Department of Pharmaceutical Technology, Karol Marcinkowski University of Medical Sciences, Poznan, Poland

Microemulsions with timolol as potential eye drops

I. MALINA, A. RADOMSKA-SOUKHAREV

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Iwona Malina, Department of Pharmaceutical Technology, Karol Marcinkowski University of Medical Sciences, 6, Grunwaldzka Str., 60–780 Poznan, Poland
imalina@amp.edu.pl

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Stable microemulsions oil-in-water (o/w) and water-in-oil (w/o) with timolol were obtained. These formulations were sterilized using two methods: by autoclaving and by sterile filtering according to the Polish Pharmacopeia V. Microemulsions were kept in the temperatures of 25 °C and 5 °C during three months. The following physical parameters were investigated: density, dynamic viscosity, refractive index, surface tension, pH and osmotic tension. All the microemulsions met the requirements for eye drops.

Microemulsions are thermodynamically stable and isotropic formulations. They are composed of polar phase, nonpolar phase, surfactant and co-surfactant. Microemulsions can also be obtained with a single surfactant or a mixture of surfactants (Tenjarla 1999). Due to their unique properties, microemulsions can improve drug stability, solubilization and bioavailability. Such characteristics as clarity, stability and possibility of sterilization justify attempts to prepare eye drops on their basis (Attwood 1994; Jachowicz 2001; Siebenbrodt and Keipert 1991; Vandamme 2002).

This paper reports physical parameters and chemical stability of the microemulsions systems (both o/w and w/o) containing timolol maleate. Physical parameters were estimated to test their suitability for the future use as eye drops. Benzalkonium chloride and chlorhexidine acetate as preservatives in concentration for eye drops according to Polish Pharmacopeia V were added, while a microemulsion without any preservative was used as a reference. After preparation, all microemulsions were sterilized used steam sterilization or filtration. After sterilization, all formulations were still transparent and single-phase.

After sterilization, the values of pH varied from 5.34 to 6.64, which was acceptable for eye drops. After 3 months of storage, in all formulations the pH value was lower than it was in the beginning, but the pH did not achieve the value of 3.5 which is generally considered to be the minimum allowable value for eye drops (Polish Pharmacopeia V 1993). The density of the systems varied from 0.89 g/cm^3 to 1.01 g/cm^3, which was acceptable as well. The dynamic viscosity of eye drops must not be higher than 20 mPas, and this requirement was met by all the systems. The light refraction index of the tears is 1.340. It is recommended that the refraction index for eye preparations should be smaller than 1.476, while the optimum value is considered to be 1.404 (Siebenbrodt and Keipert 1991). All the formulations met this requirement. The values of the refraction index of the microemulsions prepared varied from 1.373 to 1.451. The microemulsions prepared had a characteristically low surface tension – from 0.03 to 0.05 mN/m. The osmotic tension of the o/w systems varied from 320 to 331 mOsm/l and was biologically acceptable.

After three months storage at 5 °C and 25 °C, the differences in the physical parameters of the microemulsions systems were insignificant. The parameters characterizing the physical properties of the systems stored at the 25 °C after sterilization by filtration are given in Table 2. It should be mentioned that the preservatives did not affect the physical properties in all formulations. After three months of storage at the temperatures of 5 °C and 25 °C, no significant decomposition of timolol was found.

Table 1: Formulations (% w/w)

Substances	Formulation			
	1	1a	2	2a
Isopropyl myristate	1.92	1.92	72.38	72.38
Tween 80	10.69	10.69	13.87	13.87
Cremophor EL	5.88	5.88	–	–
Span 60	–	–	2.41	2.41
Epikuron 200	–	–	6.03	6.03
Water bidistilled	80.15	80.15	5.31	5.31
Glycerol	1.36	1.36	–	–
Timolol[1]	+	+	+	+
Preservatives[2]	–	+	–	+

[1] Timolol (timolol was prepared from timolol maleate) in therapeutic concentration 0.25%
[2] Preservatives (benzalkonium chloride 0.05 g/l and chlorhexidine acetate 0.10g/l)

Experimental

1. Reagents and apparatus

Timolol maleate was a gift from Polpharma S.A., Starogard Gdański, (Poland). Soybean lecithin – Epikuron 200 with 92.7% content of phosphatidylcholin was purchased from Degussa (Germany) and was used without additional purification. Tween 80, Span 60, isopropyl myristate were from Sigma-Aldrich Chemicals (Germany). Cremophor EL (polyoxyl 35 castor oil) was a gift from the BASF (Germany).

