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Research Article

PREPARATION AND EVALUATION OF ERYTHROMYCIN MICROEMULSION FOR OPTHALMIC DRUG DELIVERY

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ABSTRACT

The main goal of the present study was to prepare and evaluate a stable transparent microemulsion with good corneal penetration and reduced frequency of dosing for ocular drug delivery. Extensive pre-corneal loss caused by rapid drainage and high tear liquid are the major drawbacks associated with conventional dosage forms 70% of total dosage forms available in market are conventional forms in which only 1 to 5% of the total drug penetrates into cornea and reaches to the intraocular tissue, To overcome these problems, microemulsion based systems are developed. Microemulsion was prepared by using oleic acid as an oil phase, tween 80 as surfactant, ethanol as co-surfactant and water as aqueous phase. The appropriate amount of drug was introduced into the oil phase with stirring. Mixture of surfactant and co-surfactant was added into the oil phase with vigorous stirring followed by addition of aqueous phase at a constant rate to form a transparent and stable microemulsion. The prepared microemulsions were evaluated for pH, viscosity, drug content, particle size and zeta potential. The optimised microemulsion formulation was appeared to be transparent and have minimum globule size of 12.1nm with 100% intensity, value of zeta potential was-11.11mV, pH 7.4, viscosity 153.23cp with highest *in-vitro* drug permeation (85%). The *ex-vivo* study report of optimised formulation using goat cornea also confirmed its permeation effectiveness.

Keywords: Microemulsion, Ocular delivery, surfactants, Erythromycin

1. INTRODUCTION

A large portion of the visual infections are dealed by application or organization of medication arrangements such as eye drops 90% of the accessible ophthalmic preparations are conventional dosage forms because of the simplicity and convenience [1]. The most well-known issue related with ophthalmic medication is quick pre corneal loss because of seepage and high tear liquid, Just 5% of the medication infiltrates into the cornea and reaches to the site of activity, and rest of the medication experiencing tran's conjunctival drainage by means of nasolacrimal channel [2].

The challenging task for pharmaceutical formulator is to build up a formulation with enhanced visual maintenance, increased corneal absorption and lessened side effects. Therefore to beat this issue numerous novel drug delivery approaches are studied like *in-situ* gels, bio adhesive gels, nanoparticles, liposomes, microemulsions [3]. Microemulsions are basically thermodynamically stable and clear mixtures of oil, water and surfactants, and sometimes also available in combination with co surfactants.

In these types of preparations there are basically 2 phases, one is aqueous phase and another one is oil phase. The aqueous phase comprises of salt and different fixings while the oil phase comprises of various hydrocarbons, oils and waxes [4]. Microemulsions are generally prepared by simple blending of components with no shear or weight and these are steady arrangements because of the presence of large amount of surfactants, high retention and absorption of microemulsion is due to their lower surface tension and little bead size is the unique property of microemulsion [5].

Erythromycin is a broad-spectrum, macrolide antibiotic with antibacterial spectrum similar to or slightly wider than that of penicillin, and is often used for people who have an allergy to penicillin. For respiratory tract infections, it has better coverage of atypical organism, including mycoplasma [6]. Administration of erythromycin is used to treat trachoma, Erythromycin diffuses through the bacterial cell membrane and reversibly binds to the 50S subunit of the bacterial ribosome. This prevents bacterial protein synthesis. Erythromycin may be bacteriostatic or bactericidal in

action, depending on the concentration of the drug at the site of infection and the susceptibility of the organism involved [7].

2. MATERIAL AND METHODS

Erythromycin was obtained as a gift sample from Mankind pharmaceuticals, oleic acid, tween 80, ethanol, and distilled water was obtained from central drug house Pvt. Ltd, India.

2.1. Preparation of drug loaded microemulsion

Erythromycin microemulsion was prepared by mixing the adequate quantity of drug in oleic acid i.e. (oil phase) for about 20 minutes at a low speed in magnetic stirrer. Then the mixture of surfactant and co-surfactant (Tween 80 was taken as surfactant and ethanol was taken as a co-surfactant which provides clarity to the microemulsion) was added in the oil phase at a constant rate and allow to rotate at 400 rpm. Finally an appropriate amount of water was added to the mixture drop by drop to get a clear and transparent microemulsion and different ratios were prepared from 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9.

