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The use of some ingredients for microemulsion preparation containing retinol and its esters

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Abstract

A study of microemulsions with retinol and its esters. Physical properties of w/o and o/w microemulsions containing Tween 60, Tween 80, Epicurone 135 (soy bean lecithin) as surfactants, n-butanol, triacetin, propylene glycol as cosurfactants were examined. The drug-containing systems were characterised in regard to their ophthalmic parameters. Physiologically well-tolerated and physically stable multiple-components were developed. The concentrations of surfactants and cosurfactants which are necessary to form stable systems were evaluated. The values of the following parameters — refractive index, viscosity, pH value, osmotic tension, obtained in the study, proved suitable for the purpose and the preparations were physiologically tolerated, the use of microemulsions as potential drug delivery systems for ocular administration has been discussed. The influence of retinol and its esters on the physical parameters the preparation was investigated. Microemulsion stored at 20°C up to 6 months showed no significant physical changes. © 2000 Published by Elsevier Science B.V. All rights reserved.

Keywords: Microemulsion; Retinol; Lecithin; Physical parameters; Mixture design

A microemulsion is defined as a system of water, oil and an amphiphile which is a single optically isotropic and thermodynamically stable liquid solution (Kreuter, 1994). An important feature of microemulsions from a formulation viewpoint is their stability (Pattarino et al., 1993). This work is concerned with the administration of vitamin A and its esters using an oil-in-water and water-in-oil, multiple-component systems. Microemulsions have been proposed as carriers of pharmaceuticals to achieve a controlled release of particular drug (Lieberman et al., 1998; Trotta et al., 1989). One of the difficulties in realising the potential of microemulsions as drug delivery systems through solubilisation of drugs is the narrow range of acceptable surfactants and cosurfactants and their high concentration usually required. In order to make microemulsion systems pharmaceutically acceptable it is necessary to formulate such systems using non-toxic, safe substances (Siebenbrodt and Keipert, 1993).The use of medium and short chain length alcohols as cosurfactants limits the potential use of microemulsions due to their toxic and irritant properties. Phospholipids, particularly phosphatidylocholines (lecithins) offer a possible non-toxic alternative for parenteral, oralor ocular use (Pattarino et al., 1993; Aboofazeli et al., 1995; Trotta et al., 1996). We have prepared

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some microemulsion formulations with retinol, retinol palmitate and retinol acetate, using physiologically acceptable ingredients, for example soy bean lecithin, Tween 60 and Tween 80 as surfactants, propylene glycol and triacetin as cosurfactants. Such surfactant systems are able to improve drug availability to the eye and are expected to yield prolonged action. Some microemulsions were prepared with n-butanol in order to compare physical parameters with microemulsions containing nontoxic ingredients. We have also prepared the basis formulations (without drug) to establish the effect of the components on physical parameters of the microemulsions.

1. Microemulsions preparation

1. In the absence of the drug — the soy bean lecithin-Epicuron 135 (Lucas Meyer), propylene glycol and triacetin or n-butanol (Sigma Chemical Comp.) were dissolved in the oily phase — isopropyl myristate (Merck-Schuhard) or Miglyol 812 (Hûls) or their mixture. Afterwards bidisttilated water was added.
2. In the presence of the drug — the microemulsion containing 15.00 i.u./1 ml.-retinol (BASF AG) or retinol acetate or retinol palmitate (Merck-Schuhard) was prepared as previously described but retinol or its esters were dissolved in the oily phase. All reagents were of the highest purity available. Water was freshly triple distillated.

The composition of the microemulsions investigated is given in Table 1.

For measuring refractive index, a Zeiss refractometer was used. The viscosity of the microemu

Table 2
Viscosities (m Pa s) of investigated formulations

Microemulsion	Viscosity						
	1	2	3	4	5	6	7
A	85.75	123.97	76.53	33.67	37.21	186.96	111.16
B	83.96	184.85	80.51	88.54	90.32	189.69	193.77
C	32.06	256.32	24.93	29.15	24.94	272.70	275.82
D	28.88	34.16	26.00	30.19	0	43.19	32.24
E	79.57	66.71	80.38	61.04	69.56	58.22	64.43
F	29.40	62.96	0	0	33.70	0	48.44
G	51.14	82.79	49.59	83.41	82.63	71.35	74.75
H	105.28	66.33	116.62	104.31	100.75	66.01	0

Table 3
The osmotic tension (mOsm/l) of investigated microemulsion

Microemulsion	Osmotic tension						
	1	2	3	4	5	6	7
A	160	216	386	140	84	368	144
B	70	248	176	207	188	232	518
C	76	292	88	228	92	800	284
D	1736	2332	2314	2324	1818	2260	2724
E	1520	1990	1604	1548	1098	1092	1528
F	672	2720	0	0	2700	0	2412
G	156	160	268	116	212	120	344
H	80	104	112	72	108	60	0

Table 1
Composition of the investigated microemulsions (% w/w)

