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COMPARATIVE ANALYSIS OF PEG AND ETHANOL FOR OPTIMIZED MICROEMULSION

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ABSTRACT

Ocular drug delivery is associated with several challenges, including tear dilution, nasolacrimal drainage, blinking, and limited corneal drug absorption. The present study aimed to formulate and evaluate a gentamicin sulphate ophthalmic microemulsion to improve ocular drug delivery^[1]. Gentamicin sulphate was incorporated using oleic acid as the oil phase, Tween 80 as surfactant, and ethanol or PEG 400 as co-surfactant. Pseudo-ternary phase diagrams were constructed at different surfactant-to-co-surfactant ratios to identify the suitable microemulsion region. Fourteen formulations were prepared by spontaneous emulsification and evaluated for physical appearance, pH, viscosity, globule size, zeta potential, drug content, and *in vitro* drug diffusion. Formulation optimization was performed using Design-Expert software, considering globule size and diffusion rate as responses^[4]. The PEG-containing formulations showed comparatively better performance, and F9 was identified as the optimized formulation. F9 exhibited a globule size of 10.34 nm, pH 7.0, zeta potential of -26.8 mV, and drug content of 88.23%. The optimized formulation demonstrated a maximum diffusion rate of 88.8%. Drug-release data followed zero-order kinetics, while Korsmeyer–Peppas analysis indicated non-Fickian case-II transport. The optimized formulation showed antimicrobial activity against *Escherichia coli*, with a zone of inhibition of approximately 25.21 mm. Thus, the developed microemulsion demonstrated desirable physicochemical properties, enhanced drug diffusion, and antimicrobial activity, indicating its potential as an ophthalmic drug-delivery system^[8].

KEYWORDS: Ophthalmic microemulsion, PEG 400, Drug diffusion, Ocular drug delivery

INTRODUCTION

Ocular drug delivery remains a significant challenge in pharmaceutical research due to the complex anatomy and protective physiological mechanisms of the eye. Barriers such as tear dilution, nasolacrimal drainage, blinking reflex, and the corneal epithelial layer substantially limit drug absorption, resulting in poor bioavailability of conventional ophthalmic formulations. Typically, less than 5% of an administered dose from standard eye drops reaches the intraocular tissues, necessitating frequent dosing and leading to reduced patient compliance and potential systemic side effects^[1].

To overcome these limitations, advanced drug delivery systems have been explored, among which microemulsions have emerged as a promising approach. Microemulsions are thermodynamically stable, isotropic systems composed of oil, water, surfactant, and co-surfactant. Their unique physicochemical properties, including nanoscale droplet size, high solubilization capacity, and optical transparency, make them particularly suitable for ocular applications. The small droplet size enhances corneal penetration, while the presence of surfactants can facilitate drug transport across biological membranes^[4].

In addition, microemulsions can improve drug residence time on the ocular surface by modulating viscosity and interfacial characteristics. This contributes to sustained drug release and enhanced therapeutic efficacy. The ability to incorporate both hydrophilic and lipophilic drugs further broadens their applicability in ophthalmic formulations. Moreover, their ease of preparation and long-term stability make them advantageous over conventional emulsions and other colloidal carriers.

The development of an ophthalmic microemulsion requires careful selection of formulation components and optimization of their ratios to ensure ocular compatibility, stability, and effectiveness. Characterization of the system involves evaluation of parameters such as droplet size distribution, zeta potential, pH, viscosity, drug content, and in vitro release behavior. These factors collectively determine the performance and safety of the formulation.

In this context, the present study focuses on the development and characterization of an ophthalmic microemulsion system aimed at enhancing ocular drug delivery. The formulation is designed to overcome conventional limitations by improving drug solubility, permeability, and retention, thereby offering a more efficient and patient-compliant therapeutic strategy for the management of ocular conditions^[9].

