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FORMULATION AND EVALUATION OF GENTAMICIN SULPHATE OPHTHALMIC MICROEMULSION

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ABSTRACT

Microemulsions are thermodynamically stable-phase transition systems. They exhibit small particle size (1-100nm) with lower surface tension which facilitates higher drug absorption and permeation. The present study involves the formulation and evaluation of gentamicin sulphate ophthalmic microemulsion for the treatment of bacterial infection of eye. Gentamicin sulphate is an aminoglycoside antibiotic. It is a BCS class III drug with high solubility, low permeability and poor biological half-life of 2 to 3hours. The solution and ointment of gentamicin sulphate for ophthalmic treatment is available, but it has been found that, ophthalmic microemulsions shows better permeability and corneal residence time compared to solutions and ointments. The study is also aimed to find which cosurfactant is more effective with the penetration enhancer. Ethanol and PEG400 are the cosurfactants and tween 80 as the surfactant (penetration enhancer). The primary evaluations are carried out to find the compatibility of gentamicin sulphate with other excipients and further studies to find out the effect of penetration enhancer with different cosurfactants. Optimization studies have been done by Design Expert Software using optimal design and 14 formulations were prepared. All the formulations where evaluated for physical appearance, viscosity, pH,globule size,zetapotential,drug content and *in vitro* release study. All the formulations showed results with acceptable range of the evaluation tests. The optimized formulation F9 showed drug release 88.8% and globule size 10.34nm. Kinetic studies, microbiological studies and stability studies were conducted on the optimized formulation. The mechanism of drug release was found to be zero order and non-fickian case II transport. The optimized formulation was found to be stable and sufficient antimicrobial effect.

KEYWORDS: Gentamicin sulphate, Microemulsion, Phase titration, Design Expert.

INTRODUCTION

The human eye is an important organ in the body with a unique anatomy and physiology. The eye is composed of two major parts: anterior and posterior segments. The anterior segment consists of the cornea, conjunctiva, aqueous humor, iris, ciliary body and lens. The remaining part of the eye is occupied by the posterior segment of the eye and consists of the sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor. Both anterior and posterior segments are affected by several vision threatening diseases.

The major concern with these conventional topical delivery systems is low bioavailability. In addition, numerous peroneal factors also influence the bioavailability of topical dosage form due to which less than 5% of the instilled does reaches the deeper ocular tissues to overcome this drug is formulated as microemulsion. Microemulsions are thermodynamically stable• phase transition systems. They exhibit small particle size (1-l00nm) with lower surface tension which facilitates higher drug absorption and permeation.

Gentamicin sulphate is an aminoglycoside antibiotic. It is a BCS class III drug with high solubility, low permeability and poor biological half life of 2 to 3hours. The solution and ointment of gentamicin sulphate for ophthalmic treatment is available, but it has been found that, ophthalmic microemulsions shows better permeability and corneal residence time compared to solutions and ointments. Hence the aim of my study is to improve the permeability and corneal residence time of gentamicin sulphate by formulating it as microemulsion, thereby to reducing the dosing frequency. In this study surfactant (tween 80) used as penetration enhancer, ethanol and PEG 400 are used as cosurfactant. The study also focused to find the best surfactant – cosurfactant combination with more effectiveness.[2]

MATERIALS AND METHODS

Chemicals used

Gentamicin sulphate (Yarrow chem, Mumbai), Tween 80 (Burogyne Burdidges and co, Mumbai), Oleic acid (Finar reagents, Ahmedabad).

Instruments used

Magnetic stirrer (Rotek instruments Kerala), Double beam UV spectrometer (Systronics UV – VIS spectrometer), FTIR (Jasco model FT/IR 4100), Digital pH meter (Roy instruments,Varanasi), Brookfield viscometer(LVDV Prime-1. Brookfield Engineering Laboratory, USA), Malvern Nanozetasizer Zs90(Malvern).

Construction of pseudo ternary phase diagram

Pseudo ternary phase diagram of oil phase, surfactant, co surfactant and aqueous phase (water) were developed to determine the regions of microemulsion formation. For phase diagram were constructed with surfactant to cosurfactant ration 1: 1,2:1,3:1using water titration method. At room temperature, the final composition of clear, single phase formulation were converted to weight percentage and plotted in points in the diagram and the surfactant cosurfactant ratio was 1:1 showed better region of microemulsion formation.[3]

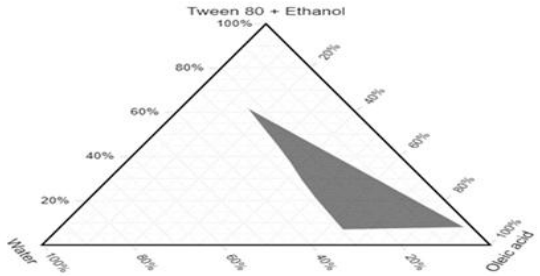


Fig 1: Pseudo ternary phase diagram of tween 80 and ethanol(1:1).

