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FORMULATION AND EVALUATION OF ATROPINE MICROEMULSION AS OCULAR DRUG DELIVERY

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ABSTRACT

In the recent past, ocuserts were promising in the ophthalmic drug delivery, but has its own limitations like reluctance of patients to abandon the traditional liquid and semisolid medications, unobserved expulsion from eye, membrane rupture etc. Ophthalmic microemulsion is one of the effective forms as it is thermodynamically stable and also appears as a solution. The nano droplets representing the internal phase of microemulsion, constitutes a reservoir of the drug on the cornea and limits lachrymal drainage. In this work, Atropine was chosen as the model drug for microemulsion, and formulated by using homogenizer and sterilized by autoclaving. Various ratios of the surfactants/cosurfactants (tween 80/span 20) were used for the formulation and the stability of the microemulsions was studied. The formulation was subjected for evaluation of physicochemical properties includes globule size, viscosity, refractive index and light scattering.

Keywords: Ocular, microemulsion, atropine, homogenizer.

INTRODUCTION

Atropine is used as cycloplegic and temporarily paralyzes the accommodation reflex. It induces mydriasis by blocking contraction of the circular papillary sphincter muscle, thereby allowing the radial papillary dilator muscle to contract and dilate the pupil. It also relieves pain associated with iridocyclitis and treats ciliary block glaucoma (Wikipedia).

The concept of microemulsions was first introduced by Hoar and Schulman in the 1940s. They are defined as a system of water, oil and amphiphile which is an optically isotropic and thermodynamically stable liquid solution (1, 2, 3). As compared to conventional formulations microemulsions are wide better as they have enhanced drug solubility, good thermodynamic stability, ease of manufacturing and enhancement effect on transdermal delivery(3,4). This system is suitable for delivery of both water insoluble drugs and water soluble drugs. Water insoluble drugs may be delivered through oil-in-water (o/w) microemulsions (5), while water soluble drug may be delivered through water-in-oil (w/o) microemulsions.

The objective of this formulation is to improve the efficacy of the drug, to reduce the total dose, to minimize the side effects, to increase absorption and to attain prolong release profile. The nanodroplets in the microemulsions, constitutes a reservoir of the drug on the cornea and limit their drainage.

MATERIALS AND METHODS

Atropine was procured from Loba Chemie; isopropyl myristate was procured from Sigma Aldrich and all other chemicals used were of AR grade and used without further purification.

SOLUBILITY STUDIES

Solvents for the study were selected based on the good solublising capacity for Atropine. In present study the solubility of atropine was investigated in different oils like isopropyl myristate, isopropyl palmitate, alcohol, glycerol, chloroform, ether surfactants and co-surfactants like tween 80, tween 60, tween 20, span 80, span 20 etc.

Excess of atropine was added to 5 ml each, of oils, surfactants, and co-surfactants in screw capped tubes and shaken on hand flask shaker at 100 RPM for 48 hours at room temperature. The suspension was centrifuged at 5000 RPM and clear supernatant liquid was decanted and filtered through 0.45µ nylon membrane filter (Whatmann).

The solubility of atropine was estimated by UV method.

METHOD OF PREPARATION

Atropine containing microemulsions were formulated by mixing oil, surfactant, and co-surfactant with varying component ratio as described in Table 1 (F – A, B, C, & D). 0.5 % w/w of atropine was dissolved in this mixture and then an appropriate amount of water was added to the mixture drop by drop with constant stirring on magnetic stirrer. Atropine containing microemulsion was obtained spontaneously on stirring the mixtures at ambient temperature. All microemulsions were stored at ambient temperature.

Table-1: Formulation of Atropine Microemulsion.