MATERIALS AND METHODS

Chemicals used

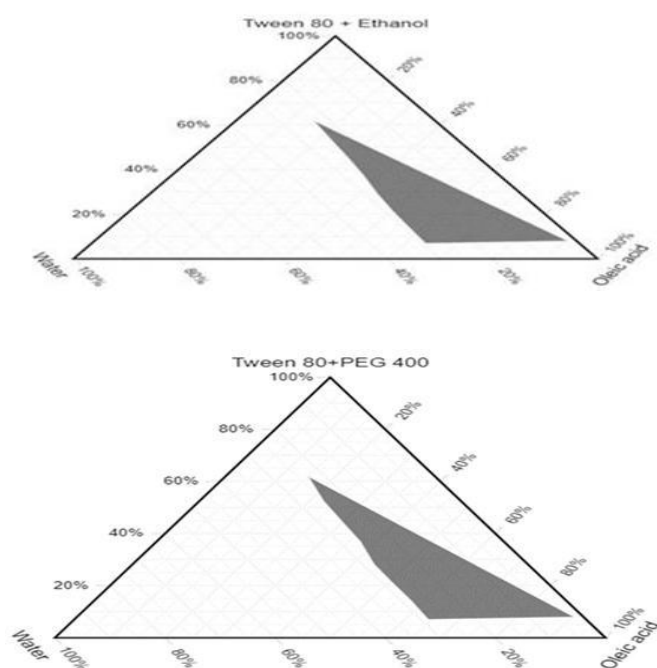
Gentamicin sulphate, Tween 80, Oleic acid.

Instruments used

Magnetic stirrer, Double beam UV spectrometer , FTIR , Digital pH meter , Brookfield viscometer, Malvern Nanozetasizer Zs90.

Construction of pseudo ternary phase diagram

The pseudo-ternary phase diagrams comprising the oil phase, surfactant, co-surfactant, and aqueous phase (water) were constructed to delineate the microemulsion region and identify the optimal compositional range for formulation development. The phase diagrams were developed using varying surfactant to co-surfactant (S:CoS) ratios of 1:1, 2:1, and 3:1, employing the aqueous titration method. During this process, water was incrementally added to mixtures of oil and surfactant/co-surfactant blends under ambient conditions to observe phase transitions. The compositions that resulted in clear, transparent, and isotropic single-phase systems were considered indicative of microemulsion formation. These compositions were subsequently converted into weight percentages and plotted on the ternary phase diagrams to demarcate the microemulsion region. Among the investigated ratios, the S:CoS ratio of 1:1 exhibited a comparatively larger and more well-defined microemulsion region, indicating its suitability for further formulation optimization..



Formulation of gentamicin sulphate ophthalmic microemulsion

Phase titration method or spontaneous emulsification

The preparation of the microemulsion was undertaken through the systematic construction of a pseudo-ternary phase diagram comprising the oil phase, aqueous phase (water), surfactant, and co-surfactant, to identify the optimal compositional range for microemulsion formation. The developed ophthalmic formulation represents a water-in-oil (W/O) microemulsion system. Initially, the surfactant was thoroughly blended with the co-surfactant to obtain a homogeneous mixture. This surfactant-co-surfactant blend was subsequently incorporated into the oil phase under continuous stirring. Thereafter, the aqueous phase was added dropwise with constant agitation to facilitate uniform dispersion and spontaneous emulsification. The process resulted in the formation of a clear, transparent, and thermodynamically stable microemulsion system, indicative of successful formulation development.

Table 1: Formulation design.

Formulation code	Gentamicin sulphate (mg)	Oleic acid (ml)	Tween 80 (ml)	Ethanol (ml)	PEG 400(ml)	Water(ml)
F1	300	41.66	23.33	23.33	0	11.66
F2	300	40	30	15	0	15
F3	300	41.66	31.23	10.41	0	16.66
F4	300	43.33	32	8	0	16.66
F5	300	50	33.3	6.66	0	10
F6	300	40	38.76	6.42	0	15
F7	300	45	35	5	0	15
F8	300	46.66	20	0	20	13.33
F9	300	40	33.32	0	16.66	10
F10	300	40	30	0	10	20
F11	300	45	36	0	9	10
F12	300	43.33	36.1	0	7.22	13.33
F13	300	43.33	37.14	0	6.19	13.33
F14	300	45	39.37	0	5.62	10