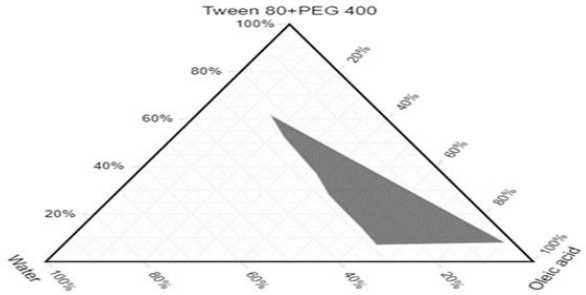


Fig 2: Pseudo ternary phase diagram of tween 80 and PEG400(1:1).

Formulation of gentamicin sulphate ophthalmic microemulsion

Phase titration method or spontaneous emulsification

The preparation of microemulsion involves the construction of a pseudo-ternary phase diagram composed of oil, water, surfactant & cosurfactant. The gentamicin sulphate ophthalmic microemulsion is water in oil microemulsion. The surfactant mix with the cosurfactant and then the mixture was added to oil phase with stirring and water was added dropwise with continues stirring and form clear transparent microemulsion.

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

In the Formulation design of Gentamicin sulphate ophthalmic microemulsion the 14 formulations suggested by design expert software. Optimaldesign was used for the study.[4]

Analytical methods

Determination of λ max

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

Preparation of standard caliberation 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. $2\mu g/ml$, $4\mu g/ml$, $6\mu g/ml$, $8\mu g/ml$, $10\mu g/ml$. 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 partitioncoefficient (Kp) was calculated using the equation.[37]

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

Drug – excepient interaction studies

In order to find out the possible interactions between gentamicin sulphate, penetration enhancer, other exipients 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 gentamicin sulphate

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 $\times$ Dilution factor $\times$ Weight taken) $\times$ 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 at37^0 C so that membrane just touched the receptor medium surface. The medium was stirred at50rpm 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.[5]

Kinetic studies of optimized formulation

To determine the kinetics of release of the optimized formulations the cumulative amound 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.

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,

1) $40^0C \pm 2^0$C at 75% +5%RH
2) $25^0C \pm 2^0$C at 60% + 5% RH
3) $5^0C \pm 3^0$C

Samples were withdrawn at 0 day,30 day time intervals for a period of 3 months and evaluated for physical appearance, pH, viscosity and drug content.[7]

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.

Standard graph of gentamicin sulphate

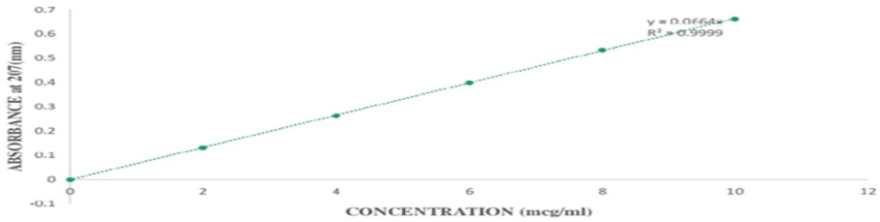


Fig 3: Standard graph of gentamicin sulphate.

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 ±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

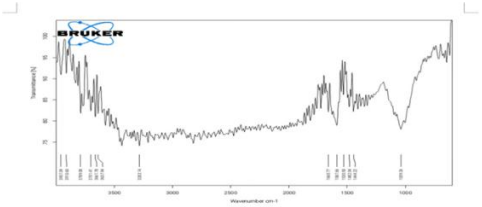


Fig 4: FTIR of gentamicin sulphate.

Table 4: FTIR of Gentamicin sulphate + Tween 80.

