RESEARCH ARTICLE

Microemulgel Delivery of Ciprofloxacin Hydrochloride

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ABSTRACT

Background: Ciprofloxacin hydrochloride is broad spectrum carboxyfluoroquinolone antibiotic from biopharmaceutics classification system (BCS) class IV. The oral dosage form exhibits gastric irritation whereas the topical cream has demonstrated poor penetration and low bioavailability.

Objective: To optimize microemulsion-based gel of ciprofloxacin hydrochloride to increase its solubility and permeability through the cutaneous layer for targeting bacterial skin infections.

Methods: To develop microemulsion, oil (soya oil, castor oil, oleic acid, isopropyl myristate and vegetable oil), surfactant (cremophore, span 80, tween 80) and cosurfactant (PEG 600 and PEG 400, propylene glycol) were evaluated. To depict the microemulsion formulation pseudo ternary phase diagram was employed. %Transmittance, zeta potential, dissolution study and size analysis were carried out for evaluation of microemulsion. 3^2 factorial design was used. Two variables i.e concentration of Sepineo P600 and Carbopol 934 effect on microemulgel was evaluated. Evaluation of gel was carried for physical parameters, antimicrobial, *in-vitro* and *ex-vivo* release study.

Results: Solubility analysis suggested tween 80, oleic acid and propylene glycol for the formulation of microemulsion. Zeta potential for microemulsion batch F1 was -11.3 mV. This indicated good stability. I*n-vitro* release study showed 91.98% percentage cumulative drug release for batch F1 at 8 hours. Microemulsion-based gel (F1) showed 22.96% inhibition against bacteria which proved its antibacterial activity.

Conclusion: The obtained results exhibited that the permeability and bioavailability of the drug was increased when given through a topical route.

Keywords: Antibacterial, Carbopol 934, Ciprofloxacin hydrochloride, Gel, Microemulsion, Topical.

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INTRODUCTION

The topical drug delivery system deals with formulation application to the skin for the treatment of various skin disorders. This route is best suited when other routes as rectal, sublingual, parenteral and oral administration fail. This route also act as targeted delivery in case of local skin infections. Ciprofloxacin hydrochloride is carboxyfluoroquinolone chemically. It is an antibiotic (broad-spectrum) belonging to BCS class IV. It acts against gram-negative and gram-positive bacteria.[1] Commercially, ciprofloxacin hydrochloride is available as oral dosage form, topical cream, ophthalmic ointment and otic solution.[2] The oral dosage form exhibits gastric irritation whereas the topical cream has demonstrated poor penetration and low bioavailability into cutaneous layers. The formulation of a microemulsion-based gel of ciprofloxacin hydrochloride is an approach to increase the drug solubility and permeability through a cutaneous layer. It will increase the therapeutic performance of the drug. Microemulsions are thermodynamically stable. They have small droplet size and high solubilization capacity. It is when converted into gel by the appropriate gelling agent to form a micro emulsion-based gel, it will increase the adherence to the skin. This will increase the bioavailability of drug and lead to less variation in the pharmacokinetics of drug.[3,4] The focus of present research was to check the therapeutic potential of microemulsion-based gel with respect to the targeted delivery of ciprofloxacin hydrochloride.

MATERIALS AND METHODS

Ciprofloxacin hydrochloride as gift sample. Tween 80, oleic acid, propylene glycol, triethanolamine, Carbopol 934, Sepineo P600 were purchased.

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Characterization of Drug

Melting point was determined. The drug was triturated in mortar pestle along with KBr (1:10). The powder mixture was compressed into a pellet. FTIR spectrum was recorded using FTIR spectroscope (Jasco 4700 series) between 4000 to 400 cm^{-1} range. The obtained FTIR was compared with the standard. DSC thermogram was recorded. Sample was heated under nitrogen up to 300°C. The heating rate was 10°C/min with flow rate of 50 mL/min.[4]

Development of Microemulsion

Surfactant, oil and co-surfactant selection

To 2 mL of oil (castor oil, isopropyl myristate, soya oil, oleic acid and vegetable oil), cosurfactant (propylene glycol, PEG 400 and PEG 600) and surfactant (span 80, cremophore and tween 80) excess amount of drug was added. This was kept on stirring for 48 hours on a mechanical stirrer. Centrifugation was done at 5000 to 7000 rpm for 15 to 20 minutess and analyzed using UV spectrophotometer at 278 nm.[5]