Analytical methods Determination of $\lambda_{\max}$

Gentamicin sulphate was dissolved in phosphate buffer pH 7.4 and scanned between range of 200-800nm

Preparation of standard calibration curve of gentamicin sulphate

10 mg of gentamicin sulphate was weighed and transferred into 100ml of volumetric flask and dissolved with phosphate buffer pH 7.4 as the first stock solution. And second serial dilution with phosphate buffer 7.4.

$2\mu\text{g/ml}$, $4\mu\text{g/ml}$, $6\mu\text{g/ml}$, $8\mu\text{g/ml}$, $10\mu\text{g/ml}$.

And absorbance measured.

Preformulation studies

Preformulation testing was an investigation of physical and chemical properties of a drug substance alone. It was first step in rational development of dosage form.

Organoleptic properties

Physical appearance of drug was observed and compared with official monographs

Solubility studies

Solubility of gentamicin sulphate was observed in different solvents such as distilled water, phosphate buffer pH 7.4, ethanol, chloroform, ether.

Partition coefficient

The partition coefficient of drug was determined by shaking equal volumes of organic phase (n-octanol) and the aqueous phase in a separating funnel. A drug solution of 1 mg/ml was prepared in phosphate buffer pH 7.4 and 50ml of this solution was taken in a separating funnel and shaken with an equal volume of n-octanol for 10 minutes and allowed to stand for 24 hours with intermittent shaking. Then, the concentration of gentamicin sulphate in aqueous phase was determined by using a UV spectrophotometer at 204 nm to get partition coefficient value. The partition coefficient (K_p) was calculated using the equation.³⁷

$K_p = \frac{\text{Concentration of drug in organic phase}}{\text{Concentration of drug in aqueous phase}}$

Concentration of drug in aqueous phase

Drug – excipient interaction studies

In order to find out the possible interactions between gentamicin sulphate, penetration enhancer, other excipients used in formulation of microemulsion, Fourier Transform Infra-red Spectroscopy (FT-IR) analysis was carried out on pure substances and their physical mixtures. FT-IR spectra of pure drug, excipients, and their physical mixtures were taken by KBr pellet technique between 600 – 4000 cm^{-1} . This is to ensure that no incompatibility between drug and excipients. Once spectra were recorded, the peaks of pure drug, excipients and physical mixtures of drug and penetration enhancers were compared for incompatibility

Characterization of microemulsion containing PEG and Ethanol for optimized microemulsion**Physical appearance**

The prepared microemulsion formulations were inspected visually for their colour, and clarity.

pH determination

1ml of microemulsion was accurately weighed and dispersed in 100ml of distilled water. The pH of dispersion was measured by using a digital pH meter.

Rheological studies

Viscosity (cps) of prepared microemulsion formulations were detected using Brookfield viscometer and this was repeated 3 times.

Globule size

Globule size of microemulsion was measured by using Malvern Nanozetasizer Zs90. Globule size of microemulsion ranges between 10-100 nm.

Zeta potential

The magnitude of the zeta potential indicates the degree of electrostatic repulsion between adjacent, similarly charged particle in dispersion. Malvern Nanozetasizer Zs90 is used to find the zeta potential.

Drug content

1 ml of sample was mixed with phosphate buffer pH7.4 and filter to obtain clear solution. Determined its absorbance using uv spectrophotometer. Standard plot of drug prepared in same solvent. Drug content is determined by using standard plot.