2.2. Evaluation of Microemulsion [8-10]

2.2.1. Determination of pH

The pH of the prepared microemulsion was determined by using calibrated digital pH meter, In this 1gm of microemulsion was added and dissolved in 100ml distilled water and kept for 2 hours, the pH of the following medium was checked using digital pH meter.

2.2.2. Viscosity

Viscosity of the prepared microemulsion was evaluated by using Brookfield viscometer. The prepared microemulsion was subjected to spindle 63 at different rpm. The data was collected and a graph was plotted.

2.2.3. Drug content

For determination of drug content, microemulsion containing 100mg drug was dissolved in 100ml of 0.1N HCL taken in volumetric flask. Then the solvent was filtered, 1 ml was taken in 50ml volumetric flask and diluted up to the mark with 0.1N HCl and then subjected to UV spectrophotometer at 285nm.

2.2.4. Particle size distribution, PDI and Zeta potential study

Particle size and zeta potential of the micro formulation was determined by using Differential light scattering with a zetasizer. The micro preparations were diluted with ultra-pure water and analyzed using zetasizer. The surface charge determination was performed using an aqueous dip call in an automatic mode by placing diluted samples in the capillary measurement cell and the position of cell was adjusted.

2.3. *In-vitro* permeation study

Drug release studies were conducted by using Franz diffusion cell employing a dialysis membrane. The membrane was initially soaked in phosphate buffer 7.4 for 24 hours. After that it was clamped between donor and receptor compartments of Franz diffusion cell. The receptor compartment was filled with phosphate buffer 7.4 and was magnetically stirred throughout the whole process. The donor compartment contain appropriate amount of preparation. Appropriate (1ml) of sample were withdrawn from the receptor compartment at specific time intervals and were replaced with fresh buffer solution to maintain sink Condition. After that samples were analysed for drug concentration using UV-Visible spectrophotometer at 285nm and then cumulative drug release was determined.

2.4. *Ex-Vivo* permeation study

Ex-vivo studies were conducted using goat's corneal membrane. Membrane is isolated and kept in 0.9% NaCl solution overnight. The membrane was clamped between donor and receptor compartments of Franz diffusion cell. The receptor compartment was filled with phosphate buffer 7.4 and was stirred throughout the whole process. Appropriate (1ml) of sample were withdrawn from the receptor compartment at specific time intervals and were replaced with fresh buffer solution to maintain sink Condition. After that samples were analyzed for drug concentration using UV-Visible spectrophotometer at 285nm and then cumulative drug release was determined.

3. RESULT AND DISCUSSION

The pH of all formulations were found to be in the range of 6.9 to 7.4 as shown in table 1 which matches with the physiological pH of human eye it shows that it will not cause any irritation after application. The viscosity of all formulations ranges from 119 to 153cp shown in (fig 1) the graph plotted shows Non-Newtonian pseudo plastic flow, this type of fluid displays a decrease viscosity with an increase shear rate, the drug content estimation was done and the absorbance were measured by UV spectrophotometer drug content was calculated. Drug content of all

formulations was found to be between 79.55 to 95.56% (fig 2).

The particle size of prepared micro formulations F1 to F5 ranges from 12.1nm to 743.4 nm. Particle size distribution graph (size distribution by intensity) for formulation (F1 and F2) is shown in (fig 3, 4). All the formulations showed uniform particle size distribution except formulations F4 and F5. Hence, it was concluded from the data that with increase in surfactant and co surfactant ratio particle size decreases, which leads to promote corneal permeation.

Table 1: pH, viscosity and drug content of prepared microemulsion

Formulation code	pH	Viscosity (Cp)	Drug content (Mean±std)
F1	7.4±0.12	153.23±0.83	95.56±0.23
F2	7.0±0.09	146.10±0.96	91.89±0.98
F3	7.2±0.02	133.45±1.22	89.76±0.83
F4	7.3±0.14	128.66±1.37	85.91±0.75
F5	6.9±0.04	119.85±0.79	79.55±0.33