Table 1: Oil: surfactant batches

Microemulsion batch	*Water added (mL)*
A1	1.21
A2	0.7
A3	0.8
A4	0.9
A5	1
A6	0.7
A7	0.6
A8	0.5
A9	0.2

Table 2: Surfactant: co-surfactant batches

Microemulsion batch	*Water added (mL)*
B1	1.21
B2	0.8
B3	0.2

Table 3: Selection of variables

Variables (Level)	*Independent variables*	
	Concentration of Carbopol 934 (%)	*Concentration of Sepineo 600 (%)*
Low (-1)	2	2
Medium (0)	3	3
High (+1)	4	4

Phase diagram (Pseudo ternary)

The titration method was used for the preparation of microemulsion. Chemix School Software was used. Tables 1 and 2 shows the Oil: surfactant and Oil: Smix ratios analyzed.[6]

The system with the highest %transmittance was considered for further development of formulation.

Characterisation of Microemulsion

%Transmittance

Distilled water was used for dilution and as blank. %transmittance was measured at 650 nm.

Globule size measurement

Size analysis of microemulsion was carried out by inverted microscope. Particle size was measured by Zetasizer (Malvern)

Zeta potential

Batch B2 zeta potential was measured by Zetasizer (Malvern) at 25ºC. After 10 mL dilution of microemulsion result was recorded.[6]

Development of Microemulsion Based Gel

Gel phase preparation

Polymers such as carbopol 934, sepineo 600, and xanthan gum were tried alone and in combination (1–5% conc). Polymers were prepared by dispersing them in warm water (70–75° C) separately and soaked (24 hours) before use.

Preparation of microemulsion-based gel

Carbopol 934 and sepineo 600 were used as gelling agents. Microemulsion was added to gel.[7]

Experimental design

3^2 level factorial design was applied (Design Expert version 11 Software). As per Tables 3 and 4 batches were prepared.[8]

Evaluation of Microemulsion based Gel

Physical examination

Microemulsion-based gels were evaluated for homogeneity, color, and consistency.[9]

Table 4: Factorial batches

Ingredients (%w/w)	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
Oleic acid	1	1	1	1	1	1	1	1	1
Tween 80	3	3	3	3	3	3	3	3	3
Sepineo 600	0.2	0.3	0.4	0.2	0.3	0.4	0.2	0.3	0.4
Propylene glycol	5.7	5.7	5.7	5.7	5.7	5.7	5.7	5.7	5.7
Carbopol 934	0.2	0.2	0.2	0.3	0.3	0.3	0.4	0.4	0.4
Drug	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Triethanolamine	pH 6 to 7								
Water	q.s.								

pH

Using digital pH meter pH was measured for 1% aqueous solutions.

Spreadability test

For transdermal formulations, spreadability inspects uniformity and ease of application which is expressed as spreading coefficient (S). The apparatus used for the measurement of spreadability consists of two glass slides.[8,9] Spreadability was calculated as the weight needed to move slide in gm multiplied by the distance traveled by glass slide in cm. This was divided by time which needed to run distance L in seconds.

Viscosity study

It was determined by Brookfield's viscometer. Viscosity was recorded at room temperature.[10]

Drug content determination

In 1-gm of microemulgel was dissolved in methanol. It was subjected for sonication for 15-20 mins, filtered and diluted with methanol. It was analyzed spectrophotometrically at 278nm.

Drug – excipient compatibility study

UV spectrum was recorded using UV spectroscopy.

FTIR spectroscopy

IR spectra of drug was recorded using a potassium bromide pressed disc. The IR spectra of ciprofloxacin hydrochloride, sepineo P600, Carbopol 934 and physical mixture (drug 1: excipients 1) were obtained using an FTIR spectrometer to compare for the common peaks.

DSC analysis

DSC for drug, excipient and physical mixture was recorded.

In-vitro Release Analysis

Cellophane membrane

In Franz diffusion cell cellophane membrane was placed. Gel (equivalent to 0.05%) was applied. Cell was agitated at 50 rpm. Absorbance was measured.[10,11]

Same procedure was followed for egg membrane.

Ex-vivo Drug Release Study

Procedure mentioned in cellophane membrane was followed for goat skin.