Drug content = (Concentration Dilution factor × Weight taken) Conversion factor

***In vitro* drug release of gentamicin sulphate microemulsion**

The *in vitro* release of gentamicin sulphate from formulations were studied using modified franz diffusion cell apparatus which was fabricated in our laboratory and used for release study. The diffusion medium used is phosphate buffer pH 7.4 for a period of 12 hours. Egg membrane was activated by soaking it in sodium chloride solution before use. Then it was mounted on diffusion cell and equilibrated with receptor fluid for 15 minutes. 25ml of microemulsion is placed on the membrane which is attached to this assembly. The donor compartment was suspended in 25ml diffusion medium

maintained at C so that membrane just touched the receptor medium surface. The medium was stirred at 50rpm using magnetic stirrer. Aliquots, each of 1ml were withdrawn at hourly intervals and replaced by an equal volume of receptor medium. The aliquots were diluted to 10ml with receptor medium and analyzed by UV spectrophotometer at 204nm and % drug

release was calculated.

Optimization of developed formulation by design expert software

Statistical design of experiments, a computer-aided optimization technique, was used to identify critical factors, their interactions and ideal process conditions that accomplish the targeted response. The best formulation was determined using Design Expert Stat ease software. I- Optimal design was used for the design. In the study water, oil and surfactant-cosurfactant mixture were selected as the 3 factor and globule size and diffusion rate were considered as the 2 responses. Hence 14 experimental trails were done, Trials were repeated twice to evaluate experimental errors and increase power ratio. Counter plots were drawn and optimum formulation was selected by optimization criteria.

Kinetic studies of optimized formulation

To determine the kinetics of release of the optimized formulations the cumulative amount of drug released from the optimized formulation (F9) was fitted in to various models representing zero order, first order, Higuchi's plot and Korsmeyer- peppas plot respectively.

Microbiological study of optimized formulation

a)Preparation of inoculums

Four or Five isolated colonies transferred into a 3ml of saline and rotate to get uniform suspension.

b) Inoculation of agar plate

Antimicrobial test was performed on previously prepared agar plate on which *E-coli* saline solution was spread with the help of glass spreader

Standard graph of gentamicin sulphate

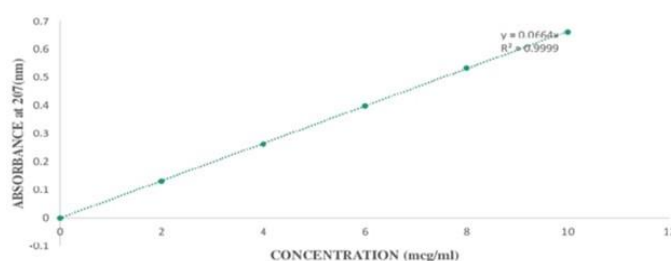


Fig 3: Standard graph of gentamicin sulphate.

c) Incubation of agar plates and measurement of zones of inhibition

The inoculated plates were incubated at 37°C for 24 h and then the zones of inhibition were measured. All the measurements were taken by viewing the back of the plate against a dark non-reflecting surface illuminated with reflected light.^[6]

Stability studies of optimized formulation

From the prepared gentamicin sulphate ophthalmic microemulsions, optimized formulation with highest *in vitro* drug release was subjected to stability studies. This study was carried out at temperature and humidity conditions as per ICH guidelines and the tests were carried out in a stability chamber. The temperature and humidity conditions used were,

RESULTS

Analytical method Determination of λ max

UV absorption spectrum of gentamicin sulphate in phosphate buffer pH 7.4 and the λ max was found to be 204nm.

Preformulation studies Organoleptic property

Gentamicin sulphate was white Colour, odour less, amorphous powder in nature

Solubility studies

Gentamicin sulphate was highly soluble in Distilled water, Soluble in Phosphate buffer pH 7.4, partially in soluble in Ethanol, Ether, Chloroform.

Partition coefficient

Partition coefficient of gentamicin sulphate in N – octanol phosphate buffer system was found to be -3 ± 0.001 (All values are expressed as a mean of $\pm$ SD, n=3).

