Formulation and evaluation of microemulsion based in situ gelling system of antifungal drug for eye fungal infections

Khatri Haresh, Patel Mayur M., Shah Jigar N
Department of Pharmaceutics, Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat – 382481, India
jigar.shah@nirmauni.ac.in

NIRMA UNIVERSITY
INSTITUTE OF PHARMACY

INTRODUCTION

For the treatment of ocular diseases, various ophthalmic applications are preferred to achieve therapeutic levels of active medicament. The physiological constraints of the eye lead to low absorption of drugs, resulting in a short duration of the therapeutic effect. Rapid elimination of solutions and suspensions administered often results in a blurred vision, poor patient acceptance, short duration of the therapeutic effect making frequent dosing regimen necessary. The problem can be overcome by using combination of dosage forms i.e. microemulsion based in situ gelling systems, a liquid dosage form, that exhibit reversible phase transitions and pseudoplastic behavior which, upon exposure to physiological conditions in eye, changes to the gel phase, thus increasing the pre-corneal residence time and ocular bioavailability.

OBJECTIVE

- The objective of present study was to increase ocular bioavailability by developing microemulsion based in situ gelling system (MEG) of Natamycin (antifungal agent) for treatment of various eye fungal infections.
- Combination of these dosage forms provide benefits like increase contact time of formulation with eye, prolong the drug release and improve bioavailability.
- The essential idea is to encapsulate the drug in droplets that form a microemulsion, and then disperse the drug-loaded droplets in a polymer solution that gels upon triggering by the pH present in the tear fluid.

MATERIALS & METHODS

- Suitable compositions of microemulsion and in situ gelling system were individually screened for the desired properties and they were used for further optimization of microemulsion based in situ gelling system.
- Step 1- Appropriate amount of oil , surfactant and co surfactant was mingled together in accordance to ME domain, and equilibrated with gentle vortex shaking to get the initial concentrate. Then appropriate natamycin was dissolved in the initial concentrate under ultra-sonication.
- Step 2– Carbopol 940 and HHPMC K4M was dispersed in sufficient deionized water separetely until it completely dissolved using magnetic stirrer and both of them were mixed to obtain solution.
- Step 3- Natamycin loaded microemulsion slowly add in carbopol 940 and HPMC K4M with stirring.

EXPERIMENTAL WORK

Selection of oil and surfactant by solubility studies

- Solubility of Natamycin in various oils, surfactants, and co-surfactants was determined visually and then they were quantified.
- Natamycin showed highest solubility in oils like Glycero Monooleate and IsoPropyl Myristate (IPM). IPM was selected as oil because Glycero Monooleate remain as solid form below 38 ºC so that it makes unstable microemulsion, and Tween 80 and PEG 200 selected as surfactant and cosurfactant respectively.

Construction of pseudo-ternary phase diagrams

- In order to find out the concentration range of components for the existence of microemulsion domain, pseudo-ternary phase diagrams were constructed using water titration method at ambient temperature (25 ºC).
- The phase diagrams were prepared with the 1:1, 2:1, 1:2, 1:3, 1:4, 1:5, 1:6, and 1:7 ratios of Tween 80 to PEG 200 respectively. For each phase diagram at specific surfactant/cosurfactant ratio, the ratios of Smix to oil were varied from 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9. The mixtures of oil, surfactant and co-surfactant at certain ratios were diluted with water dropwise, under moderate magnetic stirring. After being equilibrated, the mixtures were assessed visually and determined as being microemulsions, crude emulsions or gels.
- From all ternary diagrams, it can be concluded that as concentration of co-surfactant increases, the area of microemulsion region increases, and the globule size decrease with increase in stability.

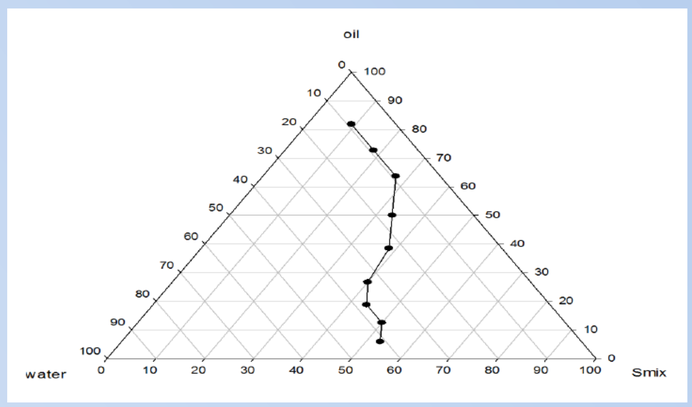

Fig. 1 Ternary phase diagram of 1:7 of S : Co-s
As Tween 80:PEG 200 (1:7) ratio show lowest globule size and good stability, it was used for further studies.