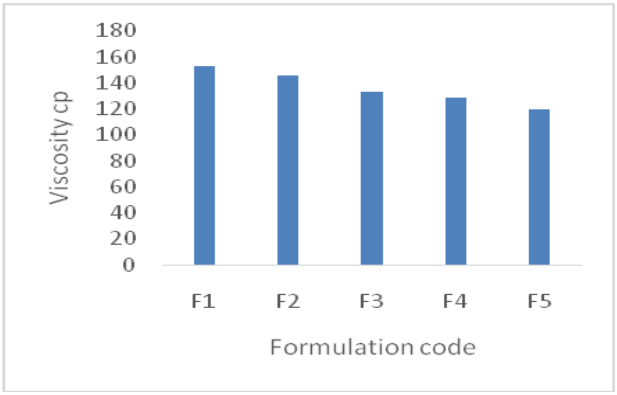

Fig. 1: Viscosity of formulation F1 to F5

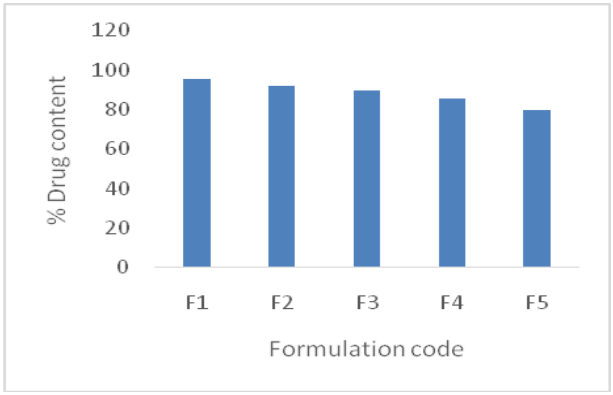

Fig. 2: Drug content of formulation F1 to F5

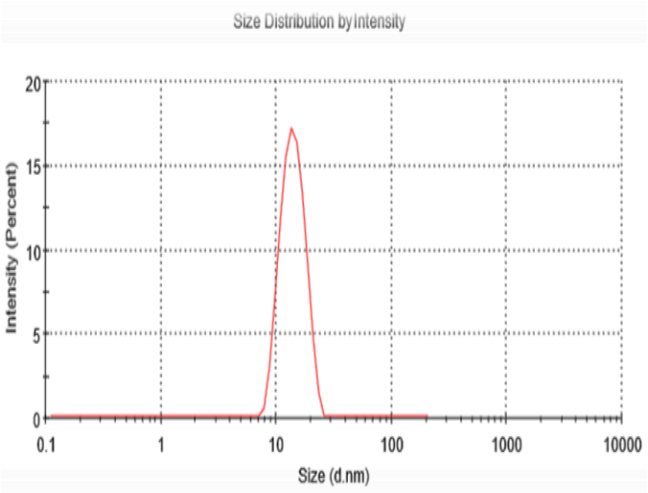

Fig. 3: Particle size distribution graph of formulation F1

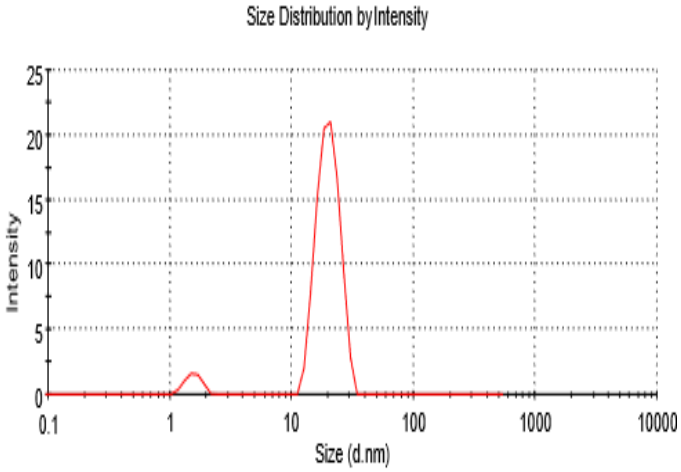

Fig. 4: Particle size distribution graph of formulation F2

The electric charge present on the developed formulation was evaluated by measuring the zeta potential. The zeta potential value of the prepared microemulsion formulation was found to be in range between -10.21mV to - 12.2mV.

Zeta potential of formulation F1 and F2 is shown in (fig 5, 6). As per the reports, micro formulations with zeta potential less than -15mV and more than +15mV are known to have high degree of stability. From the given data it was observed that the prepared micro

formulations show moderate stability for respect to eye permeation.

