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Original Article

Ophthalmic pH Triggered *in situ* Gelling System of Tobramycin: Formulation and Optimization using Factorial Design

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ABSTRACT

Objectives: The objective of present study was to formulate and optimize ophthalmic pH triggered *in situ* gelling system of tobramycin in order to enhance residence time and provide prolonged drug release. **Methods:** Two factor three level full factorial design was applied to study the effect of concentration of carbopol 980 and HPMC K4M on dependent parameters such as viscosity, gel strength and gelling capacity. Overlay plot method was used to optimize the formulation. The optimized formula was evaluated for clarity, pH, viscosity, gel strength, gelling capacity, *in vitro* drug diffusion, sterility test, ocular irritancy test, Isotonicity test, antimicrobial efficacy and stability studies. **Results and Discussion:** The results showed that increasing the concentration of carbopol980 and HPMC K4M, there was increased in the gelling capacity, its gelling strength and viscosity. All the formulations had pH around 5. The optimized formulation prolonged the drug release for eight hours which had a composition of 0.48% carbopol980 and 0.52% HPMC K4M. From the kinetic modelling it showed that it followed Higuchi model for drug diffusion. The gel formed *in vitro* produced sustained drug release up to 8 hr. Results showed no significant change in the results of appearance, pH, viscosity, gelling capacity and drug content when stored at accelerated condition and room temperature for a period of one month. **Conclusion:** Optimized formulation was sterile, non-irritant, isotonic and stable and also it can be substitute to conventional eye drops formulations of tobramycin which could provide a sustained release for a period of eight hours.

Key words: *In situ* gelling system, Tobramycin, Carbopol 980, HPMC, pH triggered method.

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INTRODUCTION

Ophthalmic *in situ* gelling systems are polymeric solution at room temperature and its get converted into gel after in contact with the ocular environment in cul-de-sac. This formed gel having the higher residence time in the eye. They are extremely beneficial over the preformed hydrogels.[1]

Bacterial infection is one of the most severe ocular infections. Several antibiotics are used for the treatment of bacterial infection. Tobramycin is a broad spectrum aminoglycoside which is used for bacterial infection and it is approved by U.S. FDA for using as ocular drug delivery system.[2]

The aminoglycosides are used to treat infections caused by aerobic gram negative bacteria. Tobramycin is highly effective against Pseudomonas aeruginosa and *Staphylococcus aureus* which is common cause of ocular infection. Tobramycin is produced by *Streptomyces tenebrarius*.[3]

Tobramycin is available as conventional eye drops, which are used 3-4 times a day to treat bacterial infection. However conventional drops are associated with extensive drug loss by ocular drainage mechanism which results in poor ocular drug availability. Moreover the half-life of tobramycin is 2-3 hr.[4,5]

Therefore it is desirable to develop a tobramycin *in-situ* gelling system, which is instilled in a liquid form and shifts to the gel form immediately by change in pH, in the cul-de-sac of the eye.

Hence, tobramycin *in-situ* gelling system will decrease the frequency of drug administration. Also it will provide sustained release of tobramycin and will increase the residence time of drug in the eye for longer period of time. In addition to this will improve the patient compliance.

MATERIAL AND METHODS

Tobramycin was received as gift sample from Cipla Pharmaceuticals, Mumbai. Carbopol 980 was received as gift sample from Astron chemicals, Ahmedabad. HPMC K4M was a gift sample from Ozone International, Mumbai. HPMC K4M was purchased from Chemdyes Corporation, Rajkot Gujarat. All other chemicals were of analytical grade.

Preliminary batches of Tobramycin *in situ* gelling system containing carbopol 980 and HPMC K4M

Tobramycin *in situ* gelling systems containing different concentrations of carbopo l980 and HPMC K4M were prepared as shown in the Table 1. HPMC K4M was dissolved in 70ml of water by proper mixing. Carbopol 980 was dispersed/sprinkled in above solution. The solutions were kept overnight to hydrate. Next day, pH was adjusted up to 5.5 with 0.5M NaOH. Sodium chloride (isotonic agent) and benzalkonium chloriden (as a preservative) were added to above solution. Then drug solution (prepared in distilled water) was added to carbopol 980 - HPMC K4M solution with constant stirring until uniform dispersion is obtained. Finally volume was made up to 100 ml with distilled water. All the preliminary batches were evaluated for gelling capacity and viscosity.