Peaks (cm^{-1})	Groups
3579.76	N – H stretching
3256.87	O – H stretching
1287.16	C – C stretching
1028.12	C – O stretching

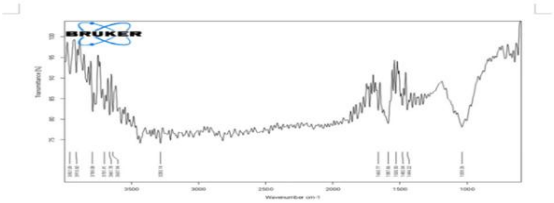


Fig 5 : FTIR of Gentamicin sulphate + Tween 80.

Table 5: FTIR of Gentamicin sulphate + Ethanol.

Peaks (cm^{-1})	Groups
3521.34	N – H stretching
3298.13	O – H stretching
1457.23	C – C stretching
1042.14	C – O stretching

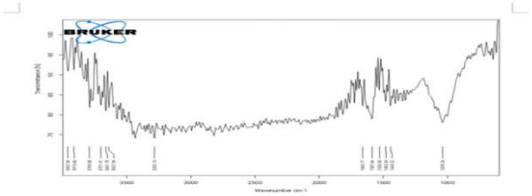


Fig 6: FTIR of Gentamicin sulphate + Ethanol.

Table 6: FTIR of Gentamicin sulphate + PEG 400.

Peaks (cm^{-1})	Groups
3461.32	N – H stretching
3213.87	O – H stretching
1612.12	C – C stretching
1032.67	C – O stretching

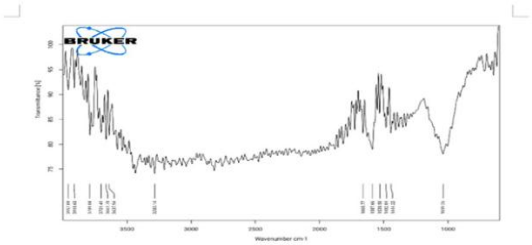


Fig 7: FTIR of Gentamicin Sulphate + PEG 400.

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.

This illustrated that gentamicin sulphate compatible with both surfactant and cosurfactants.

Formulation and characterization

Appearance of formulation

Microemulsion formulations F1 to F14 are all found to be slight yellow in colour, clear and transparent

pH, viscosity, globule size and zetapotential

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

Formulation code	Ph	Viscosity(cpc)	Globule size(nm)	Zetapotential (mV)
F1	6.5±0.024	205±0.02	10.95	-23.2
F2	6.5±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	7.2±0.092	207.4±0.06	14.64	-24.6
F8	7.2±0.012	205±0.03	16.48	-25.2
F9	7±0.083	204.9±0.04	10.34	-26.8
F10	7.1±0.072	205.9±0.02	14.65	-25.9
F11	6.9±0.042	206±0.02	11.5	-23.2
F12	6.9±0.031	206.6±0.01	14.54	-23.3
F13	6.8±0.034	207.2±0.01	14.6	-24.5
F14	6.6±0.021	207.2±0.02	11.25	-24.8

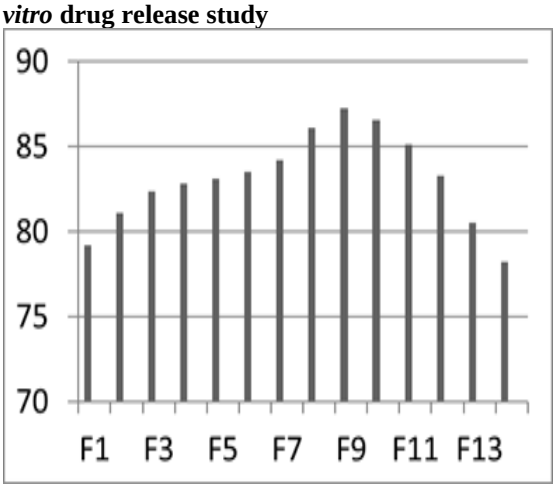
All values are expressed as mean ± SD, n=3

Drug content

Table 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	87.23±0.021
F10	86.56±0.041
F11	85.12±0.081
F12	83.26±0.043
F13	80.52±0.091
F14	78.23±0.042

***In vitro* drug release study**



All values are expressed as mean ± SD, n=3

Fig 8: Drug content.

Table 9: Cumulative amount of drug released.