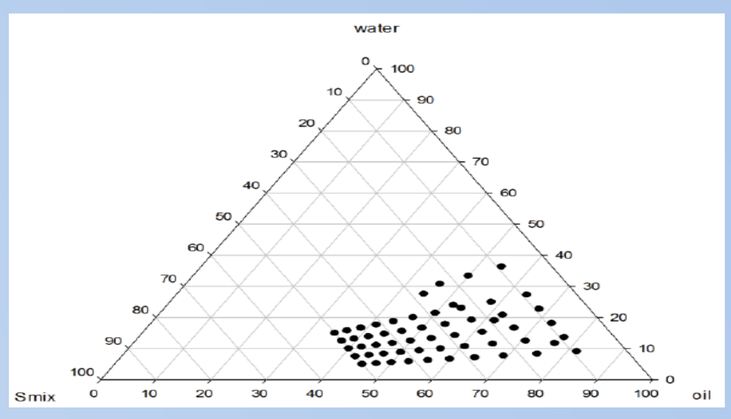

Fig. 2 Ternary phase disgram of Smix: Oil ratio
Ternary diagram it was decided to formulate microemulsion in range of Smix 50-70%, oil 10-20% , water 10-40% .

Microemulsion Preparation

Table 1. Formulation of microemulsion batches A-I with evaluation

Formulation	% SMIX	% IPM	% WATER	Particle Size (nm)	pH	Solubility (mg/ml)	In- vitro permeation study (%)
A	50	10	40	158	6.16	21	95
B	50	15	35	120	5.91	15	78
C	50	20	30	120	6.52	17	82
D	60	10	30	138	6.71	14	75
E	60	15	25	182	6.21	16	76
F	60	20	20	182	6.06	11	82
G	70	10	20	182	6.24	13	73
H	70	15	15	120	6.20	12	79
I	70	20	10	160	6.9	16	81

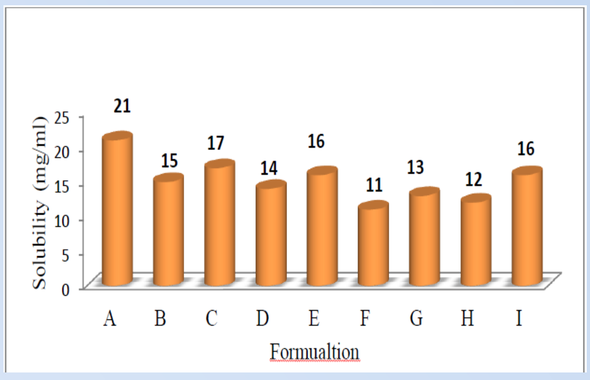

Fig. 3 Comparison of solubility of batches A - I

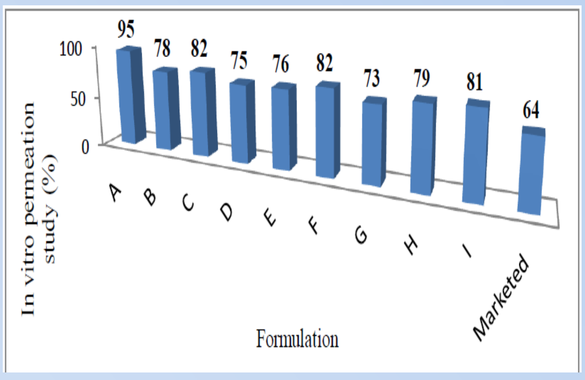

Fig. 4 Comparison of in vitro permeation study (%)

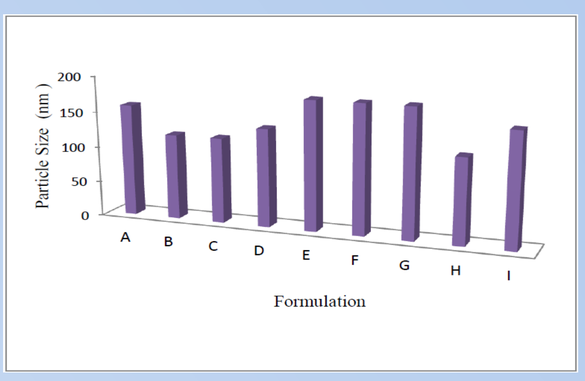

Fig. 5 Comparison of particle size of Batches A - I

From result of particle size distribution, it was concluded that Baches A ,B, C and D were having particle size within range (100-160) of standard microemulsion droplet. Out of these batches, batch A showed maximum solubility and in vitro permeation of prepared microemulsion formulations. Hence, the batch A contained least amount of oil and Smix, it was selected for further studies.