In-vitro Antimicrobial Study

The antimicrobial study was determined by using disk diffusion method. *Staphyloccocus aureus* was used as a standard bacterial strain against a standard drug, microemulsion, microemulgel and marketed preparation (Cipro-cf). Sterilized molten agar (20 mL) was poured evenly on petri dish previously cleaned and sterilized. The drug concentration of 1000 µg/mL were prepared in phosphate buffer 6.8. *S. aureus* was inoculated into the agar plates and incubated for 24 hours.[12,13]

%Zone of inhibition = Length of inhibition ÷ Total length of streaked culture × 100 -- Eqn. 1

Ex-vivo Drug Dissolution Study

Chick ileum was used for study in USP type II apparatus. The ileum was tied at one end and 1-mL microemulsion equivalent to (0.05% Ciprofloxacin Hydrochloride) was filled in it. Similar was done for plain drug and optimized microemulsion-based gel F1. Ileum parts were then suspended in 900 mL distilled water with continuous aeration. Withdrawn samples were analyzed by UV.[11]

Release Kinetics

Best fit model was determined,[14] correlation coefficient (R^2) was found out. PCP disso was used.

ANOVA study

Design Expert 11 was used

Permeation data analysis (Flux)

Drug permeated through skin per unit time (PCP disso v3 software) at a steady state was determined.

Stability study

After 3 months at 30 and 40°C at 65 and 75% RH viscosity, consistency, physical appearance, and drug content was determined for samples.

RESULTS AND DISCUSSION

Drug Characterization

The drug was crystalline faint yellow to light yellow powder. The melting point was 230°C matching to reference 225 to 257°C. UV, DSC and FTIR studies confirmed drug identification.

Saturation solubility in surfactant, oil and co-surfactant

Ciprofloxacin Hydrochloride exhibited the highest solubility in oleic acid which was 4.22 mg/mL and in surfactant tween

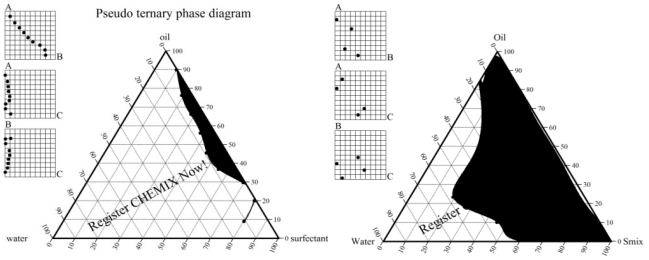


Figure 1: (A) Oil, surfactant, water (B) oil , Smix, Water ; Pseudo-Ternary Phase Diagram

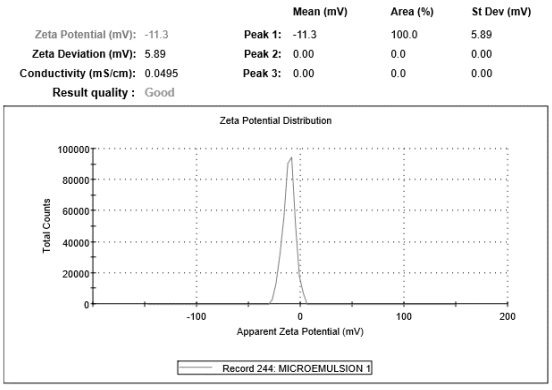


Figure 2: Zeta potential

80 it was 3.31 mg/mL. Cosurfactant propylene glycol was selected with a solubility of 0.538 mg/mL. Tween 80, oleic acid and propylene glycol were used for the formulation of microemulsion.

%Transmittance

Batch B2 showed 94.28 %transmittance indicating transparency of prepared microemulsion.

Construction of pseudo-ternary phase diagram

It was constructed. Shaded area (Figure 1) shows a transparent or clear microemulsion region.[15,16] Microemulsion was found at S_{mix} ratio 1:2 (Figure 1B).

Characterisation of Microemulsion

Zeta potential

Batch F1 showed -11.3 mV zeta potential indicating good stability (Figure 2). Values ± 30 mV or more are considered as stable. Poly disperse partials have major hurdle in drug diffusion.[13] The optimized batch F1 showed PDI 0.487 which is below 0.5 with good interpretation. Particle size analysis showed 195.3 nm size for microemulsion (Figure 3).