Factorial design

Full factorial design layout of pH triggered *in situ* gelling system is Table 2. The formulations were prepared in similar manner as procedure described above in the preliminary batches. Stat-Ease design software version 8 was used. The prepared formulation was subjected to ANOVA

Table 1: Preliminary batches of Tobramycin *in situ* gelling system.

Ingredient (%w/v)	K1	K2	K3
Tobramycin	0.3	0.3	0.3
Carbopol 980	0.3	0.4	0.4
HPMC K4M	-	0.75	1.5
NaCl	0.9	0.9	0.9
Benzalkonium chloride	0.1	0.1	0.1
Deionized Distilled water	100ml	100ml	100ml

Table 2: Full factorial design layout of pH triggered *in situ* gelling system.

Batch	Carbopol 980	HPMC K4M
F1	0.3	0.5
F2	0.4	0.5
F3	0.5	0.5
F4	0.3	0.75
F5	0.4	0.75
F6	0.5	0.75
F7	0.3	1.0
F8	0.4	1.0
F9	0.5	1.0
F10	0.35	0.6

*F10 Validation batch

analysis at 95% confidence interval. The formulations were evaluated for clarity (formulations were visually examined against white and black background) and pH (measured using digital pH meter).

Evaluation of pH trigged *in situ* gel

Gelling capacity

The drop of the formulation was placed in the vial containing 2 ml of phosphate buffer 7.4. The time required to form a gel was noted also the time taken by the formed gel to dissolve was noted.[6]

Gelling strength

Preformed *in situ* gel (25gm) was placed in 50ml measuring cylinder. A plunger was placed into the gel. 10gm weight was applied to plunger. The time required for the plunger to sink/ penetrate down to 5 cm was measured.[7]

Viscosity

Viscosity of solutions as well as formed gel was measured by Brookfield viscometer with spindle No. 62

Drug content

1 ml of gel was taken and mixed it with 50 ml phosphate buffer 7.4 in conical flask. The flask was sonicated in bath sonicator. Volume was made up to 100ml with phosphate buffer 7.4. Absorbance was measured using UV-VIS spectrophotometer against phosphate buffer 7.4 as a blank.

In vitro drug release study

The *in vitro* drug release studies were carried out through dialysis membrane (Molecular weight- 12000-14000 daltons) using Franz diffusion cell.[8] The previously soaked dialysis membrane was kept between the donor and receptor compartment. Receptor compartment was filled up with phosphate buffer 7.4. And 1 ml gel was placed in the donor compartment. Aliquots each of 1 ml were taken up to 8 hr and were analyzed by UV- VIS spectrophotometer.

Sterility testing

It was performed by direct inoculation method as per IP96.[9] One ml of the optimized formulation was added in fluid thioglycolate media (FTGM) and soya bean casein digest media (SCDM) (10 ml each) aseptically. FTGM was incubated at 32-35°C and SCDM at 20-25°C for 7 days. Controls (positive and negative) were used to compare the results.

In vivo ocular irritancy test

Ocular irritancy test was performed as per the reported draize test method[10] using albino rabbits. The sterile optimized *in situ* gelling formulation was placed into cul-de-sac and was observed at different time points for redness, swelling or excessive tear production. Scores were given as per the draize evaluation.

Isotonicity Test

One drop of blood was taken on the glass slide. One drop of optimized formulation was mixed thoroughly with RBCs. After 10 min, the sizes of the RBC were examined under microscope. The size of the RBC in isotonic solution was taken as standard and size of the RBC in other solutions {hypertonic solution (1.5%NaCl) and hypotonic solution (0.1% NaCl)}were compared.[11]

Antimicrobial efficacy of optimized formula with compare to marketed eye drop

It was determined by the agar diffusion test with cup plate technique.[12] Blank optimized formulation (without drug) and optimized formulation (with drug), each of 1 ml was added in to cups bored in to sterile nutrient agar previously seeded with *Staphylococcus aureus/E. coli*. After allowing diffusion of the solutions for 2 hr, the agar plates were incubated at 37°C for 24 hr. The zone of inhibition (ZOI) was measured around each cup. The entire operation except incubation was carried out in a laminar air flow unit. Positive (Dioctyl sodium sulfosuccinate) and negative control(0.9% Nacl) were used to compare the results.