Ingredients (%W/W)	F-A	F-B	F-C	F-D
Isopropyl Myristate	25	20	15	10
Tween 80/Span 20	65	60	55	50
Water	10	20	30	40

CONSTRUCTION OF PSEUDOTERNARY PHASE DIAGRAMS

The microemulsion existence region was determined by constructing pseudo-ternary phase diagrams. Titration method was employed for its determination. These diagrams will be best suited for making different possible compositions of oil surfactant/co-surfactant and water. Pseudoternary phase diagrams were constructed to examine the formation of O/W microemulsions using 4 components: oil, surfactant, cosurfactant, and aqueous phase system. The 4-component system consisted of (1) isopropyl myristate; (2) a low-HLB (HLB = 4.3) surfactant (span 20); (3) a high-HLB (HLB = 15) surfactant (tween 80); and (4) distilled water (aqueous phase). Different mixtures of surfactant to co-surfactants were prepared and the weight ratios were fixed to 1:2, 1:1, 2:1 and 4:1. These mixtures (S/CoS) were mixed with oil phase to give weight ratio of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9, water was added drop by drop and stirred using magnetic stirrer until homogeneous dispersion or solution was obtained. After each addition the system was examined for appearance and flow property. The end point of the titration was the point in which the solution becomes cloudy or turbid. The quantity of aqueous phase required to make the mixture turbid was noted.

For convenience, the phase diagrams were constructed by drawing "water dilution lines" representing increasing water content and decreasing surfactant-cosurfactant levels.[2] If turbidity appeared followed by a phase separation, the samples were considered to be biphasic. If clear and transparent mixtures were visualized after stirring, the samples were considered monophasic. The samples were marked as points in the phase diagram. The area covered by these points was considered to be the microemulsion region of existence.

PHYSICOCHEMICAL EVALUATION (6, 7, 8, 9)

Particle Size Measurements:

The droplet size of the emulsions was determined by using optical microscope.

Determination of pH:

The pH values of the samples were measured by a pH meter (Elico Instruments), at 20 ± 1°C.

Viscosity:

The viscosities of microemulsions were measured with a Brookfield rotational viscometer (LVDV, Brookfield Inc., USA) equipped with spindle no. 4. The measurement was done at 30°C at 5 rpm. Viscosities were determined in triplicate.

Electroconductivity Study:

The electroconductivity of the resultant system was measured by an electroconductometer. For the conductivity measurements, the tested microemulsions were prepared with a 0.01N aqueous solution of sodium chloride instead of distilled water.

Refractive Index and Percent Transmittance:

The refractive index of the system was measured by an Abbe refractometer by placing 1 drop of solution on the slide. The percent transmittance of the system was measured at 650 nm using a UV spectrophotometer keeping distilled water as a blank.

RESULTS AND DISCUSSION:

Solubility Studies

To develop microemulsion formulations for ocular delivery of poorly water-soluble atropine, proper selection of oil is needed (10, 11, 12, 13). The optimization of the components to be used in formulating microemulsion was decided based on the solubility of atropine in the various oils, surfactants and co-surfactants. The solubility data is shown in Table 2.

Table-2: Solubility of atropine in different oils, surfactant and co-surfactant.

Phase type	Excipient	Solubility (mg/ml)
Oil	Isopropyl myristate	1.60 ± 0.034
	Isopropyl palmitate	0.44 ± 0.15
Surfactant	Tween 80	17.08 ± 0.532
	Tween 60	12.58 ± 0.521
	Tween 20	10.43± 0.032
Co-surfactant	Span 80	3.21± 0.235
	Span 20	6.89 ± 0.350

The solubility of atropine amongst various oils investigated was found to be highest in isopropyl myristate (1.60 ± 0.034mg/ml). Amongst surfactant, tween 80 showed maximum solubility (17.08 ± 0.532mg/ml) followed by Tween 60 and 20. Span 20 showed highest solubility among the co-surfactants (6.89 ± 0.350).

Based on the solubility studies of atropine in oil, surfactant and co-surfactant and the preformulation studies we found IPM, tween 80, span 20 could be the most appropriate combination for development of microemulsion.

