NOTE: margins on each side 2.5 cm
Time New Roman font
Abstracts, References: 10 font
Main text: 12 font
Line spacing: 1.5
Please, use square brackets in the main text !

DOI: 10.32383/appdr/xxxx

MANUSCRIPT TITLE

Full NAME and Full SURNAME [1], and Full NAME and Full SURNAME [2]

[1] Department of xxxxx, Faculty of xxxxx,
University of xxx, full address, city, country
[2] Department of xxxxx, Faculty of xxxxx,
University of xxx, full address, city, country

NAME and SURNAME https://orcid.org/xxxx-xxxx-xxxx-xxxx
NAME and SURNAME https://orcid.org/xxxx-xxxx-xxxx-xxxx

Abstract: The purpose of this study was to develop and characterize novel gel formulations of oleogels and oleo-hydrogels (bigels) as topical drug delivery systems for ketoconazole (KET). Oleogels were prepared using paraffin oil, rapeseed oil or castor oil as a solvent and Aerosil® 200 as organogelator with addition of surfactant Tween 80. Bigels were prepared by mixing castor oil oleogels with sodium alginate hydrogel. The received formulations were analyzed microscopically, for pH, viscosity and the texture profile analysis was also conducted to examine the mechanical parameters. In addition, the *in vitro* release of KET was evaluated and *ex vivo* bioadhesive properties of obtained oleogels and bigels on the rat skin model were estimated. It was found that most of the obtained formulations were non-Newtonian systems, showing a shear-thinning behavior and thixotropic properties, with proper textural features such as firmness, compressibility, adhesiveness. Moreover, they were characterized by beneficial bioadhesive properties. Prepared oleogels and bigels were considered as better formulations in terms of drug release compared to commercially available ketoconazole cream.

Keywords: ketoconazole, oleogel, bigel, bioadhesiveness, textural properties

Corresponding author: e-mail: xxx

Topical semisolid products are important class of drug delivery systems and their use in therapy is becoming more widespread. However, dermal application of drugs is not easy because of impermeable nature of the skin. When developing these formulations, the goal is to obtain systems with optimized drug loading and release properties which are able to ensure

NOTE: margins on each side 2.5 cm
Time New Roman font
Abstracts, References: 10 font
Main text: 12 font
Line spacing: 1.5
Please, use square brackets in the main text !
---

adequate penetration of the active substance [1, 2]. In the recent years organogels, also named oleogels, have been proposed as a way of structuring of liquid oils in various fields, including pharmaceutical or cosmetics applications. The gelling agent forms aggregates and linkages between aggregates which results in the formation of three-dimensional networks. The formation of oleogels is similar to hydrogels, with weak interactions such as Van der Waals forces or hydrogen bonding [1, 3-7].

EXPERIMENTAL

Materials

KET was received as a gift sample from Polfarmex S.A. (Kutno, Poland). Aerosil® 200 (a gift from Evonik Industries AG, Hanau, Germany), tocopheryl acetate (vitamin E), liquid paraffin and rapeseed oil (Pharma Cosmetics, Kraków, Poland), castor oil (PPH Galfarm Sp. z.o.o, Kraków, Poland), 2 - bromo – 2 - nitropropane - 1,3 - diol - bronopol (Sigma Aldrich, Buchs, Switzerland), Tween 80 (Sigma Aldrich, Madrid, Spain), sodium alginate (Sigma Aldrich, Steinheim, Germany), sodium hydroxide potassium, dihydrogen phosphate, disodium hydrogen phosphate, sodium acetate anhydrous, acetic acid 80% anhydrous (Chempur, Piekary Śląskie, Poland), ethanol 99.9% (J.T. Baker, Deventer, Holland), methanol HPLC grade (Witko, Łódź, Poland), acetonitrile HPLC grade, sodium dodecyl sulphate - SDS and ethyl alcohol 96% (POCH, Gliwice, Poland) were used as received. All chemicals and solvents used for the study were of analytical grade. Commercially available product - Nizoral® cream 20 mg/g (Janssen-Cilag, Beerese, Belgium) was used as a control. Cuprophan® was received from Medicell (London, UK).