RESULTS

Results of preliminary batches of Tobramycin *in situ* gelling system containing carbopol 980 and HPMC K4M

Preliminary batches of tobramycin *in situ* gelling system were formulated using different concentration of carbopol 980 and HPMC K4M (as shown in Table 1). Formulation K1 showed gelation but the gel dissolved in 1hr. Therefore HPMC K4M was added as a viscosity enhancer to provide sufficient strength to the gel. Formulation K2 showed gelation within 2 min and gel remained for 7-8hrs and had optimum viscosity. When the concentration of HPMC K4 was increased from 0.75 to 1.5%, there was drastic change in the viscosity of the formulations. Formulation K3 was very viscous and it gelled within one minute and the formed gel remained for more than 12hr. Hence composition of formulation K2 was further used for optimization of pH trigged *in situ* gelling system.

Evaluations of factorial batches

Results of the evaluation of factorial batches are shown in Table 3. All the formulations were evaluated for clarity. All the formulations were clear. The pH of solution plays a major role in pH triggered *in situ* gelling system. All the formulations had pH around 5. All the formulation had drug content between 95.23% to 99.26%. These results showed that drug is uniformly distributed in all the formulations.

Table 3: Evaluation of *in-situ* gelling system.

Batch No	Clarity	pH	Gel Strength sec	Gelling capacity	Drug Content %	Viscosity of Solution
F1	Clear	5.39	8	+	99.26±	303.13
F2	Clear	5.25	26	+	96.79±	449.87
F3	Clear	5.53	35	++	98.36±	515.69
F4	Clear	5.40	63	++	99.00±	789.91
F5	Clear	5.60	86	+++	97.82±	973.29
F6	Clear	5.23	97	+++	98.63±	1054.0
F7	Clear	5.48	112	+++	95.33±	1172.0
F8	Clear	5.42	129	+++	97.23±	1298.0
F9	Clear	5.52	137	+++	95.23±	1343.0

+ slow gelation and dissolves in 1 hr

+++ gelation within 2 min and remains for 7-8 hr

+/- gelation within one min and remains for more than 12 hr

Experimental design

Based on the preliminary trials, two factors, three levels, factorial design (3^2) was used to formulate pH trigged *in situ* gel of tobramycin. Different composition of concentration of Carbopol 980 (X1) and concentration of HPMC K4M (X2) were selected as independent variables. The dependent variables selected where gelling capacity (Y1), viscosity (Y2) and gelling strength (Y3).

Table 3 shows gelling capacity of all the formulations. Gelling capacity of the formed gel is based on the concentrations of the polymers used in the different formulations. A linear model was recommended by the stat ease software and following equation was generated for gelling capacity.

$$Y1 = 2.33 + 0.33X_1 + 0.83X_2$$

The positive sign of both the independent variables indicated that as the concentration of X1(carbopol 980) and X2 (HPMC K4M) increases, there is increase in gelling capacity. The relationship between X1 and X2 is clarified further with respect to gelling capacity using contour plot as shown in Figure 1a.

A quadratic model was suggested by the stat ease software and following equation was generated for viscosity.

$$Y^2= 968.47+107.94X_1+424.05X_2-10.39X_1X_2-44.10X_1^2-92.12X_2^2$$

The positive sign of both the independent variables signifies prominent effect on viscosity. As compared to carbopol 980, HPMC K4M (coefficient of term X2) had pronounced effect on formulation viscosity, when concentration was increased from 0.5 to 1.0%. The relationship between X1 and X2 is clarified further with respect to viscosity using contour plot as shown in Figure 1b. The formed *in situ* gel is responsible for the sustained release of drug from the formulation. A quadratic model was recommended by the stat ease software and following equation was generated for gelling strength.

$$Y3= 85+14.3X_1+51.50X_2-0.50X_1X_2-5X_1^2-7.50\ X_2^2$$

Gel strength is the important parameter for the controlled *in situ* gelling system. Here X1 and X2 both responsible for gel strength of all the formulation. The relationship between X1 and X2 is elucidated further with respect to gel strength (Y2) using contour plot. Relationship is shown in the Figure 1c. It clearly showed that increase in the concentration of the polymers, increase in the gel strength.