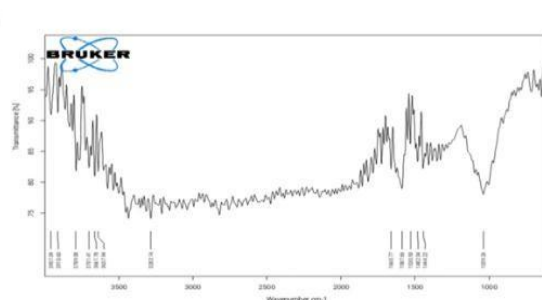
Identification and compatibility by FTIR studies FTIR studies were conducted in pure gentamicin sulphate, tween 80, PEG 400, ethanol and their physical mixture.

The FTIR spectrum is shown below.

FTIR of gentamicin sulphate

Table 3: FTIR of gentamicin sulphate.

Peaks (cm^{-1})	Groups
3561.78	N – H stretching
3283.14	O – H stretching
1587.66	C – C stretching
1039.26	C – O stretching



It is observed that there is no significant changes in the peak of pure drug gentamicin sulphate in the FITR of the pure drug with the combination of surfactant and cosurfactant. This indicate no significant incompatibility.

pH, viscosity, globule size and zetapotential

Table 7: pH, Viscosity, Globule size, Zetapotential.

Formulation code	Ph	Viscosity(cpc)	Globule size(nm)	Zeta potential (mV)
F1	6.4±0.024	206±0.02	10.95	-23.2
F2	6.6±0.013	205.8±0.01	12.56	-23.5
F3	6.6±0.064	205.9±0.06	15.81	-23.8
F4	6.8±0.052	206.2±0.02	16.54	-24
F5	6.9±0.023	206.9±0.01	14.35	-24.2
F6	6.9±0.013	207.2±0.03	10.95	-24.3
F7	7±0.092	207.4±0.06	14.64	-24.6
F8	7±0.012	205±0.03	10.48	-25.2
F9	7±0.083	204.9±0.04	10.34	-26.8
F10	7.1±0.072	205.9±0.02	10.65	-25.9
F11	7.4±0.042	205±0.02	10.5	-25.2
F12	7.4±0.031	205.6±0.01	10.54	-25.3
F13	7.4±0.034	205.2±0.01	10.6	-25.5
F14	7.4±0.021	205.2±0.02	10.25	-25.8

Drug content

Formulation code	Drug content (%)
F1	79.2±0.034
F2	81.1±0.021
F3	82.35±0.034
F4	82.85±0.087
F5	83.12±0.056
F6	85.52±0.041
F7	84.21±0.011
F8	86.13±0.031
F9	88.23±0.021
F10	87.56±0.041
F11	87.12±0.081
F12	87.26±0.043
F13	87.52±0.091
F14	88.23±0.042

Table 9: Cumulative amount of drug released.

