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# OLEOGELS AND BIGELS AS TOPICAL DRUG CARRIERS FOR KETOCONAZOLE – DEVELOPMENT AND *IN VITRO* CHARACTERIZATION

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**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

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. The main challenge to translocate the drug molecule across the skin is to overcome the *stratum corneum* – the outermost layer which determines the skin barrier functions. The therapeutic efficacy of topical formulations depends on both the physicochemical properties of the active substance and the type of the vehicle. It is well known that vehicles used in topically applied formulations can greatly affect the rate and extent of drug permeation. When developing these formulations, the goal is to obtain systems with optimized drug loading and release properties which are able to ensure 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. Oleogels are semisolid systems which consist of a lipophilic liquid phase (mineral or vegetable oils, isopropyl myristate) gelled with suitable gelling agent referred as organogelator. 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). Several types of gelators can be found in the literature and one of the often used is colloidal silicon dioxide (fumed silica). Fumed silica-based gels are characterized by pronounced thixotropic behavior, high viscosity, and they are stable over a wide temperature range (8, 9). Oleogels offer numerous advantages over conventional gel formulations. They are easy to prepare and due to the absence of water, they are resistant to microbial contamination and hence do not require addition of preservatives. Moreover, they can improve drug penetration through the *stratum corneum* because of their lipophilic nature (1). However, oleogels are considered as oily in nature and difficult to remove after application, therefore

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bigels were introduced as an alternative gel system. Bigels combine the features of both oleogels and traditional aqueous gels and are characterized by good spreadability, cooling effect, ease of washing with water, and simplicity of preparation. Furthermore, they increase hydration of the *stratum corneum* and possess advantages over other semisolid systems that include synergistic effect of hydrogels and oleogels with less risk of irritation due to the absence of emulsifiers at high concentration and the possibility of delivery both lipophilic and hydrophilic drugs. Bigels are novel semisolid formulations prepared by mixing two gels: oleogel and hydrogel. They are stabilized by entrapment of the oil and water phases *via* a three-dimensional gel network resulting in an extra fine dispersion (1, 9-14).
Ketoconazole (KET) is an imidazole antifungal agent, which is used both in the treatment of topical or systemic fungal infections (15). It interferes with the fungal synthesis of ergosterol, a constituent of cell membrane specific for fungi. KET inhibits biosynthesis of triglycerides, phospholipids and oxidative or peroxidative enzyme activity, which results in intracellular buildup of toxic concentrations of hydrogen peroxide. Moreover, it inhibits the transformation of blastospores to invasive mycelial forms in the treatment of *Candida albicans* infections (15, 16). KET is lipophilic and practically insoluble in water (0.0866 – 40.0 µg/mL; logP 4.31) (17, 18). Poor water solubility of drug is a major problem in the development of highly effective pharmaceutical formulations, and oleogels or bigels may be potential drug delivery vehicles for the poor aqueous soluble drugs such as KET. Therefore, the aim of this study was to formulate and evaluate physicochemical characteristics of designed oleogels and bigels containing KET. Moreover, the *in vitro* KET release from prepared formulations and their *ex vivo* bioadhesive properties were examined.