Preparation of Oleogels and Bigels

Oleogels and bigels were prepared by using mechanical stirrer RZR 2020 (Heidolph Instruments, Schabach, Germany). The composition of designed formulations is given in Table 1. For the preparation of oleogels, Tween 80 was added to the heated oil (70°C) with constant mechanical stirring at 300 rpm. KET was uniformly dispersed or dissolved in oils and next the gelling agent Aerosil® 200 was dispersed. After complete mixing of gelling agent, tocopheryl acetate as an antioxidant was added to the mixture. Once the mixture was

NOTE: margins on each side 2.5 cm
Time New Roman font
Abstracts, References: 10 font
Main text: 12 font
Line spacing: 1.5
Please, use square brackets in the main text !
---

homogenous, heating was stopped and mixture was cooled down to the room temperature as it gradually solidifies to form oleogel.

Place Table 1 here

Physicochemical Properties of Oleogels and Bigels

Drug Content Analysis by HPLC Method

KET content was determined after extraction of oleogels or bigels samples in ethanol 99.9% and analysed by HPLC method using an Agilent Technologies 1200 HPLC system equipped with a G1312A binary pump, a G1316A thermostat, a G1379B degasser and a G1315B diode array detector (Agilent, Waldbronn, Germany) in the following conditions: Zorbax Eclipse XDB - C18, 4.6 × 150 mm, 5 µm column (Agilent, Waldbronn, Germany); mobile phase: methanol - acetonitrile - phosphate buffer pH 6.8 (35 : 40 : 25, v/v); flow rate 1.0 mL/min; detection at 231 nm; retention time 4.0 min (19); the standard calibration curve was linear over the range of 5-150 µg/mL ($R^2 = 0.999$).

Statistical Analysis

Results are presented as the mean ± standard deviation (SD) based on six independent experiments. Statistical analysis was done by one-way analysis of variance (ANOVA) using Statistica 10.0 software (StatSoft, Kraków, Poland). A probability level of $P < 0.05$ was considered as significant.

RESULTS AND DISCUSSION

Physicochemical Characteristics of Oleogels and Bigels

During designing topical formulation, the choice of appropriate vehicle and selection of suitable excipients play an important role, since they largely affect the quality of the dosage form, its stability, drug release profile and therapeutic efficacy. The possibility of transforming liquid oils into soft, viscoelastic gels opens up a number of opportunities for

NOTE: margins on each side 2.5 cm
Time New Roman font
Abstracts, References: 10 font
Main text: 12 font
Line spacing: 1.5
Please, use square brackets in the main text !
----

their applications as transdermal or topical drug delivery systems for poorly water soluble drugs.

The results of the texture analysis confirmed observations obtained from rheological measurements. The highest mechanical parameters were noticed in case of oleogel containing castor oil and ethanol (O4) and the lowest for oleogel with liquid paraffin (O1). Bigels possessed lower firmness, compressibility and adhesiveness than oleogels used for their preparation.

Ex vivo Bioadhesive Properties of Oleogels and Bigels

Bioadhesion refers to the phenomenon where natural or synthetic materials adhere to biological surfaces. Strong adhesion can occur if the two surfaces are capable of forming either covalent or ionic bonds. At the same time, weaker forces, such as polar (dipole-dipole), hydrogen bonding or van der Waals interactions also participate in bonding the two surfaces [24, 32]. The bioadhesive properties of the polymers used to formulate topical drug delivery systems ensure the oleogels or bigels to adhere to the skin and in the consequence elongate the retention time of the dosage form at the site of application. The results of experiments carried out using the shaved rat skin as model of adhesive layer are shown in Figure 1.

Place Figure 4 here

CONCLUSIONS

The oil structuring properties of fumed silica were exploited to prepare oleogels using different oils. Moreover, relatively new class of soft matter systems called bigels were obtained by mixing fumed silica and castor oil oleogels with alginate hydrogel. Designed preparations exhibited acceptable physicochemical features: pH, drug content, viscosity and textural properties. The viscosity of oleogels was affected by the type of oil used in the formulation and by the oil polarity. Obtained formulations present promising potential for further investigations and development of vehicles for topical drug delivery.