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±0.012	6.3±0.011	5.9±0.13	5.6±0.011	6.9±0.034	9.3±0.011	6.2±0.031	5.9±0.011	**8.9±0.013**	5.8±0.011	8.9±0.031	5.7±0.061	6.6±0.012	9±0.011
2	19±0.021	15±0.032	13±0.023	10±0.011	14±32	19±0.012	14±0.011	11.3±0.012	**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±0.023	17±0.031	**28.6±0.042**	20±0.021	31±0.031	24±0.031	20±0.041	33.3±0.012
4	36±0.012	29±0.31	21±0.42	18.8±0.012	26±0.012	36±0.043	23.6±0.011	22±0.011	**39.7±0.021**	26±0.013	45.3±0.041	30±0.021	24.8±0.011	48.6±0.12
5	43±0.013	41.3±0.12	36±12	31±0.011	35±0.012	43±0.012	39±0.021	30±0.011	**53.8±0.021**	38±0.031	52±0.011	46±0.012	40.6±0.021	54±0.011
6	54.3±0.013	51.3±0.041	48±23	40±0.13	48±0.011	55±0.032	53.3±0.012	43.2±0.031	**69.2±0.014**	47±0.052	63.3±0.011	55.2±0.012	53±0.013	68.7±0.012
7	66.1±0.014	61.3±0.013	59±32	56±0.42	66±0.011	73.2±0.011	66±0.012	55.3±0.011	**78.3±0.031**	59±0.032	74±0.011	66.3±0.012	68±0.013	76.9±0.041
8	69.4±0.011	66.4±0.12	61.8±12	58.4±0.021	69.3±0.013	75.8±0.042	68.3±0.042	58.9±0.011	**80±0.012**	62.6±0.013	76.8±0.011	67.9±0.021	68.5±0.031	79.7±0.031
10	72.3±0.11	69.4±0.011	65.4±12	60.4±0.012	70.1±0.011	81.1±0.012	70.4±0.013	63.2±0.041	**83.6±0.011**	67.5±0.021	81.2±0.012	69.1±0.031	70.8±0.014	81.2±0.031
12	78±0.052	74.2±0.011	70±32	65±0.012	72±0.32	84.6±0.042	73±0.011	68.2±0.021	**88.8±0.041**	70±0.061	85±0.051	70.5±0.011	73±0.031	86±0.041

All values are expressed as mean ± SD, n=3

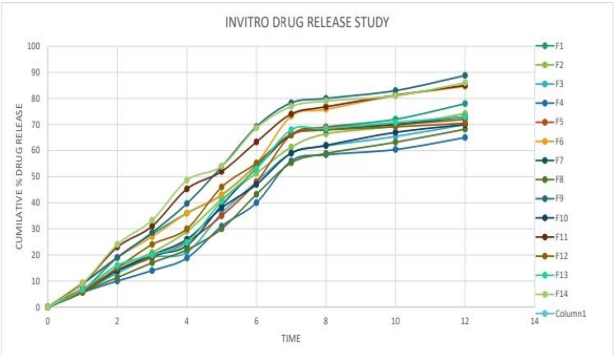


Fig 9: Cumulative amount of drug released.

The evaluation studies conducted and it was concluded that formulation F9 was the best formulation from the 14 formulation prepared. The cumulative percentage data of F9 was fitted into various kinetic models to study the drug release pattern and similarly formulation F9 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.

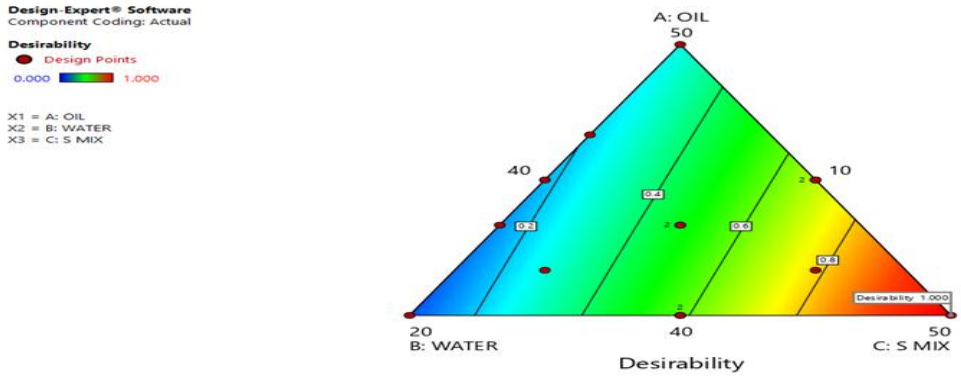


Fig 10: Counter plot.