Appearance

All batches were white to yellowish-white in appearance with a smooth and creamy consistency.

pH, Viscosity, spreadability and drug content

pH was in 5.5 to 6.22 range. Batch F1 and F2 showed the highest spreadability. The viscosity of microemulgel was in the range of 8900 to 78000 cps. Batch F7, F8, and F9 showed the highest viscosity (Table 5). Drug content was in the range of 30 to 94%.

In-vitro Drug Release

Cellophane membrane

The percentage cumulative drug release at end of 8 hours for batch F1 was 91.98% and for F2 was 84.28%. Release was decreased with the increase in the concentration of carbopol 934. This was due to an increase in viscosity which negatively affected the release of a drug. F1 sowed the highest release (Figure 4).

- *Egg membrane*

Drug release was 80% at 8 hours for F1 and 70% for F2 which was less as compared to cellophane membrane.

- *Goat skin*

Batch F1 and F2 were subjected for diffusion study through Goat skin and the obtained release were compared with other membrane. The drug release was less at 15 and 30 minutes. An increase in drug release was observed at the end of 1-hour and later, at the end of 8 hours the release was observed to be decreasing. Fat content and thickness of goat skin was the reason of the difference. Batch F1 exhibited a slightly higher 73% drug release as compared to F2, i.e., 67%.

Ex-vivo Drug Dissolution Study

The drug release from microemulgel (82.3%), microemulsion (56.29%) and plain drug (40.34%) was observed. Release of drug from microemulsion was greater. The increase may be due to more penetration because of surfactant and co-surfactant

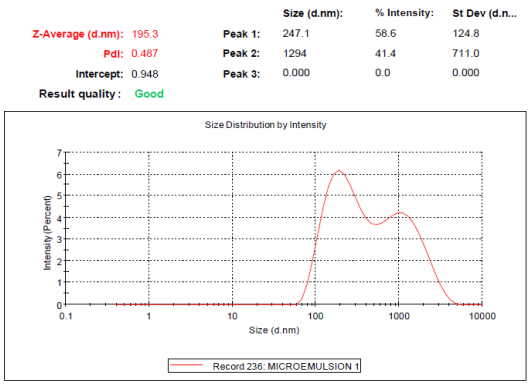


Figure 3: Zeta size

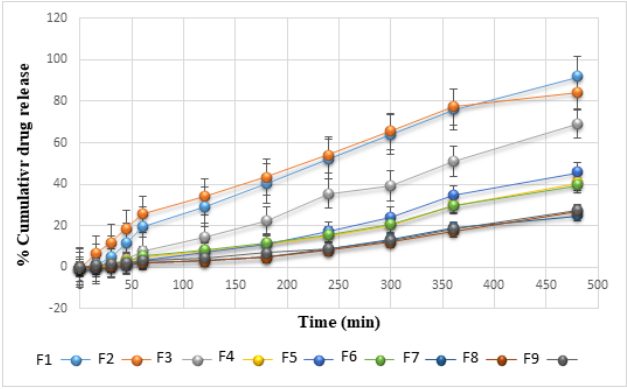
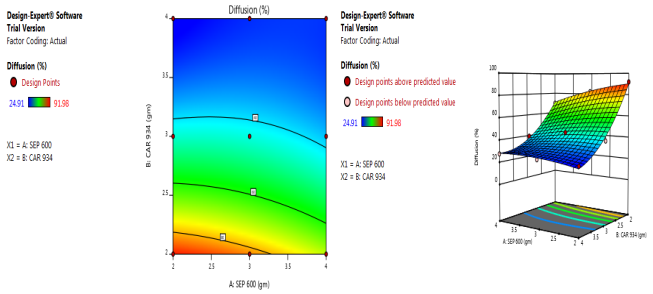


