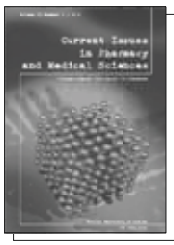

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The influence of excipients on physicochemical properties of Miglyol 812 – based oleogels

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ABSTRACT

In this paper, we presented the technology of preparation, as well as quality evaluation methods of the lipophilic gel based on a medium chain triglyceride (MCT) – Miglyol 812. In so doing, glyceryl stearate and glyceryl dibehenate were used as the gelling agents. The compounded gels were analyzed in terms of organoleptic properties, microscopic analysis, and rheological properties (yield point, thixotropy, viscosity at shear rates 10, 100 and 1000 s^{-1}). Following this, two model active substances: hydrocortisone (2%) as the lipophilic one, and oxytetracycline hydrochloride (0,5%) as the hydrophilic one, were incorporated into gels made of Miglyol 812 and 15% glyceryl stearate. After this, the influence of these active substances on the properties of gel was investigated. Moreover, a spectrophotometric method of content evaluation of these substances in a gel was established.

Keywords: rheology, oleogels, medium-chain triglycerides

INTRODUCTION

Oleogels are semisolid formulations and consist of an organic liquid gelled with appropriate polymers or other suitable auxiliary substances. These are not as well investigated as hydrogels, but can become an interesting drug formulation. Due to the lack of water in such oleogels, it is possible to incorporate active pharmaceutical substances that are unstable in the presence of water. Among these are antibiotics which can often undergo a hydrolytic degradation [9]. Therefore, by way of the application within a lipophilic base, one problem brought about with the physicochemical instability of semisolid formulations, may be eliminated. In formulating such drugs, manufacturers might therefore take into consideration the development of semisolid formulations which do not contain water, and at the same time, have rheological properties similar to hydrogels [1, 2, 7].

Oleogels are more commonly prepared by dissolving a gelling agent in heated solvent. Usually, the concentration of gelling agent does not exceed 15 percent and in regard to carbohydrates, derivatives exist that are even at 0.1 percent [4, 6]. After cooling the system, as a result of the varied chemical interactions (hydrogen bonds, van der Waals forces, electrostatic dipole-dipole interactions) between solvent and gelling agent molecules, a network structure is formed. The affinity of this two components of an oleogel guarantees the stability of the system and prevents phase partition [3, 5, 8].

In this study, as a continuous phase medium chain, the triglyceride (MCT) Miglyol 812 was used.

MATERIALS AND METHODS

Substances: Miglyol 812 Ph. Eur. 5.0 Caelo, Germany; Glyceryl stearate, Degussa Goldschmidt GmbH, Essen, Germany; Hydrocortisone, Ph.Eur. 5.0, Pharma Cosmetics, Kraków, Poland; Oxytetracycline hydrochloride, Ph.Eur. 5.0, Caelo, Germany; Glyceryl dibehenate, Gattefosse Sas, Saint Priest Cedex, France; Methanol pure., POCH S.A., Gliwice, Poland; Chloroform pure, POCH S.A., Gliwice, Poland.

Gel preparation: Miglyol 812 was heated in a beaker to the temperature of 75°C and agitated (375 rpm), a gelling agent was then added (see Table 1), and agitation was continued until dissolution was completed. Following this, agitation was continued without heating to obtain the appropriate consistency of the gel. All tests were performed after 24 hours.

Active substances: hydrocortisone (2%) and oxytetracycline hydrochloride (0.5%) were incorporated into selected formulations of these prepared gels (see Table 1).

The composition of gels in terms of auxiliary substances was developed mainly based on literature data. The concentration of active substances was assumed based on standard concentrations used in health care.