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	6.5± 0.01 2	6.3± 0.01 1	5.9± 0.13	5.6± 0.01 1	6.9± 0.03 4	9.3± 0.01 1	6.2± 0.03 1	5.9± 0.01 1	8.9± 0.01 3	5.8± 0.01 1	8.9± 0.03 1	5.7± 0.06 1	6.6± 0.01 2	9±0. 011
2	19±0 .021	15±0 .032	13±0 .023	10±0 .011	14±3 2	19±0 .012	14±0 .011	11.3 ±0.0 12	19±0 .031	14±0 .013	23±0 .041	15±0 .011	16±0 .013	24±0 .031
3	28±0 .01	21±0 .13	19±0 .011	14±0 .021	19±0 .21	27±0 .011	19.8 ±0.0 23	17±0 .031	28.6 ±0.0 42	20±0 .021	31±0 .031	24±0 .031	20±0 .041	33.3 ±0.0 12
4	36±0 .012	29±0 .31	21±0 .42	18.8 ±0.0 12	26±0 .012	36±0 .043	23.6 ±0.0 11	22±0 .011	39.7 ±0.0 21	26±0 .013	45.3 ±0.0 41	30±0 .021	24.8 ±0.0 11	48.6 ±0.1 2
5	43±0 .013	41.3 ±0.1 2	36±1 2	31±0 .011	35±0 .012	43±0 .012	39±0 .021	30±0 .011	53.8 ±0.0 21	38±0 .031	52±0 .011	46±0 .012	40.6 ±0.0 21	54±0 .011
6	54.3 ±0.0 13	51.3 ±0.0 41	48±2 3	40±0 .13	48±0 .011	55±0 .032	53.3 ±0.0 12	43.2 ±0.0 31	69.2 ±0.0 14	47±0 .052	63.3 ±0.0 11	55.2 ±0.0 12	53±0 .013	68.7 ±0.0 12
7	66.1 ±0.0 14	61.3 ±0.0 13	59±3 2	56±0 .42	66±0 .011	73.2 ±0.0 11	66±0 .012	55.3 ±0.0 11	78.3 ±0.0 31	59±0 .032	74±0 .011	66.3 ±0.0 12	68±0 .013	76.9 ±0.0 41
8	69.4 ±0.0 11	66.4 ±0.1 2	61.8 ±12	58.4 ±0.0 21	69.3 ±0.0 13	75.8 ±0.0 42	68.3 ±0.0 42	58.9 ±0.0 11	80±0 .012	62.6 ±0.0 13	76.8 ±0.0 11	67.9 ±0.0 21	68.5 ±0.0 31	79.7 ±0.0 31
10	72.3 ±0.1 1	69.4 ±0.0 11	65.4 ±12	60.4 ±0.0 12	70.1 ±0.0 11	81.1 ±0.0 12	70.4 ±0.0 13	63.2 ±0.0 41	83.6 ±0.0 11	67.5 ±0.0 21	81.2 ±0.0 12	69.1 ±0.0 31	70.8 ±0.0 14	81.2 ±0.0 31
12	78±0 .052	74.2 ±0.0 11	70±3 2	65±0 .012	72±0 .32	84.6 ±0.0 42	73±0 .011	68.2 ±0.0 21	88.8 ±0.0 41	70±0 .061	85±0 .051	70.5 ±0.0 11	73±0 .031	86±0 .041

The evaluation studies conducted and it was concluded that formulation containing PEG was the best formulation from the 14 formulation prepared. The cumulative percentage data of F 8-F14 was fitted into various kinetic models to study the drug release pattern and similarly formulation F 8- F14 was used for microbiological study and stability studies as per ICH guidelines.

Optimization of developed formulation by design expert software

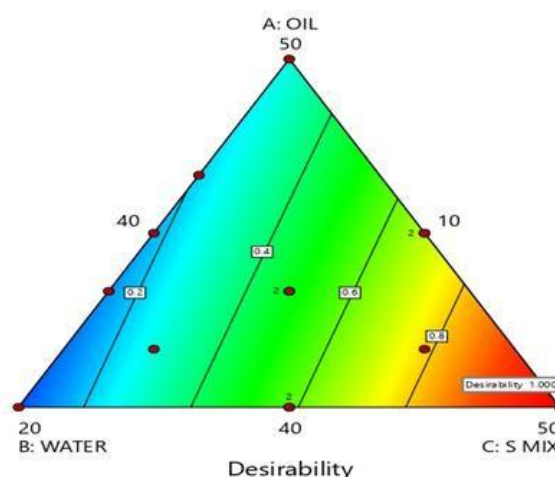
The formulation was optimized by Design Expert Software. Optimal design is used to find best formulation. 14 run were performed. To determine the best formulation two response will be considered that are globule size and diffusion.