The Polydispersity index data of the prepared formulation is given in fig 7. It was observed that all the formulations are mid-range polydisperse. This may be due to wide-ranging size distribution of the particles.

The in vitro study of all formulations was performed using Franz's diffusion cell assembly. The drug release profile from the prepared formulations is shown in (fig 8). Experimental results showed that all formulations release more than 70% of drug during 12 hours study period. Formulation F1 shows maximum drug release of (85.68%) and formulation F5 shows least drug release of (74.74%).

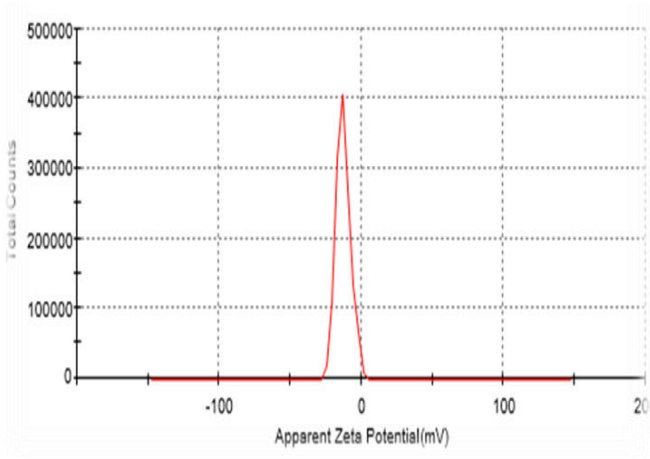

Fig. 5: Zeta potential of formulation F1

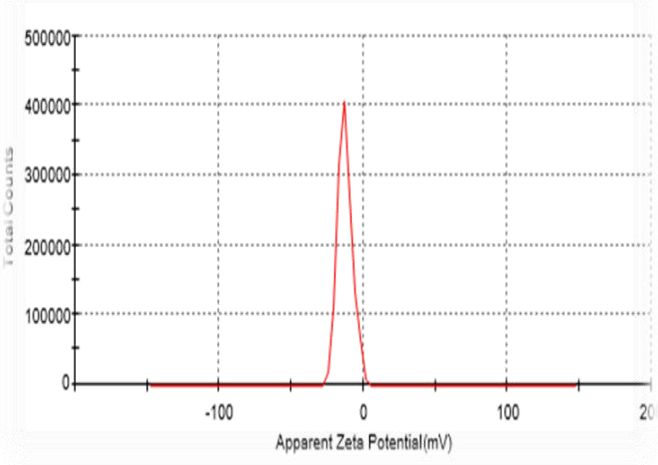

Fig. 6: Zeta potential of formulation F2

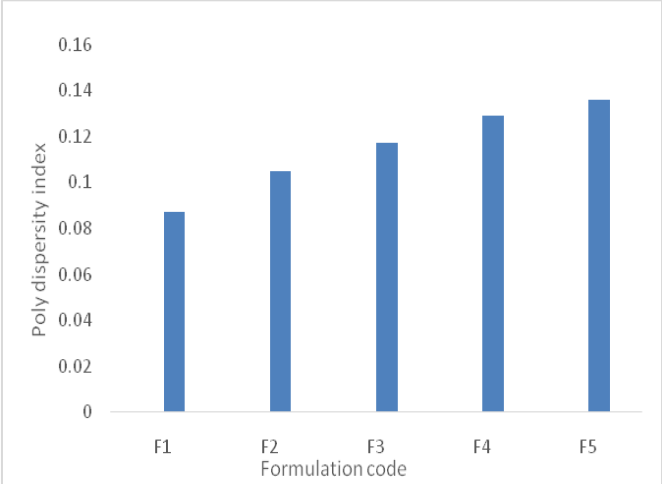

Fig. 7: Polydispersity index of formulation F1 to F5

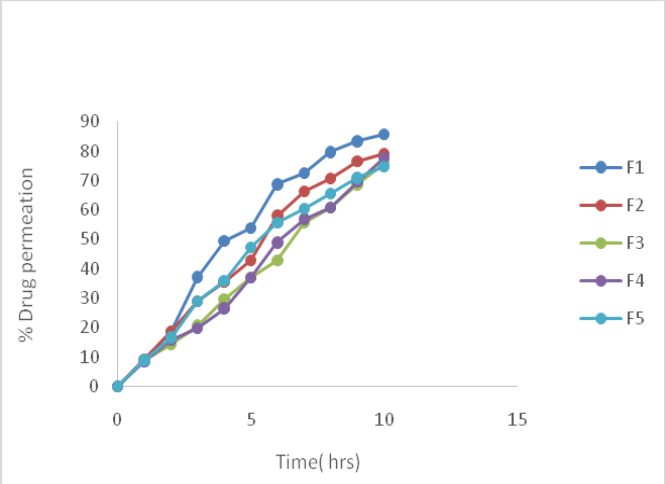

Fig 8: % Drug permeation study

Kinetic models describe drug release from dosage forms. Thus the model fitting analysis (Zero Order, Higuchi, First Order and Korsmeyer-Peppas Model) were done by comparing the coefficient of regression (R^2) values and corresponding n value of all the kinetic equations. The correlation coefficient (R) values were used as criteria to choose the best model for the drug release from the micro formulations. From table 2, it was observed that the individual formulation have different R^2value for different model. Except formulation F1 (first order) all other formulations follows zero order release kinetics for release of erythromycin from prepared microemulsion. On the basis of higher value of R^2 we select the best fit model. Now First Order Model poses great importance to know the release mechanism of the drug from the formulation. When