Acknowledgments

NOTE: margins on each side 2.5 cm
Time New Roman font
Abstracts, References: 10 font
Main text: 12 font
Line spacing: 1.5
Please, use square brackets in the main text !
----

xxx

Author's Contribution

A - Research concept and design: X.X. and Y.Y.;

B - Collection and/or assembly of data: X.X.;

C - Data analysis and interpretation: X.X.;

D - Writing the article: X.X., Y.Y., Z.Z.;

E - Critical revision of the article: X.X.;

F - Final approval of the article: X.X.

REFERENCES

1. Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. *Transl Oncol.* 2021; 14(10): 101174. doi:10.1016/j.tranon.2021.101174.
2. Morgan E, Arnold M, Gini A, et al. Global burden of colorectal cancer in 2020 and 2040: Incidence and mortality estimates from GLOBOCAN. *Gut* 2023; 72(2): 338-344. doi:10.1136/gutjnl-2022-327736.
3. Adebayo AS, Agbaje K, Adesina SK, Olajubutu O. Colorectal cancer: Disease process, current treatment options, and future Perspectives. *Phamaceutics* 2023; 15(11): 2620. doi:10.3390/pharmaceutics15112620.
4. Baxter-Holland M, Dass CR. Doxorubicin, mesenchymal stem cell toxicity and antitumour activity: Implications for clinical use. *J Pharm Pharmacol.* 2018; 70(3): 320-327. doi:10.1111/jphp.12869.
5. Kciuk M, Gielecińska A, Mujwar S. Doxorubicin-an agent with multiple mechanisms of anticancer activity. *Cells* 2023; 12(4): 659. doi 10.3390/cells12040659.
6. Sun T, Zhang L, Feng J, et al. Characterization of cellular enescence in doxorubicin-induced aging mice. *Exp Gerontol.* 2022; 163: 111800. doi:10.1016/j.exger.2022.111800.
7. Schmitt CA, Wang B, Demaria M. Senescence and cancer - role and therapeutic opportunities. *Nat Rev Clin Oncol.* 2022; 19(10): 619-636. doi:10.1038/s41571-022-00668-4.

NOTE: margins on each side 2.5 cm
Time New Roman font
Abstracts, References: 10 font
Main text: 12 font
Line spacing: 1.5
Please, use square brackets in the main text !

Table 1. Compositions of designed semisolid systems

Ingredient (g)	**Oleogels**				**Hydrogel**	**Bigels**			
	O1	**O2**	**O3**	**O4**	**H**	**B3 (O3+H 30:70)**	**B3A (O3+H 50:50)**	**B4 (O4+H 30:70)**	**B4A (O4+H 50:50)**
KET	2.0	2.0	2.0	2.0		2.0	2.0	2.0	2.0
Silicon dioxide (Aerosil®200)	5.0	5.0	5.0	5.0	-	1.5	2.5	1.5	2.5
Tween 80	1.0	1.0	1.0	1.0	-	0.3	0.5	0.3	0.5
Ethyl alcohol 96%	-	-	-	30.0	-	-	-	9.0	15.0
Tocopheryl acetate	0.05	0.05	0.05	0.05	-	0.02	0.025	0.02	0.025
Paraffin oil (up to)	100.0	-	-	-	-	-	-	-	-
Rapeseed oil (up to)	-	100.0	-	-	-	-	-	-	-
Castor oil (up to)	-	-	100.0	100.0	-	30.0	50.0	30.0	50.0
Sodium alginate	-	-	-	-	5.0	3.5	2.5	3.5	2.5
Bronopol	-	-	-	-	0.01	0.007	0.005	0.007	0.005
Purified water (up to)	-	-	-	-	100.0	100.0	100.0	100.0	100.0

NOTE: margins on each side 2.5 cm
Time New Roman font
Abstracts, References: 10 font
Main text: 12 font
Line spacing: 1.5
Please, use square brackets in the main text !