Design-Expert® Software
Component Coding: Actual

Desirability

● Design Points
0.000 1.000

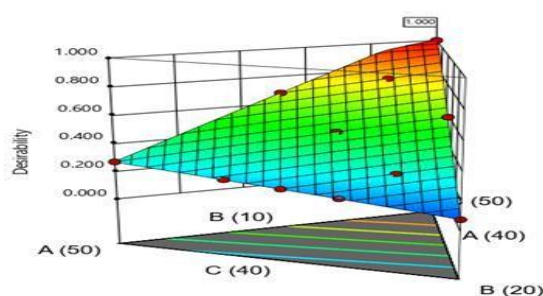
X1 = A: OIL
X2 = B: WATER
X3 = C: S MIX



Design-Expert® Software
Component Coding: Actual

Desirability
0.000 1.000

X1 = A: OIL
X2 = B: WATER
X3 = C: S MIX

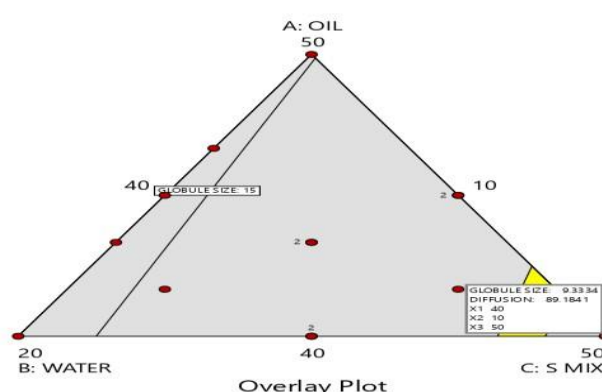


Design-Expert® Software
Component Coding: Actual

Overlay Plot
GLOBULE SIZE
DIFFUSION

● Design Points

X1 = A: OIL
X2 = B: WATER
X3 = C: S MIX



The optimized formulation show minimum globule size(10.48-10.56) and maximum diffusion rate(88.8), hence it was concluded that formulation PEG which showed the same values as that of the solutions offered by the software.

Kinetic studies of optimized formulation

The data from *in vitro* drug release of the optimized formulations was fitted to various kinetic equations of zero order, first order, higuchi model and korsmeyer – peppas model.

Table 10: Drug release Kinetics of optimized formulations.

Formulation code	Zero Order (R^2)	First order (R^2)	Higuchi (R^2)	Korsmeyer-peppas (R^2)
F9	0.901	0.051	0.8871	0.5767
F10	0.901	0.052	0.8872	0.5764
F11	0.902	0.052	0.8878	0.5766
F13	0.902	0.053	0.8876	0.5767
F14	0.902	0.053	0.8875	0.5768
F15	0.902	0.053	0.8873	0.5769

In the formulation F9, that R^2 value of zero order kinetic was found to be 0.901, first order release kinetic was 0.05 and higuchi plot was found to be 0.8871. Hence the formulation follows zero order kinetics.

To confirm exact mechanism of drug permeation from microemulsion, data was fitted to korsmeyer- peppas plot.

The R^2 value of Korsmeyer – peppas plot was found to be 0.5767. The value of slope of plot 'n' gives indication of release mechanism. The 'n' exponent value of best batch was found to be 2.1993. Hence it shows non- fickian case II transport mechanism.

Microbiological study of optimized formulation

The microbiological study was done on the optimized formulation and zone of inhibition measured with *E-coli* bacteria

Table 11: Zone of inhibition.

Formulation code	Zone of inhibition (mm)
F8	25.21mm
F9	25.21mm
F10	25.22mm
F11	25.22mm
F12	25.23mm
F13	25.24mm
F14	25.24mm

Stability studies of optimized formulation

From *in vitro* release studies of prepared formulations of microemulsion containing tween

80 as surfactant and PEG 400 as cosurfactant at the ratio of 2:1 showed best drug release profile. Hence, it was used for stability studies.

CONCLUSION

The present study successfully developed and evaluated a gentamicin sulphate ophthalmic microemulsion using oleic acid as the oil phase, Tween 80 as surfactant and PEG 400 as co-surfactant. The pseudo-ternary phase diagram approach was useful in identifying the suitable composition range for microemulsion formation. Fourteen formulations were prepared and systematically evaluated for their physicochemical and performance characteristics.

Among the developed formulations, the PEG-containing formulations exhibited better performance, and formulation F9 was identified as the optimized formulation. F9 showed a globule size of 10.34 nm, pH 7.0, zeta potential -26.8 mV and drug content 88.23%. Design-Expert optimization further confirmed that the optimized formulation provided a globule size of approximately 10.48–10.56 nm with a maximum diffusion rate of 88.8%.

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