Pseudo-ternary phase diagram study:

The microemulsion existence region was determined by constructing phase diagrams. Fig.1 describes the pseudo ternary phase diagrams with various weight ratios of tween 80 to span 20. The translucent region

presented in phase diagram reveals the microemulsion existence region. No distinct conversion from water-in-oil (w/o) to oil-in-water (o/w) microemulsion was observed. The rest of region on the phase diagram represents the turbid and conventional emulsions based on visual inspection.

The phase study clearly revealed that microemulsion existence region increased with increase in the weight ratio of surfactant (0.5 - 4). The maximum proportion of oil was incorporated in weight ratio 4:1 of tween 80 to Span 20.

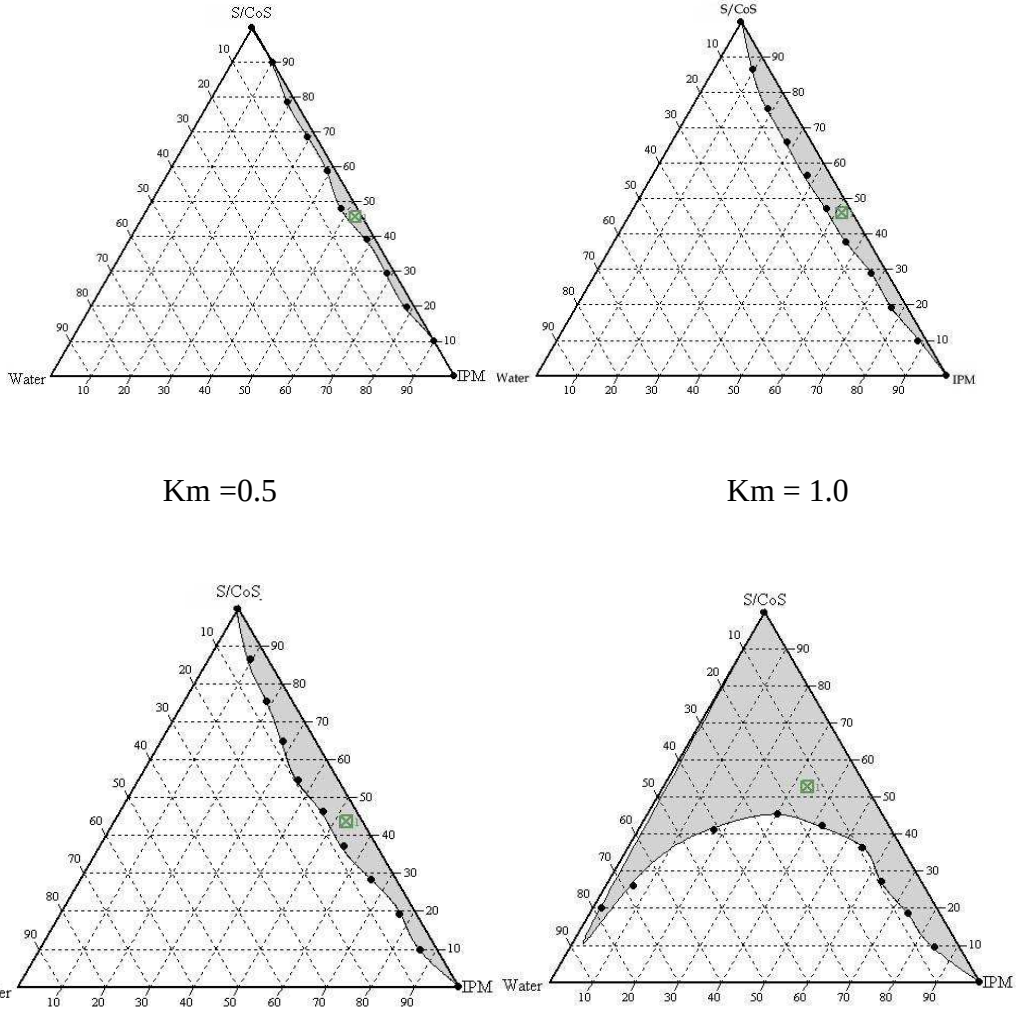

Fig-1: Pseudo ternary phase diagrams for microemulsion composed of oil (Isopropyl Myristate), surfactant (S, Tween 80), co-surfactant (Co-S, span 20) and water.