Statistical analysis of dependent variables (ANOVA) is shown in Table 4. Regression co-efficient values (r^2) for independent variables was found to be 0.9997(for gelling strength), 0.8056 (for gelling capacity) and 0.9985 (for viscosity) respectively, indicating excellent correlation between the between formulation variables and responses. Results concluded that models were significant as *P* value <0.05. A validation batch F10 was formulated to validate the model. The results are shown in Table 2. The relative percentage error was less than 5%.

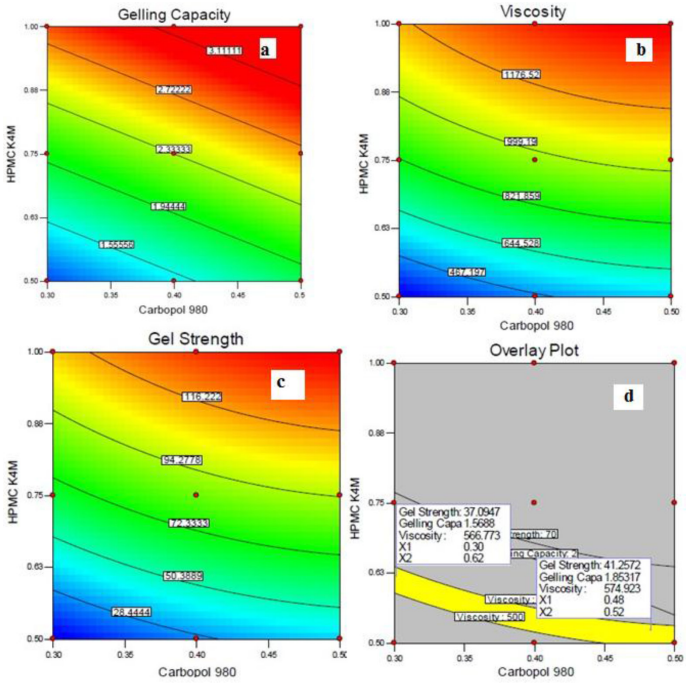

Figure 1: Contour plots for a) Gelling capacity b) viscosity c) Gel strength d) Overlay plot.

Optimization of pH trigged *in situ* gel of tobramycin

Overlay plot method was used to optimize the formulation (as shown in Figure 1d). The following constrains were applied optimal gelling strength and capacity (++) and viscosity in the range of 500 to 600 cp. The yellow portion shows the design space. Form the design space optimize formulation was selected. The composition of optimized formulation was as follows Tobramycin 0.3%, Carbopol (980) 0.48%, HPMC K4M 0.52%, Nacl 0.9%, Benzalkonium chloride 0.1% and water upto 100ml. optimized formulation was subjected to terminal sterilization process.

Evaluation of optimized formulation

There was no change in the clarity of the formulations before and after sterilization. The pH of the optimized formulation before and after sterilization was found to be 5.48 and 5.49 respectively. Viscosity and gelling strength of the optimize formulation was found to be 567.28 and 568.14 respectively. The drug content was found to be 97.45%.

An *in vitro* drug release study of optimized formulation is shown in Figure 2. The gel formed *in vitro* produced sustained drug release up to 8 hr. *In vitro* release data was fitted into various mathematical models to find out the mechanism of drug release. The models were evaluated on the basis of regression coefficient values (r^2). The regression coefficient values for zero order model, first order model, Higuchi model and Korsmeyer peppas model was found to be 0.9441, 0.9714, 0.9946 and 0.970 respectively. Results illustrated that optimized formula followed Higuchi model for diffusion.

Table 4: Statistical analysis of dependent variables.

Response	Model	Std Dev	Adjusted r^2	Predicted r^2	F value	*P* value	$Predicted Values	$Observed Values
Viscosity	Quadratic	24.46	0.9959	0.9815	391.07	0.0002	613.52	609.12
Gelling Capacity	Linear	0.44	0.7407	0.6020	12.43	0.0074	++	++
Gelling Strength	Quadratic	2.73	0.9987	0.9966	465.04	0.0003	43.22	47