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Table 1. Composition of oleogels (in grams per 100 g of gel)

Ingredient	Formulation							
	A	B	C	D	D*	E	F	G
Glyceryl stearate	8.0	10.0	12.0	15.0	14.625			
Glyceryl dibehenate						10.0	12.0	15.0
Hydrocortisone					2.0			
Oxytetracycline hydrochloride					0.5			
Miglyol 812	92.0	90.0	88.0	85.0	82.875	90.0	88.0	85.0

Analytical procedure: Active substances were extracted from the lipophilic base with a mixture of 0.1 M hydrochloric acid (solvent for oxytetracycline hydrochloride) and chloroform (solvent for hydrocortisone). The sample of chloroform extract was then diluted with methanol, and the absorbance (242 nm wavelength) was measured. The sample of aqueous solution was then diluted with buffer (pH = 2), and the absorbance (269 nm wavelength) was measured. Extracts from placebo material were used as a blank. The quantity of active substances was calculated from the calibration curves (see figures below) prepared earlier.

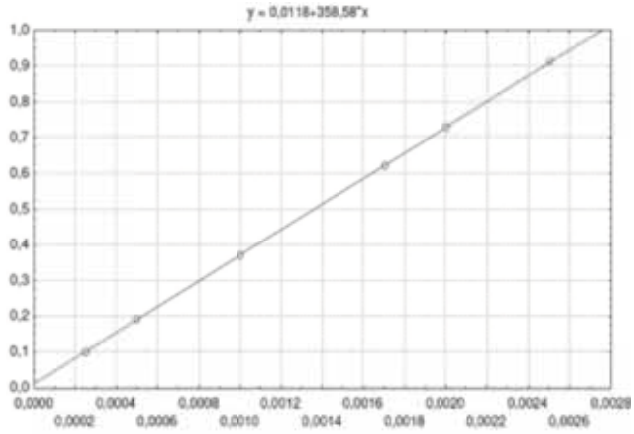

Fig. 1. Calibration curve for oxytetracycline hydrochloride

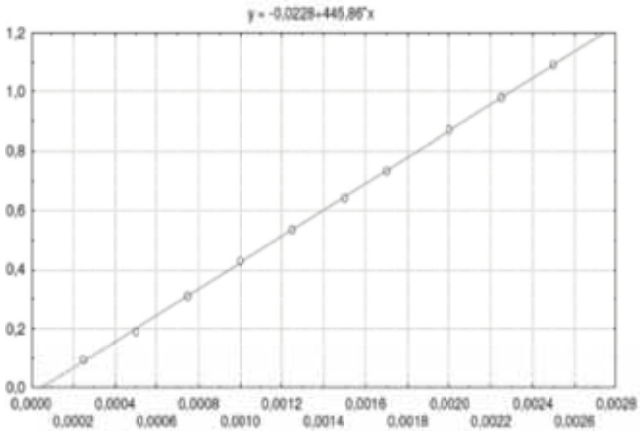

Fig. 2. Calibration curve for hydrocortisone

A statistical evaluation of the obtained data was performed with STATISTICA software. A conducted analysis of variance revealed regression equations that fit the empirical data to 99.98% for hydrocortisone and to 99.99% for oxytetracycline hydrochloride. The results are presented in Tables 2 and 3.

Table 2. Statistical parameters for the oxytetracycline hydrochloride calibration curve

Parameter	Value
Regression equation	y=358.58+0.0118
Correlation coefficient r	r=0.9999
Regression coefficients	a=358.58 b=0.0118
Average error of estimation of parameter "a"	s_a=1.1937
Significance level of parameter "a"	p=0.0000 (p<0.05)
Average error of estimation of parameter "b"	s_b=0.00185
Significance level of parameter "b"	p=0.001389 (p<0.05)

Table 3. Statistical parameters for the hydrocortisone calibration curve

Parameter	Value
Regression equation	y=445.86-0.0228
Correlation coefficient r	r=0.9998
Regression coefficients	a=445.86 b=-0.0228
Average error of estimation of parameter "a"	s_a=2.076
Significance level of parameter "a"	p=0.0 (p<0.05)
Average error of estimation of parameter "b"	s_b=0.003209
Significance level of parameter "b"	p=0.000102 (p<0.05)

Rheological measurements: All measurements were performed at 20 C using a rheometer Rheotest RN 4.1, Medingen, Germany. The device was equipped with a cone-plate system (65 m gap).