Components	A							B							C							D						
	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Isopropyl myristate	7.1	6.2	11.9	8.8	8.8	8.1	8.1	3.0	2.0	6.2	3.7	3.7	4.6	4.6	7.2	1.9	14.8	8.9	8.9	3.6	3.6	4.0	4.0	9.7	4.1	4.1	2.1	2.1
Miglyol 812	–	1.0	–	–	–	1.3	1.3	–	1.2	–	–	–	2.7	2.7	–	1.0	–	–	–	1.9	1.9	–	1.0	–	–	–	0.5	0.5
Bidest. Water	0.7	0.4	1.1	0.97	0.97	1.0	0.5	0.5	0.4	1.0	0.62	0.62	0.9	0.9	0.4	0.54	0.8	0.49	0.49	1.04	1.04	7.7	3.0	18.6	8.0	8.0	1.6	1.6
Epicurone 812	3.5	6.6	5.8	4.3	4.3	8.6	8.6	7.1	6.2	14.2	8.8	8.8	14.2	14.2	3.5	1.8	7.2	4.3	4.3	3.4	3.4	2.7	3.1	6.5	2.8	2.8	1.6	1.6
Tween 60	1.0	2.3	1.6	1.2	1.2	3.0	3.0	–	–	–	–	–	–	–	1.0	2.5	2.0	1.2	1.2	4.8	4.8	–	–	–	–	–	–	–
Tween 80	2.6	2.5	4.3	0.3	0.3	3.3	3.3	–	–	–	–	–	–	–	1.0	2.5	2.0	1.2	1.2	4.8	4.86	6.2	6.2	15	6.4	6.4	3.3	3.3
n-Butanol	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.25	–	–	–	–
Retinol/miglyol 812	–	–	0.12	–	–	–	–	–	–	0.12	–	–	–	–	–	–	0.12	–	–	–	–	–	–	–	0.32	–	0.14	–
Retinol acetate	–	–	–	0.28	–	0.375	–	–	–	–	0.225	–	0.45	–	–	–	–	0.22 5	–	0.225	–	–	–	–	0.32	–	0.14	–
Retinol palmitate	–	–	–	–	0.28	–	0.37	–	–	–	–	0.22	–	0.45	–	–	–	–	0.22	–	0.22	–	–	–	–	0.32	–	0.14

Components	E							F							G							H					
	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6
Isopropyl myristate	5.0	5.0	6.8	4.1	4.1	5.0	5.0	4.0	4.0	–	–	4.8	–	4.0	6.8	6.8	7.1	6.3	4.2	6.0	6.0	7.2	7.2	12	10	12	12
Miglyol 812	–	1.0	–	–	–	3.1	1.0	–	1.0	–	–	–	–	1.0	–	1.0	–	–	–	0.65	0.65	–	1.0	–	–	–	1.7
Bidest. Water	1.21	0.72	1.6	0.65	0.65	0.7	0.7	0.36	0.88	–	–	0.55	–	0.88	0.6	0.25	0.6	1.13	0.48	0.25	0.25	0.3	0.2	0.5	0.4	0.4	0.3
n-Butanol	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Triacetine	6.2	6.2	8.5	5.1	5.1	6.7	6.2	5.0	8.3	–	–	7.5	–	8.3	–	–	–	–	–	–	–	–	–	–	–	–	–
Propylene glycol	–	–	–	–	–	–	–	1.3	1.2	–	–	1.5	–	1.2	13.4	13.5	14.0	12.6	8.4	8.7	8.7	–	–	–	–	–	–
Tween 80	5.8	5.8	8.0	6.1	4.7	6.1	5.8	1.7	6.0	–	–	3.6	–	6.8	3.0	7.3	3.1	6.4	4.3	4.9	4.9	2.5	2.5	4.1	3.7	3.7	4.3
Retinol/miglyol 812	–	–	0.12	–	–	–	–	–	–	–	–	–	–	–	–	–	0.12	–	–	–	–	–	–	0.08	–	–	–
Retinol acetate	–	–	–	0.22	–	0.28	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.2	–	0.28
Retinol palmitate	–	–	–	–	0.28	–	0.28	–	–	–	–	0.22	–	0.45	–	–	–	–	0.22	–	0.28	–	–	–	–	0.2	–

lsions was monitored by Abbe viscosimeter. The kinetic viscosity of the sample is calculated by multiplying the efflux time in seconds by the viscosimeter constant. Multiplying this value by the density of the sample gives the viscosity in mcP units. The preparations stored at 25°C were single-phase and clear after 6 months. Data are given in Tables 2 and 3. Microemulsions were tested for stability by means of repeated centrifuging (for 30 min at 13 000 rpm) (Gasco et al., 1989). After 6 months systems were still clear, stable dispersions and no phase separation could be observed. It was shown that the addition of n-butanol into microemulsion system reduced the viscosity of formulation. Also micremulsions with triacetine had the lower viscosity then the others. It is significant that formulations with Epicurone 135 and Tween 80 as surfactant and isopropyl myristate as oily phase had the lower viscosity then formulations with Miglyol 812 (oily phase) and Tween 60 (surfactant). The osmotic tension in most formulations with n-butanol was too high. In general microemulsions with Epicurone 135, Tween 60 and Tween 80 as surfactant and propylene glycol as cosurfactant had the lower osmotic tension than the others. The pH value and refractive index were suitable for ophthalmic drugs. Microemulsions with Epicurone 135 had the most suitable parameters for the ophthalmic drugs. In most of cases the addition of vitamin A into the formulation did not have the significant changes on physical parameters. The chemical stability will be continued.

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