## 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,

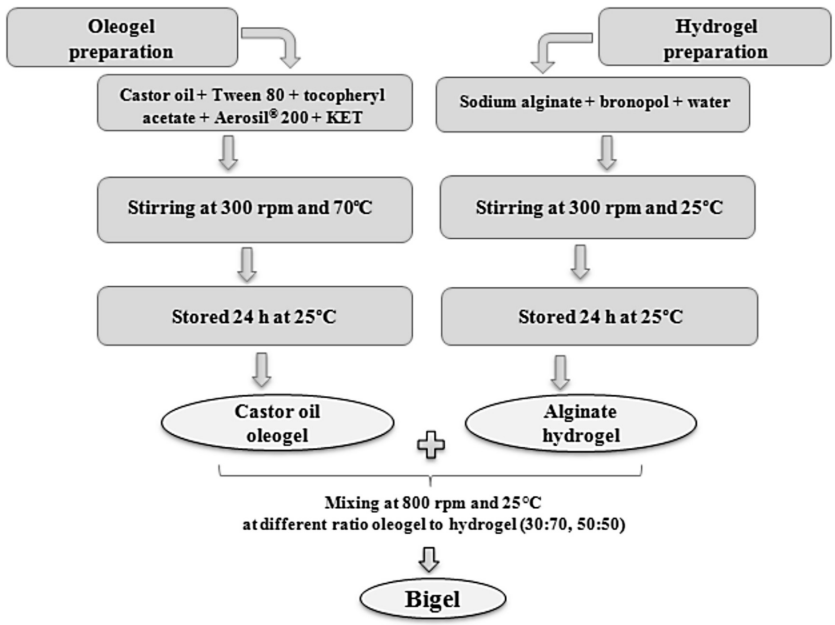


Figure 1. Schematic diagram of bigel preparation

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 |

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). Shaved rat skin (excised from the dorsal region of male Wistar rats weighing 150 – 200 g) was collected according to a protocol approved by Ethics Commission of the Medical University of Białystok, Poland. Samples of rat skin were stored at – 20°C and before the experiment were defrosted and cut into 5 mm diameter pieces.

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

Alginate hydrogel was prepared by dissolving bronopol in purified water and then sodium alginate (5% w/w) was gradually added into the solution and steered using mechanical stirrer. Mixing was continued until a transparent gel was received.

Bigels were produced by separately preparing oleogel and hydrogel, and then mixing them with a mechanical stirrer (800 rpm) at a room temperature. Bigel formulations were made at different oleogel to hydrogel weight ratio: 30:70 or 50:50. Figure 1 presents schematic diagram of bigel preparation. Concentration of KET in oleogels and bigels was 2% w/w. KET was uniformly dispersed or dissolved in oils before adding Aerosil® 200. During bigels preparation, KET was dispersed in oleogels and then oleogels were mixed with alginate hydrogel with constant mechanical stirring at 800 rpm.

**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).

***pH determination***

The pH was measured by a glass electrode of the pH-meter Orion 3 Star (Thermo Scientific, Waltham, MA, USA).

***Particle size analysis***

Oleogels and bigels samples (in quantity corresponding to 10 μg of KET) were observed under magnification 100× and particles size was analyzed by using optical microscope Motic BA 400 equipped with a camera (Moticon, Wetzlar, Germany) (20).

***Viscosity measurement and determination of rheological properties***

The viscosity was determined using Brookfield viscometer (RVDV-III Ultra, Brookfield Engineering Laboratories, Middlebro, MA, USA) equipped with the cone/plate type CPA52Z (plate diameter 24 mm, cone angle 3°) measuring system viscosity at temperature 25°C ± 1°C. The viscosity of formulations at shear rate 10.00 $s^{-1}$ was recorded and the rheograms were evaluated by plotting the obtained values of shear stress versus shear rate (2.00-20.00 $s^{-1}$) (21).

***Texture analysis***

Texture properties of prepared formulations were examined using a Texture Analyser TA.XT Plus (Stable Micro System, Godalming, UK) for backwards extrusion measurements. A disc (35 mm diameter) was pushed at a speed of 2 mm·$s^{-1}$ for a distance of 5 mm into the oleogel/bigel sample (30 g) and redrawn. Data collection and data analysis were performed using the Texture Exponent software package. Parameters such as firmness, compressibility and adhesiveness were determined from the resultant force-time plots (22-24).

***Ex vivo* bioadhesive properties of oleogels and bigels**

Evaluation of bioadhesiveness was performed using TA.XT.Plus Texture Analyser (Stable Micro Systems, Godalming, UK) on the rat skin model. Samples of the shaved rat skin excised from the dorsal region were frozen at -20°C and stored no longer than 4 weeks. On the day of the experiment skin samples were defrosted and cut into 5 mm diameter pieces, then they were thawed in physiological saline solution (0.9% NaCl) at 25°C ± 0.5°C for 30 min. Next skin was attached to the lower end of a cylindrical probe using a cyanoacrylate glue. The oleogels and bigels in amount of 0.5 g were placed below the probe and immersed in a 32°C ± 0.5°C water bath to mimic skin temperature. Experimental parameters of the process were chosen during preliminary tests and set as follows: pretest speed 0.5 mm·$s^{-1}$, test speed 0.1 mm·$s^{-1}$, contact time 120 s, post test 0.1 mm·$s^{-1}$, applied force 0.5 N. The adhesive properties were determined as the maximum detachment force ($F_{max}$) and the work of adhesion ($W_{ad}$) – calculated from the area under the force *versus* distance curve, expressed in μJ.