Formulation of Microemulsion based In-Situ gel system

Table 2. Formulation of microemulsion in situ gelling systems

Components	C10	C11	C12	C13
Natamycin (%w/v)	1	1	1	1
Carbopol 940 (%w/v)	0.3	0.3	0.3	0.3
HPMC K4M (%w/v)	0.25	0.5	0.75	1
Sodium Chloride (%w/v)	0.9	0.9	0.9	0.9
BAK (%w/v)	0.02	0.02	0.02	0.02
De ionized Water	Up to 100 ml	Up to 100 ml	Up to 100 ml	Up to 100 ml
Gelling Capacity	+++	+++	+++	+++
Instillation	Easily	Easily	Easily	Difficult
Viscosity Cps at 20 rpm	1019	1203	1324	1700

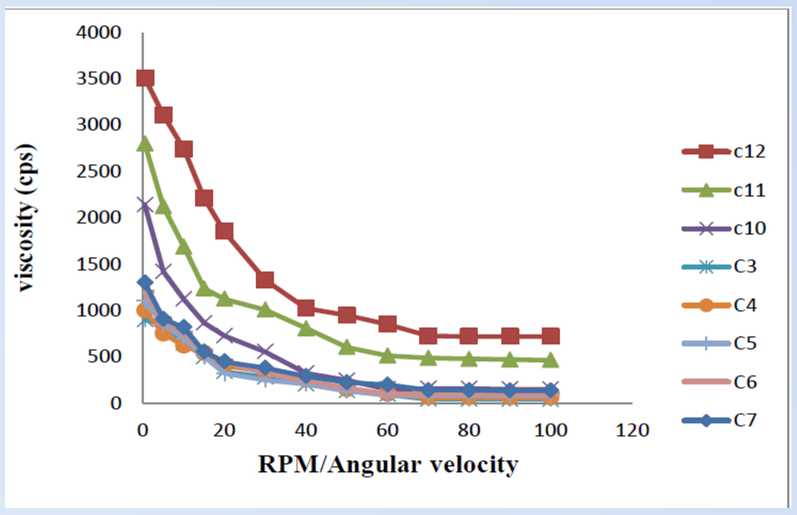

Fig. 6 Rheological profile of in situ gelling system

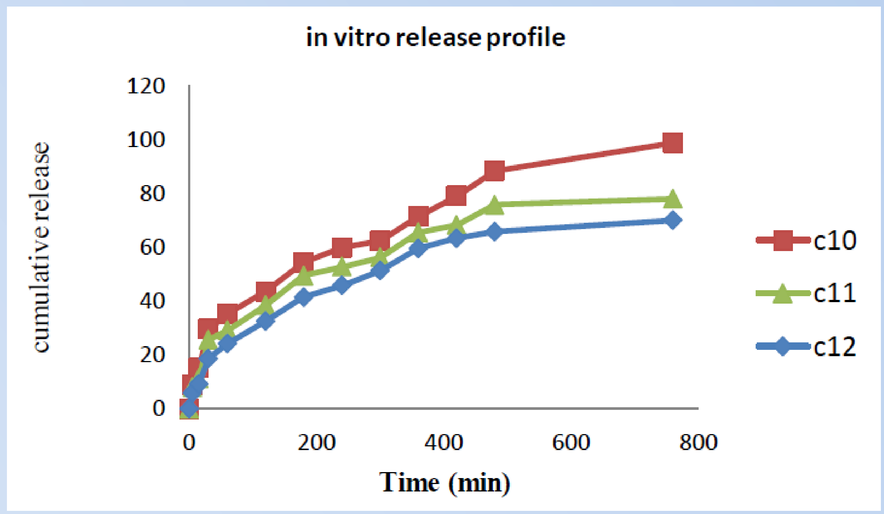

Fig. 7 Comparison of in vitro release of of in situ gelling

From above result we concluded that batch C10 showed good gelling and dropping capacity and drug release up to 99 % within 12 hours, which was more than other batches. Hence batch C10 was the best batch for preparation of microemulsion in situ gel of Natamycin.

CONCLUSION

The MEG formulation showed 100% drug release in 12 hours with Carbopol 940 (0.3%w/v), HPMC K4M (0.25% w/v), Smix (Tween 80 & PEG 200). Transmission electron microscopy (TEM) studies showed that there was no significance difference in globule size after addition of gelling agents. The prepared systems showed good antifungal efficacy, no cular irritation and stable for recorded stability periods. Thus, novel microemulsion based in situ gelling formulation could be potential drug delivery system for treatment of fungal infections to eye.

REFERENCES

1. Gan L, Gan Y, Zhu C, Zhang X, Zhu J. Novel microemulsion in situ electrolyte-triggered gelling system for ophthalmic delivery of lipophilic cyclosporine A: In vitro and in vivo results. Int J Pharm 2009; 365: 143-9.

2. Zhai G, Zhu W, Guo C, Yu A, Gao Y, Cao F. Microemulsion-based hydrogel formulation of penciclovir for topical delivery. Int J Pharm 2009; 378: 152-158.