The following physical parameters were estimated: density (by the DA 110 M, Mettler Toledo, Germany), dynamic viscosity (by Viscosimeter DV-1 P Anton Paar, Austria), light refraction index (by refractometer RL 3, PZO, Warszawa, Poland), pH (by pH-meter CG 842, Schott, Germany), osmotic tension (by Osmometer Trident 800 d (Trident, Poland) and surface tension (by stalagmometer, Agat, Poland). The pH was estimated using a special electrode for emulsion systems – Electrode Blue Line 13 pH (from Schott Glass, Germany). The content of timolol maleate was estimated using an UV-VIS Shimadzu Spectrophotometer 2401 PC (Shimadzu, Japan).

2. Preparation of microemulsions

Appropriate amounts of surfactants were dissolved in the oily phase (isopropyl myristate). The samples were stirred and then bidistilled water containing 0.25% timolol was added. The systems obtained were classified as microemulsions on the basis of the criterion of transparency. After preparation, all formulations were filtered through a 0.20 μm membrane filter (Sartorius, Germany). The compositions of the microemulsions systems and their physical parameters are given in Tables 1 and 2.

3. Determination of timolol maleate in the microemulsion systems

The measurements of the chemical stability were performed at 5 °C and 25 °C. The values of absorption of the samples taken at the appropriate time intervals (t = 0, t = 1 and t = 3 months) were measured spectrophotometrically at 298 nm.

Table 2: Physical parameters of the microemulsions (after sterilization by filtration) stored at 25 °C (mean ± SD; n = 3)

Parameter	Microemulsion											
	1			1a			2			2a		
Time (mth)	0	1	3	0	1	3	0	1	3	0	1	3
Density (g/cm^3)	1.0140 ± 0.0003	1.0141 ± 0.0002	1.0106 ± 0.0002	1.0141 ± 0.0001	1.0140 ± 0.0002	1.0101 ± 0.0003	0.8977 ± 0.0001	0.8963 ± 0.0001	0.8945 ± 0.0001	0.8924 ± 0.0001	0.8958 ± 0.0001	0.8930 ± 0.0001
Dynamic viscosity (mPas)	4.7	4.6	4.6	4.7	4.6	4.4	18.0	17.7	15.4	13.3	13.8	13.8
Refraction index n^{d}20	1.3730 ± 0.0002	1.3732 ± 0.0001	1.3726 ± 0.0003	1.3740 ± 0.0002	1.3729 ± 0.0001	1.3722 ± 0.0002	1.4512 ± 0.0001	1.4500 ± 0.0002	1.4490 ± 0.0002	1.4512 ± 0.0001	1.4503 ± 0.0003	1.4495 ± 0.0002
Surface tension (mN/m)	0.04	0.04	0.04	0.04	0.04	0.04	0.03	0.03	0.03	0.03	0.03	0.03
pH	5.34 ± 0.02	5.31 ± 0.02	5.15 ± 0.01	5.48 ± 0.01	5.33 ± 0.04	5.14 ± 0.01	6.53 ± 0.10	6.48 ± 0.05	6.44 ± 0.06	6.58 ± 0.01	6.53 ± 0.03	6.39 ± 0.02
Osmotic tension (mOsm/l)	322 ± 2.65	318 ± 1.73	319 ± 4.36	331 ± 3.20	318 ± 2.08	319 ± 3.79	–	–	–	–	–	–

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