Physicochemical Evaluation

The droplet size, pH, Viscosity, Conductivity and Refractive index for the formulations are represented in Table 3. The result shows that the droplet diameter decreases with increasing ratio of oil:surfactant/co-surfactant. These results are in accordance with the report that the addition of surfactant to microemulsion system causes the interfacial film to condense and to be stable, while the co surfactant causes the film to expand.

Table- 3: Various parameters of atropine microemulsion.

S.No.	Formulation	Droplet Size**(µm)	pH*	Viscosity* (mPas)	Conductivity* (mV)	Refractive index
1.	F-A	41.8 ±0.2	7.2±0.02	27.5 ± 0.03	254 ± 3	1.341
2.	F-B	27.4±0.5	7.1±0.01	25.5 ± 0.5	245 ± 2	1.321
3.	F-C	18.7±0.3	7.1±0.02	22.3 ± 0.31	241 ± 3	1.330
4.	F-D	12.2±0.4	7.3±0.02	20.1± 0.45	232 ± 4	1.340

**** Each value represents mean±SD (n=100); *Each value represents mean±SD (n=5)**

CONCLUSION

The atropine ocular microemulsions were formulated and the different compositions of components were obtained by constructing pseudoternary phase diagrams. The ratio of tween 80: span 20: isopropyl myristate played a major role in microemulsion formulation. The optimum microemulsion contained isopropyl myristate (10%), tween 80: span 20 (50%), and water (40%), was a transparent and less viscous system.

REFERENCE:

1. I. Danielson, B. Lindmann, 1981. Colloid Surf., *3*, pp.391.
2. S.Tenjarla. 1999.Crit. Rev. Ther. Drug Carrier Syst. *16*(5), pp. 461-521.
3. J. Lawrence. and G. Rees. 2000. Adv. Drug Deliv. Rev., *45*, pp. 89–121.
4. M.R.Gasco. 1997. Industrial Applications of Microemulsions. Marcel Dekker Inc., New York, pp. 97–122
5. J.H. Kweon, S.C. Chi, and E.S.Park. 2004. Arch.Pharm. Res. *27*(3), pp. 351 – 356.
6. H.M. El Laithy, K.M. El-Shaboury. 2002. AAPS PharmSciTech. *3*(4), pp. E35.
7. M. Trotta, M. Gallarate, M.E. Carlotti , S. Morel 2003. Int. J. Pharm. *254*, pp. 235–242
8. S. Peltola, P. Saarinen-Savolainen, J. Kiesvaara., T.M. Suhonen, A. Urtti. 2003. International Journal of Pharmaceutics. *254*, pp. 99–107
9. B. Biruss, H. Kahlig, C. Valenta. 2007. Int. J. Pharm. *328*, pp 142–151.
10. A.A. Nasseri, R. Aboofazeli, H. Zia, T.E. Needham. 2003. Iranian J. Pharmaceutical Research pp. 117-123.
11. F. Podlogar, M. Rogaˇc, M. Gaˇsperlin 2005. Int. J. Pharm., *302*, pp. 68–77.
12. Z. Mei, H. Chen, T. Weng, Y. Yang, X. Yang. 2003. Eur. J. Pharm. Biopharm. *56*, pp. 189 –196.
13. N. Garti, A.Aserin, I.Tiunova, M.A.Fanun. 2000. Colloids Surf B: Physicochem Eng Aspects.*170*, pp.1-18.

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