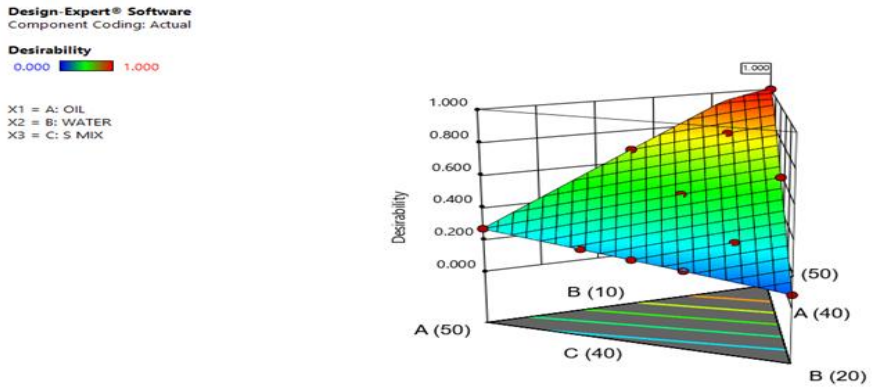


Fig 11: 3D plot.

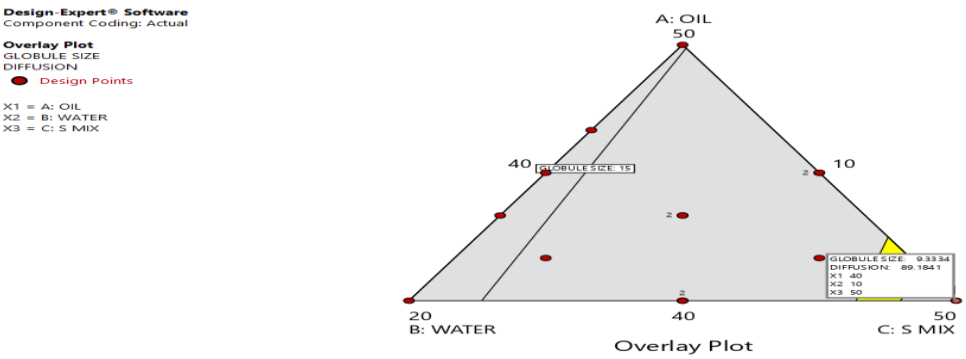


Fig 13: Overlay plot.

The optimized formulation show minimum globule size(10.34) and maximum diffusion rate(88.8), hence it was concluded that formulation F9 which showed the same values as that of the solutions offered by the software.

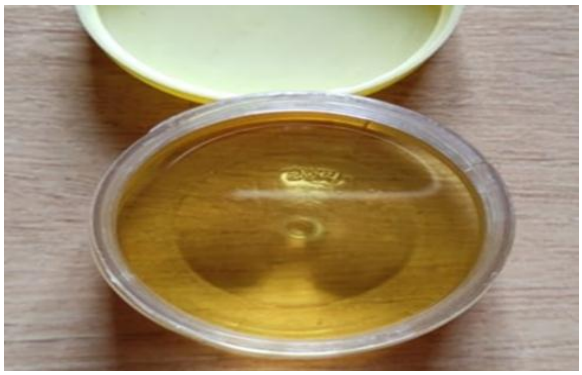


Fig 14: Photograph of optimized formulation F9.

Kinetic studies of optimized formulation

The data from *in vitro* drug release of the optimized formulation F9 was fitted to various kinetic equations of zer order, first order, higuchi model and korsmeyer – peppas model.

Zero order

Fig 15: Zero order release model.

First order

Fig 16: First order release model.

Higuchi plot

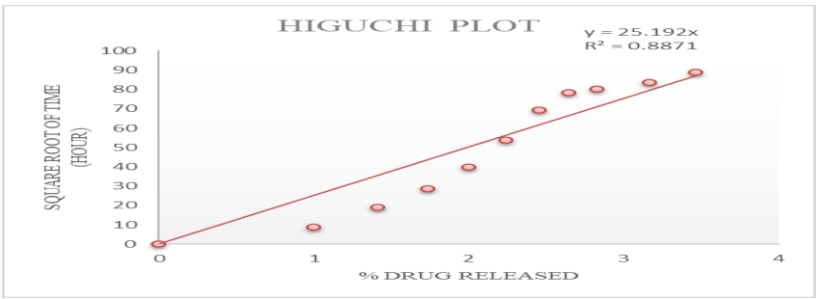


Fig 17: Higuchi release model.