the release data were analyzed using the first order, the n values indicated that the mechanism of drug release was strictly followed anomalous transport. On the basis of experimental result formulation F1 was selected as optimized formulation and subjected for *ex-vivo* study.

Table 2: Model fitting analysis

Formulation code	r^2			n	Best Fit Model	Mechanism Of Action
	Zero order	First order	Higuchi			
F1	0.9447	0.9899	0.9353	0.9877	First order	Anomalous Transport
F2	0.9843	0.9802	0.9234	0.9749	Zero order	Anomalous Transport
F3	0.9969	0.9571	0.9177	0.9809	Zero order	Anomalous Transport
F4	0.9930	0.9528	0.9195	0.9920	Zero order	Anomalous Transport
F5	0.9950	0.9730	0.9275	0.8008	Zero order	Anomalous Transport

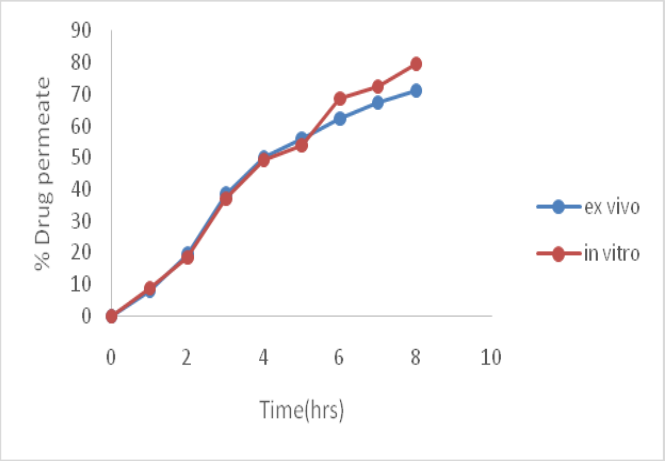

Fig. 9: *ex-vivo* drug permeation study of optimized formulation

4. CONCLUSION

Drug delivery to the eye is the most challenging part because of several problems like lachrymal drainage and corneal barrier. In the present research work drug loaded microemulsion was prepared by taking different ratios of oil, surfactant and co-surfactant and evaluated for various parameters like viscosity, particle size, PDI, zeta potential study, pH, *ex-vivo* drug permeation study, *in-vitro* drug permeation and its kinetic data. On the basis of all parameters formulation F1 was selected to optimise for the formulation of ophthalmic microemulsion with (pH; 7.4±0.12, viscosity; 153.23±0.83, drug content; 95.56±0.23, particle size; 12.1, zeta potential; 11.1 and PDI; 0.087, *in-vitro* drug permeation release of 85%, *ex-vivo* permeation release 71.06%). This optimized formulation is efficient to deliver drug into cornea with increased corneal absorption and lessened side effects.

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