RESULTS AND DISCUSSION

The oleogels containing glyceryl stearate as the gelling agent at a concentration of 8, 10 and 12 percent were unstable, and these liquefied and divided into separate layers during storage. In addition, formulations A and B divided into separate phases in the second week of storage. However, formulation C, which contained a higher concentration of gelling agent, was stable for a longer period of time, with phase separation being observed in the third week of storage. Moreover, formulation D, with the highest concentration of gelling agent, was stable. This oleogel retained its homogenous consistency and its white color during four weeks of storage at a 20°C temperature. What is more, no phase separation was observed. Formulation D, therefore, was chosen as the optimal gel base for the incorporation of active substances: hydrocortisone at a concentration of 2%, and oxytetracycline hydrochloride at a concentration of 0.5% (formulation D*).

As opposed to the formulation based on glyceryl stearate, none of the gels containing glyceryl dibehenate shown physicochemical stability during 4 weeks of storage time. Oleogel E separated into layers in the 3rd week of storage, whereas formulations with higher concentration of gelling agent (F and G) became more stable, but their structure was damaged in the 4th week of tests. This revealed that the physicochemical stability of oleogels depends on the concentration of the gelling agent: the higher concentration, the longer time of appropriate stability of the gel.

The internal structure of the gels and dimensions of their particles were analyzed with polarizing microscope. In re-

gard to D and D* formulations, the structure was homogenous, no agglomerates of auxiliary substances were observed. In addition, the size of hydrocortisone and oxytetracycline hydrochloride particles was measured. This work showed that the particles of oxytetracycline hydrochloride were between 2.4 and 3.5 μm, while the hydrocortisone particles were in the range of 10 to 20 μm.

What is more, the validation of the spectrophotometric method of content determination of hydrocortisone and oxytetracycline hydrochloride was performed, as one of the important parameters was the specificity of the method. In so doing, UV-absorption spectra were measured for active substances and for the solutions used in the analytical procedures. These spectra, shown in Figures 3 and 4, show that auxiliary substances do not interfere with active substances in the analytical wavelength for oxytetracycline hydrochloride (λ_{max} = 269 nm) and hydrocortisone (λ_{max} = 242 nm).

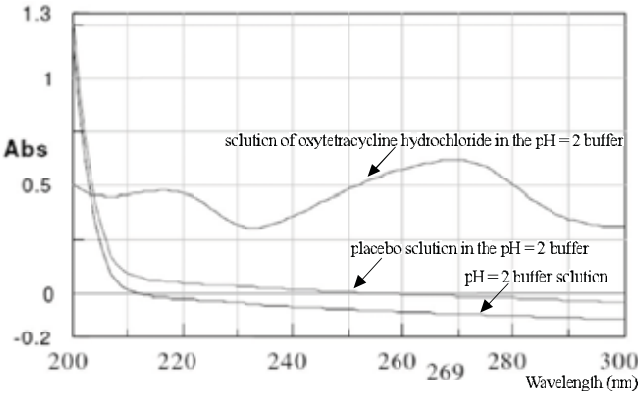

Fig. 3. Specificity of the oxytetracycline determination method

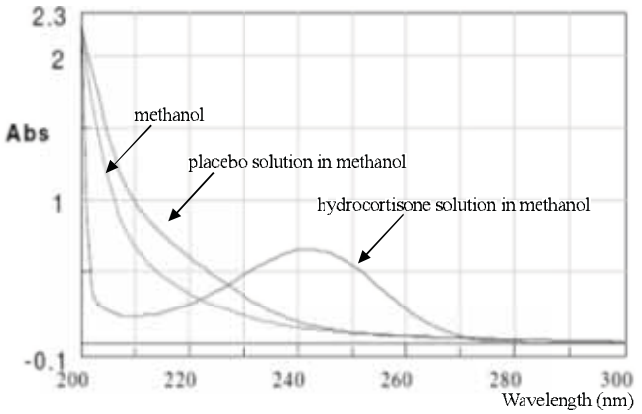

Fig. 4. Specificity of the hydrocortisone determination method

The accuracy, linearity and precision of the spectrophotometric method were also evaluated in the analyzed range of concentrations (0.00025–0.0025 g/100mL) for both substances. This analysis showed that the method meets specified requirements. In this regard, the limit of quantification is 0.52 μmg/mL for oxytetracycline hydrochloride, and 0.72 μg/mL for hydrocortisone. What is more, the limit of detection is 0.17 μg/mL for oxytetracycline hydrochloride and 0.24 μg/mL for hydrocortisone. Both of those parameters are below the concentrations of active substances in the analyzed gels.