Korsmeyer peppas plot

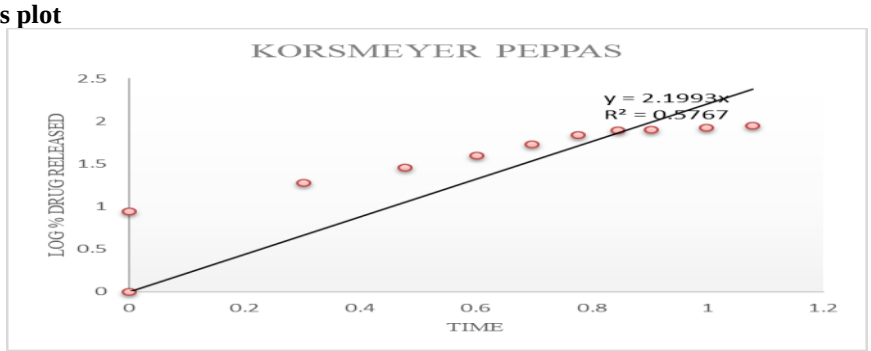


Fig 18: Korsmeyer peppas release model.

Table 10: Drug release Kinetics of optimized formulation F9.

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

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 korsemeyer- peppas plot.

The R^2 value of Korsemeyer – 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)
F9	25.21mm

Stability studies of optimized formulation

From *in vitro* release studies of prepared formulations of microemulsion, F9 containing tween 80 as surfactant (penetration enhancer) and PEG400 as cosurfactant at the ratio of 2:1 showed best drug release profile. Hence, it was used for stability studies

Table 12: Stability study of optimized formulation.

Formulation Code	Storage condition	Sampling interval	Appearance	pH	Viscosity (cpc)	Drug content (%)	*In vitro* drug release (%)
F9	40°C ±2°C at 75%±5%RH	0 day	Slight yellow, clear transparent	7±0.083	204.9±0.04	87.23±0.02	88.8±0.001
		30 day	Slight yellow, clear transparent	7±0.014	204.6 ±0.05	86.21±0.012	-------
		60 day	Slight yellow, clear transparent	7±0,043	204.63±0.02	86.13±0.032	--------
		90 day	Slight yellow, clear transparent	7±0.044	204.66±0.05	86.11±0.054	87..53±0.001
	25 °C ±2°C at 60%±5% RH	0 day	Slight yellow, clear transparent	7±0.03	204.9±0.04	87.23±0.02	88.8±0.001
		30 day	Slight yellow, clear transparent	7±0.032	204.68±0.04	87.22±0.056	-------
		60 day	Slight yellow, clear transparent	7±0.040	204.69±0.08	87.21±0.076	-------
		90 day	Slight yellow, clear transparent	7±0.038	204.72±0.05	87.12±0.076	88.13±0.001
	5°C±2°C	0 day	Slight yellow, clear transparent	7±0.083	204.9±0.04	87.23±0.02	88.8±0.001
		30 day	Slight yellow, clear transparent	7±0.042	204.75±0.02	87.21±0.098	-----
		60 day	Slight yellow, clear transparent	7±0.041	204.76±0.06	87.12±0.076	------
		90 day	Slight yellow, clear transparent	7±0.043	204.81±0.09	87.11±0.065	88.11±0.001

CONCLUSION

Gentamicin sulphate is an antibiotic belonging to the class of aminoglycoside antibiotic used in treating eye infection. It was BCS class III. it shows low permeability which needs to be improved during formation of microemulsion. Gentamicin sulphate is available in market in the form of solution. So, in order to improve the bioavailability of drug, It is formulated as microemulsion. The poor permeation of drug is improved by addition of penetration enhancer.

Gentamicin sulphate ophthalmic microemulsion were successfully developed using oleic acid as oil phase, tween 80 as surfactant (penetration enhancer), PEG 400 and ethanol are co surfactants, water is used as aeques phase. The microemulsion is formed by phase titration method and phase diagram is used to find the concentration range of microemulsion.

The optimization study is done with design expert software and the optimal design is used to select the optimized formulation from the 14 formulation suggested by the software. it was found that formulation

F9 with globule size 10.34nm and drug release 88.8% was found to be optimized. From the kinetic studies it was found that formulation F9 explained by zero order drug release and korsmeyer peppas plot which indicated non fickian diffusion. The optimized formulation was found to be stable and sufficient antimicrobial effect.

Thu from study concluded that gentamicin sulphate in the form of ophthalmic microemulsion increases the permeability and corneal residence time compared to solutions.

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