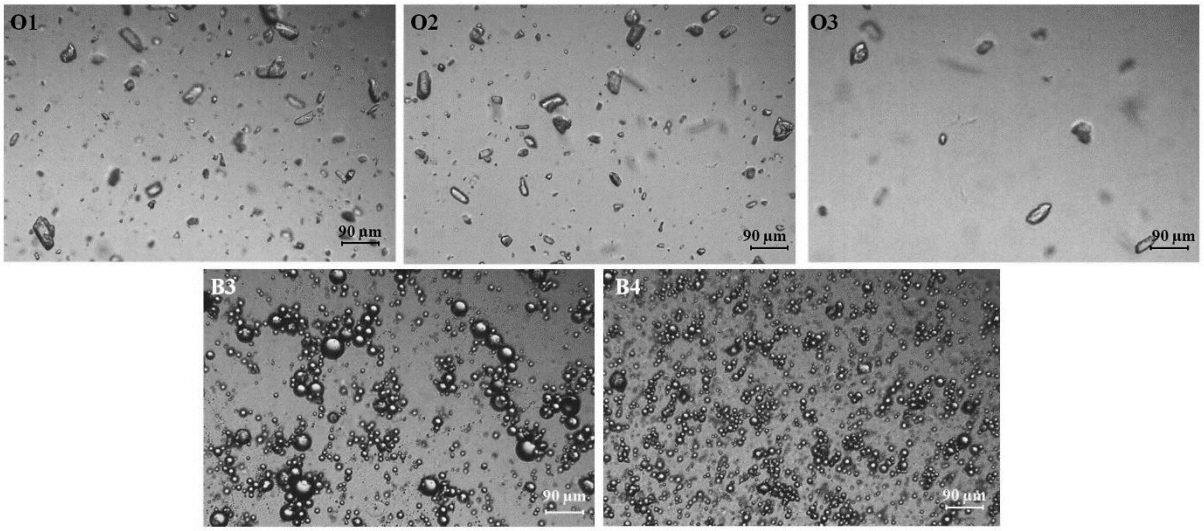

Figure 1. Microscopic images of oleogels (O1, O2 and O3) and bigels (B3 and B4) containing KET under magnification 100×.

NOTE: margins on each side 2.5 cm
Time New Roman font
Abstracts, References: 10 font
Main text: 12 font
Line spacing: 1.5
Please, use square brackets in the main text !

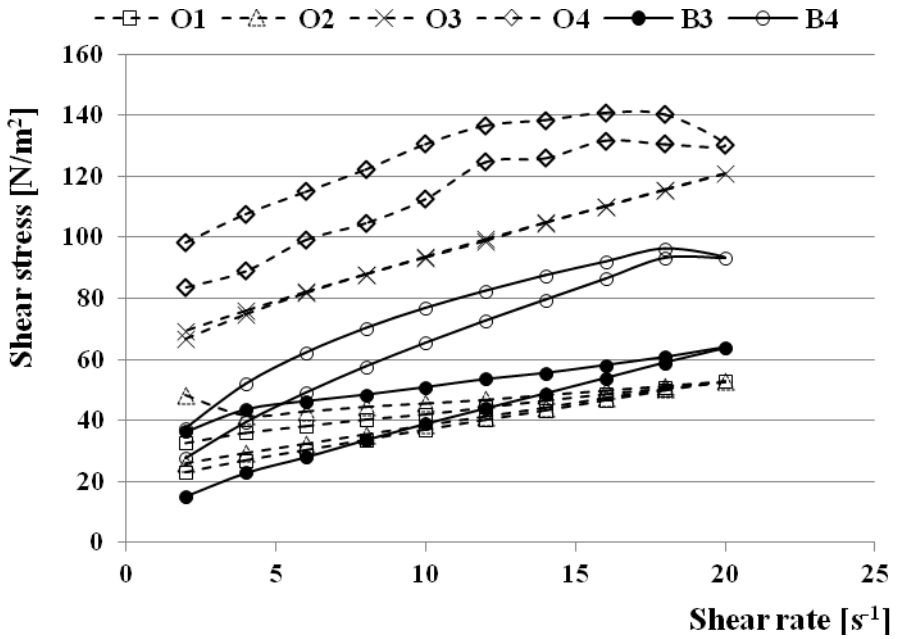

Figure 2. Rheograms of oleogels (O1 - O4) and bigels (B3 and B4) containing KET.

NOTE: margins on each side 2.5 cm
Time New Roman font
Abstracts, References: 10 font
Main text: 12 font
Line spacing: 1.5
Please, use square brackets in the main text !