If *P* value less 0.05 then model is significant

$ For validation of model

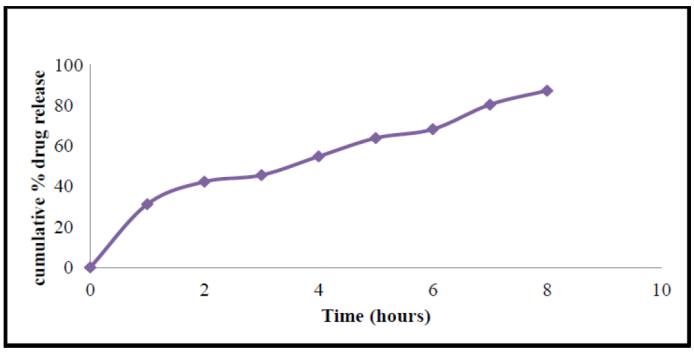

Figure 2: *In vitro* drug release studies of optimized formulations.

Figure 3: Sterility testing of optimized formulation in a)Soya bean casein digest media b) Fluid Thioglycolate medium.

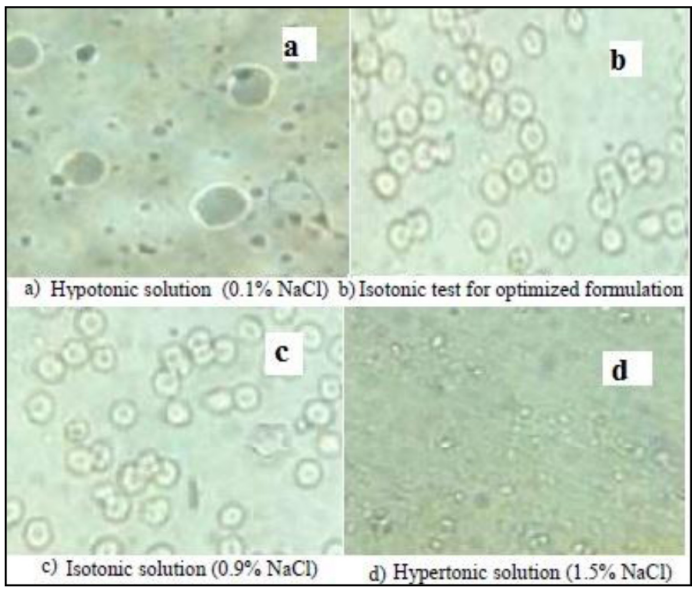

Figure 4: Results of the isotonicity studies of optimized batch.

Ophthalmic formulations should be sterile in nature. Results of the sterility test are shown in Figure 3. There was no appearance of turbidity in the test solution (*in situ* gelling optimized formulation) when incubated fluid thioglycolate media at 32°C to 35°C and soyabean casein digest media at 20°C to 25°C for not less than 7 days. Results pass the sterility test as there was no growth of micro-organism.

In addition to sterility the ophthalmic formulations should also be isotonic. Results of the isotonicity are shown in Figure 4. The optimized formulation showed no change in the shape (Figure 4b) of blood cells (enlargement or shrinkage), which confirms the isotonic nature of the formulation when compared with hypertonic solution (1.5%NaCl) and hypotonic solution (0.1% NaCl).

The optimized formulation was subjected for antimicrobial studies. The zone of inhibition (for pure drug)was found to be 27 mm and 28 mm for *S. aureus* and *E. coli* micro-organism. Similarly zone of inhibition for optimized *in situ* gelling formulation was found to be 25 mm 29 mm for *S. Aureus* and *E. coli* microorganism. The study indicates that optimized formulation containing tobramycin when formulated into pH trigged *in situ* gelling system; it retained its antimicrobial efficacy.

The optimized formulation was subjected to ocular irritation studies. Positive control (Dioctyl sodium sulfosuccinate) Negative Control (0.9% Nacl) was sued in the study. Damage is scored for cornea, iris, conjunctivae and chemosis. The score for the positive control was found to be 9 while for negative control blank optimized formulation and optimized formulation was zero. Thus the results confirmed that the optimized formulation was non-irritant and no ocular damage was seen except the positive control.

The stability studies were carried out for optimized formulation. Stability studies was tested for one month and was found to be clear with no change in pH (about 5.4), drug content (97-98%), viscosity (567±5) and *in vitro* drug release. Results indicated that there is no noteworthy change in the characteristic of optimized formulation when stored at room temperature and at accelerated conditions when stored for a period of one month.