Figure 4: Release profiles

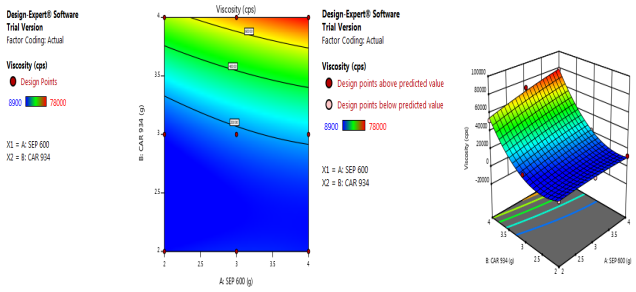
Table 5: Evaluation for F1-F9 batches

Formulation	*Viscosity (cps)*	*pH*	*Spreadability (g/cm)*	*%Drug content*
F1	8900 ± 2.21	5.5 ± 1.2	54.5 ± 2.31	94.8 ± 0.94
F2	10000 ± 1.36	6.04 ± 0.9	42.7 ± 4.4	82.1 ± 0.75
F3	12000 ± 2.28	5.8 ± 1	35.55 ± 3.25	74.28 ± 1.1
F4	13300 ± 0.75	7 ± 1.4	40.64 ± 1.64	38.21 ± 0.87
F5	15520± 3.31	6.8 ± 1.7	38.82 ± 1.25	50.42 ± 1.8
F6	22000 ± 1.54	5.9 ± 1.55	29.22 ± 1.25	42.49 ± 1.45
F7	52000 ± 1.28	6.66 ± 2.21	37.6 ± 1.25	32.58 ± 3.6
F8	72000 ± 3.32	6.04 ± 2.25	28.79 ± 2.2	28.58 ± 1.96
F9	78002 ± 3.32	6.22 ± 2.25	39.5 ± 2.4	30.78 ± 4.2



(A) **(B)**

Figure 5: %drug release and polymer concentration (A) Contour plot and (B) response surface plot



(A) **(B)**

Figure 6: Viscosity and concentration of polymers (A) contour plot (B) response surface plot

Kinetic Study

The release kinetics (Table 6) data indicated F1 follows matrix drug release. Korsmeyer-Peppas kinetics was followed by F2, F3, F4, F6, F8 and F7. Whereas F5 and F7 followed matrix kinetics.

Statistical Study

ANOVA study

The concentration of Sepineo P 600 (X_1) in %w/w and concentration of Carbopol 934 (X_2) in %w/w was independent variables and *in-vitro* drug release and viscosity were dependent variables[17,18] (Table 7).

- *Effect on drug release*

Drug Release = 108.10 +7.53*A -12.12*B +9.67*AB - 6.06*A2 -24.50*B … Eqn. 3

Where, A=Sepineo P 600 conc. and B = Carbopol 934 conc. The model terms were significant (R^2 0.9458) with adequate fitting to a quadratic model. Prob > F less than 0.05 confirmed the significance. Sepineo P 600 had a positive and Carbopol 934 had a negative effect (Figure 5). A ratio of 10.152 indicated adequate signal.

- *Effect on gel viscosity*

Gel Viscosity = 44116.67+15533.33*A+5241.67* B…… Eqn. 4

Where, A=Sepineo P 600 concentration and B = Carbopol 934 concentration

The model terms was significant (R^2 0.7799) indicating adequate fitting to a linear model. Prob > F less than 0.05 indicated significance. Ratio of 8.2636 indicates an adequate signal. Gel viscosity increases with an increase in the concentration of polymer (Figure 6). The coefficients of X_1 and X_2 were < 0.05, confirming significance.

Due to high degree of gelling capacity, Sepineo P 600 had a linear effect on viscosity. Values of $p < 0.0500$ indicated significance.

Table 6: Kinetics and drug release study

Batch	*R^2 Value*						
	Zero-order	*First order*	*Matrix*	*Hixon Crowell*	*Korsmeyer Peppas*		*Best fit model*
					n	*K*	
F1	0.8650	0.8650	0.9870	0.8650	0.4270	0.0002	Matrix
F2	0.6145	0.6145	0.9460	0.9662	0.3842	0.0002	Peppas
F3	0.2406	0.2406	0.9035	0.2406	0.3117	0.0003	Peppas
F4	0.6008	0.6008	0.9517	0.6008	0.3141	0.0003	Peppas
F5	0.6653	0.6653	0.8864	0.8002	0.3966	0.0003	Matrix
F6	0.2653	0.2653	0.8841	0.9684	0.2578	0.0003	Peppas
F7	0.6421	0.6421	0.8743	0.6421	0.2420	0.0003	Matrix
F8	0.6711	0.6711	0.9664	0.6711	0.3646	0.0003	Peppas
F9	0.6636	0.6636	0.9351	0.6636	0.3559	0.0003	Peppas