Table 4. Experimental data of the active substances determination method in lipophilic gels

Time [days]	Hydrocortisone			Oxytetracycline hydrochloride		
	Content [g/10g]	Recovery [%]	SD	Content [g/10g]	Recovery [%]	SD
0	0.19654	98.32	0.003364	0.05290	105.59	0.000178
7	0.19416	97.13	0.001989	0.05199	103.78	0.001405
14	0.19132	95.71	0.003058	0.05237	104.54	0.000133
21	0.19648	97.39	0.002823	0.05186	103.51	0.000307
28	0.19334	96.72	0.001479	0.05079	101.38	0.000401

The results of the rheological measurements (Table 5) revealed that yield point and viscosity of analyzed gels did not change in a statistically significant manner during 4 weeks storage. To check if there is a functional dependence between the rheological parameters, a trend analysis was performed. In the first step, a Levene's test was used to assess the equality of variances in different samples. A value of significance parameter $p > 0.05$ showed that variances are equal. In the second step, the trend analysis was performed. This analysis showed a lack of correlation between the rheological parameters of these gels and their time of storage. There is no linear increase (and no linear decrease) of values of those parameters.

The influence of the incorporation of active substances on the properties of these gels was observed. The incorporation of hydrocortisone resulted in an increasing of yield point that is typical for an oleogel. Moreover, viscosity and the hysteresis loop area were also increased. These effects might be evidence that the participation of hydrocortisone particles results in the strengthening of the gel structure. However, a simultaneous incorporation of 2% hydrocortisone and 0.5% oxytetracycline hydrochloride resulted in a tenfold decrease of yield point. This is evidence of the diminishing influence of these substances on the internal structure of the gel. In addition, after the incorporation of the active substances, the thixotropy value decreased. This might suggest that these systems have a better ability to re-build structure after the shear stress is discontinued. This is probably because the area under the hysteresis loop is proportional to the energy needed to destroy the structure of gel.

Table 5. Results of the rheological measurements

Time [days]	Thixotropy [W/m^3]		Yield point [Pa]		Viscosity [Pa s]					
					10 [s^{-1}]		100 [s^{-1}]		1000 [s^{-1}]	
	D	D*	D	D*	D	D*	D	D*	D	D*
0	27200	2190	37.3	3.67	10.15	3.90	1.14	1.10	0.22	0.28
7	26000	2280	35.1	2.91	8.65	6.71	1.08	1.08	0.21	0.27
14	27000	2100	33.1	2.63	8.02	4.15	1.04	1.00	0.20	0.25
21	27400	2400	33.8	2.75	8.22	7.05	1.04	0.92	0.20	0.23
28	27500	2880	38.3	2.51	8.64	6.45	1.05	1.09	0.20	0.20

Our study, therefore, showed that there is no statistical significant difference in viscosity of formulations containing active substances and formulations without those substances, especially at higher shear rates.

Furthermore, our study revealed that it is possible to obtain physicochemically and rheologically stable lipophilic

gel based on medium chain triglyceride Miglyol 812. The properties of gels, thus, depends on the type of gelling agent: its properties and the quantity used in the formulation. In the analyzed range of concentrations of gelling agents, the more of the agent was used, the more a stable formulation was developed. The optimal content of glyceryl stearate in Miglyol 812 is 15%. Moreover, it was shown that such active substances as hydrocortisone and oxytetracycline hydrochloride caused change in the internal structure of lipophilic gel. This was seen as a change of the hysteresis loop area and change of yield point value. Finally, the results of the spectrophotometric content determination indicate that the chosen active substances are stable in developed formulations of gel as analyzed in the study period of time.

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