CA did not retain the viscosity on sterilization and storage. The values of flow behavior index (n) were found less than unity after sterilization and storage at 25°C for 1 and 3 month(s) and at 40°C for 1 month indicating shear-thinning (pseudoplasticity) behavior of the formulations [Figures 13 and 14]. Good physical stability following sterilization and storage, retaining the flow behavior index, and consistency index values, makes H2-SA and H2-SA-CA formulations as promising novel guar gum derivative-based *in situ* gels.

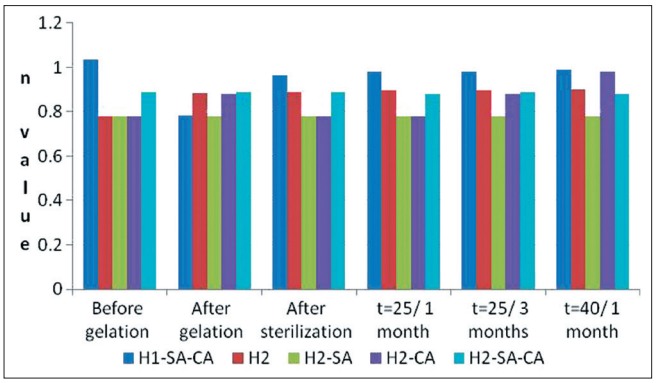

Figure 13: Comparison of flow behavior index (n) values before gelation, after gelation, after sterilization, and storage at 25°C/1 and 3 months, 40°C/ 1 month.

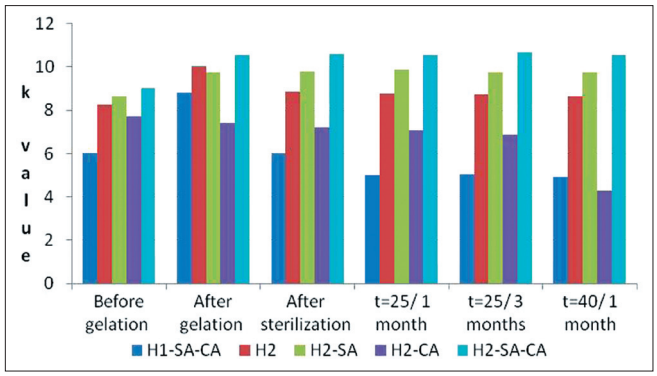

Figure 14: Comparison of consistency index (K) values before gelation, after gelation, after sterilization, and storage at 25°C/1 and 3 months, 40°C/ 1 month.

CONCLUSIONS

From the above studies, it can be concluded that Linezolid is compatible with HPG, a novel guar gum derivative and with all the ingredients intended to be used in the formulations. Qualitative assessment can be made by DSC analysis (thermal) and FTIR spectroscopy (spectral analysis). Quantitative analysis can be made by using HPLC technique (isothermal method). Therefore, a combination of thermal, spectral, and isothermal techniques is useful for qualitative and quantitative analysis during preformulation stage to assess the compatibility of the drug in dosage designing.

H2-SA, H2-SA-CA formulations exhibited good physical stability following steam sterilization and storage. The values of flow behavior index (n values) were found less than 1 after sterilization and storage at 25°C for 1 month and 3 months and at 40°C for 1 month indicating shear-thinning (pseudoplasticity) property of the formulations. Good physical stability following sterilization and storage by retaining flow behavior index (n values) and consistency index (K values), makes H2-SA and H2-SA-CA formulations a promising novel guar gum derivative-based *in situ* ophthalmic gels. The application of the power law model enables us to assess the change in rheological parameters efficiently in contrast to the conventional techniques.

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