Table 7: ANOVA

Sr. No.	*Response model*	*Sum of squares*	*Df*	*Mean square*	*F value*	*p-value*	*R^2*	*Adequate precision*
1	Drug Release (480 minutes)	5069.50	5	1013.2	88.2	0.0019	0.9458	10.1517
2	Viscosity	6.210E + 09	5	1.242E + 09	86.87	0.0019	0.7799	8.2636

Table 8: Comparison of predicted and actual value

Polymers	*Coded levels*	*Actual levels*	*Response*	*% drug release at 8 hrs*	*Viscosity*
			Predicted value	91.98	9000
			Observed value	92.95	8900
Sepineo P 600	2	2	Standard deviation	7.40084	6602.55
Carbopol 934	2	2	Standard error mean	5.51626	3479.85

Table 9: Zone of inhibition

Formulation	*Total length of streaked culture (mm)*	*Length of inhibition*			*Average*	*%zone of Inhibition*
		1	*2*	*3*		
Pure drug	120	20	22	21	21	17.5
Standard	120	48	47	46	47	39.16
ME (batch A1)	120	12	10	14	12	10
Microemulgel (batch F1)	120	29	33	37	33	27.5
Cipro-cf Cream	120	16	20	17	17.66	14.7

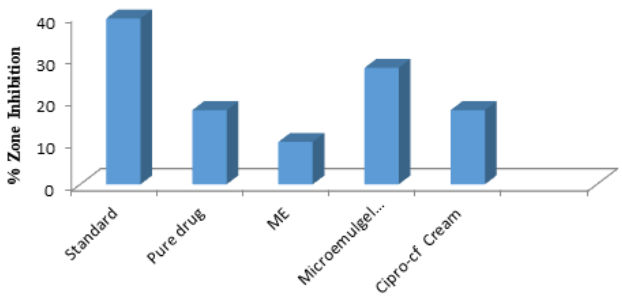


Figure 7: %zone of inhibition against *S. aureus*

Validation of Statistical Model

Validation for optimized batch F1 is in Table 8.

Flux

The flux of batch F1 was found to be more than other batches which was 0.2256 µg/cm^2/min.

Similarity factor

Batch F1 and marketed formulation (Cipro-cf cream IP) f2 (Similarity) was 19 and f1 (difference) was 65 indicating no similarity.[18]

Microbiological Assay

%Inhibition

Figure 7 shows antimicrobial activity. The %inhibition was a measure of antibacterial action against *S. aureus*. Ciprofloxacin hydrochloride, microemulsion, optimized batch of microemulsion bases gel (F1) and the marketed formulation of the drug (Cipro-cf Cream IP) were tested. Microemulgel (F1) showed 22.96% inhibition which proved that the prepared formulation exhibits antibacterial activity that is comparatively superior to that of pure drug (15.8 % inhibition), microemulsion (8.89% inhibition) and marketed formulation (13.08% inhibition) as shown in Table 9. This indicated microemulsion base gel of ciprofloxacin hydrochloride has been successfully developed for use as an antibacterial skin preparation.[19-21]

Minimum inhibitory concentration

Four concentrations (20, 30, 40 and 50 µg/mL) of optimized batch F1 were taken for the study. Zone of inhibition was found at 40, 45 and 50 µg/mL. It was lower than 40 µg/mL indicating it as Minimum inhibitory concentration (MIC).[22]

Stability Study

Appearance, %drug content, and viscosity (cps) for an optimized batch of microemulsion-based gel (F1) had not show in any changes after the stability study so it can be said to be a stable formulation.

CONCLUSION

Microemulgel was formulated using Carbopol 934 P and Sepineo P 600 as a gelling agent. UV, FTIR, and DSC studies proved compatibility in between the drug and the proposed excipients. Drug release and viscosity were dependent on the concentration of polymers. Sepineo P 600 has a greater linear effect on drug release and viscosity. This may be due to its high degree of gelling capacity. Statistical studies showed formulation F1 followed matrix release kinetics. In 40 µg/mL was the MIC of microemulgel. In conclusion, a stable, effective, and elegant microemulgel formulation, exhibiting good *in-vitro* drug release, viscosity, and antibacterial activity was formulated.

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