DISCUSSION

Carbopol is an acrylic (cross linked) polymer which shows pH dependent phase transition. Carbopol forms a low viscosity aqueous solutions and gets transformed to a stiff gel when the pH is raised. As per the literature, benzene as a residual solvent is present in the different grades of Carpobol (such as carbopol 934, carpobol 941 and carpobol 940) which might be irritating to eyes.[13] Hence in the present study carbopol 980

(which is free from benzene) was used as a pH dependent *in situ* gelling agent. HPMC (hydroxy propyl methyl cellulose), is also called as hypromellose. It is one of the most excellent cellulosic polymers used in the formulation of controlled released drug delivery. In the ophthalmic dosage form, HPMC is used as a matrix that swells and expands. HPMC K4M was added as a viscosity enhancer to provide sufficient strength to the gel so to control the drug release for a period of 8 hrs.

Full factorial design was applied to optimize the formulation where gelling capacity, gelling strength and viscosity were taken as dependent variables. The dependent variables were concentration of Carbopol 980 and HPMC K4M.One of the crucial factor of in pH triggered situ gelling is gelling capacity. Before administration formulation must be in liquid form and after administration solution should quickly converts into the gel. Thus the formed gel is responsible for the sustained release of drug from the formulation. Gelling capacity of the formed gel is based on the concentrations of the polymers used in the different formulations. Another vital parameter of pH triggered situ gelling is viscosity. *In situ* gelling formulations should have optimum viscosity so that it is easy to administer. There was significant increase in the viscosity of solution as concentration of HPMC K4M was increased. The viscosity of the formulations F7, F8 and F9 was more as compared to formulations F1, F2 and F3. The formed *in situ* gel is responsible for the sustained release of drug from the formulation. Moreover gel formed must retain its integrity without dissolving/eroding for a prolonged period. Comparing all the nine formulations F1 showed least gel strength, formulation F4 and F5 indicated moderate gel strength and formulation F9 had highest gel strength. This is attributed due to increase in polymer concentration which in turn increases the gel strength.

The optimized formulation was selected form design space after the application of constraints. A model validation was done by formulation a validation batch. The model is said to be validated when the percentage bias is less than 5%.

The optimized formulation did not showed any significant difference in the clarity, pH, viscosity and gelling strength of the when subjected for sterilization process. The results of the optimized batch clearly demonstrated that optimized formulation was able to retain drug for prolonged period of time (8 hr). Initially the formulations showed burst release effect, then the drug released occurred slowly from the polymeric matrix. This may be owing to structural reformation of the hydrophilic polymer HPMC K4M. Increasing its concentration resulted in increase in the tortuosity or gel strength of the polymer. The pH triggered *in situ* gelling system of to bramycin formulation would have good patient acceptance because it is easy to in still and gradually erodes by dissolution of the gel, avoiding the need for removal. Optimized formulation followed Higuchi diffusion controlled mechanism.

The developed formulation passed the sterility test as there was no growth of micro-organism. No ocular damage were observed and also no abnormal clinical signs to the cornea, iris or conjunctivae were visible in rabbits, which concluded that the pH triggered *in situ* gelling system of tobramycin formulation was non-irritant to eye. Optimized formula had no significant change in antimicrobial efficiency when it was formulated into pH triggered *in situ* gelling system against the tested *E. coli* (Gram negative, aerobic) and *S. aureus* (Gram positive, anaerobic) micro-organism. Results showed no significant change in the results of appearance, pH, viscosity, gelling capacity and drug content when stored at accelerated condition and room temperature for a period of one month.

CONCLUSION

Ophthalmic *in situ* gelling system of tobramycin was successfully formulated using pH sensitive polymer (carbopol 934) and viscosity enhancing agent (HPMC K4M). The optimized formulations remained in liquid at non-physiologic conditions while it gets converted to gel form at physiologic pH condition. Optimized formulation was sterile, non-irritant, isotonic and stable and also it can be substitute to conventional eye drops formulations of tobramycin which could provide a sustained release for a period of 8 hr.

ACKNOWLEDGEMENT

Nil.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

ABBREVIATIONS

ZOI: Zone of Inhibition; **ANOVA:** Analysis of variance; **HPMC:** Hydroxypropyl methylcellulose; **RBC:** Red blood cells; **FTGM:** Fluid thioglycolate media; **SCDM:** Soya bean casein digest media.

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