The work of adhesion ($W_{ad}$) was calculated by using the following formula:

$$W_{ad} = A \times 0.1 \times 1000$$

where A – area under the force *versus* distance curve, multiplication by 0.1 – conversion time measurement to distance (the sampler was raised at 0.1 mm·$s^{-1}$), then multiply by 1000 in order to express the result in units of work μJ (24, 25).

Table 2. Drug content, pH, particles or droplets size and viscosity of prepared oleogels and bigels with KET.

| Formulation code | Drug content (%) | pH | Particles size in formulations O1-O3/ Droplets size of the dispersed phase in formulations B3-B4 (μm) | Viscosity*** (mPa·s) |
|---|---|---|---|---|
| O1 | 106.0 ± 0.3 | 6.5 ± 0.02 | 26.5 ± 23.1 | 4207 ± 147 |
| O2 | 94.7 ± 0.7 | 6.3 ± 0.03 | 26.0 ± 16.8 | 4842 ± 196 |
| O3 | 98.2 ± 0.6 | 6.1 ± 0.01 | 31.6 ± 21.2* | 9339 ± 129 |
| O4 | 100.1 ± 0.1 | 7.0 ± 0.03 | -** | 11754 ± 73 |
| B3 | 105.9 ± 0.1 | 6.6 ± 0.03 | 17.2 ± 12.6 | 5093 ± 163 |
| B4 | 100.8 ± 0.3 | 6.8 ± 0.02 | 13.2 ± 12.0 | 7686 ± 109 |

*in formulation O3 only single suspended KET particles were observed; **in formulation O4 KET was completely dissolved in the vehicle; ***viscosity was measured at the shear rate 10.00 $s^{-1}$

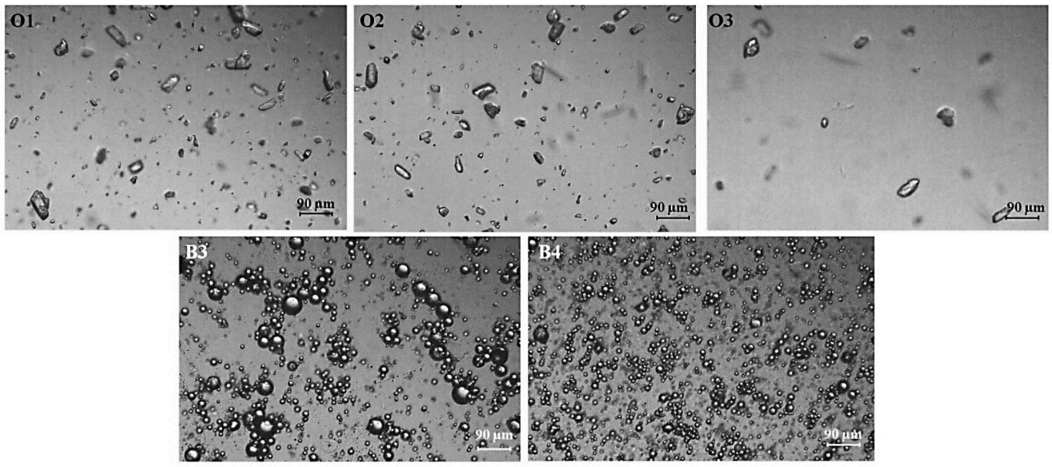


Figure 2. Microscopic images of oleogels (O1, O2 and O3) and bigels (B3 and B4) containing KET under magnification 100×

Table 3. Textural properties of oleogels and bigels containing KET.

| Formulation code | Firmness (g) | Compressibility (g·s) | Adhesiveness (g·s) |
|---|---|---|---|
| O1 | 32.1 ± 0.2 | 67.9 ± 1.2 | -60.4 ± 1.5 |
| O2 | 48.7 ± 0.4 | 93.3 ± 1.2 | -86.7 ± 0.9 |
| O3 | 69.0 ± 6.2 | 138.9 ± 10.0 | -151.2 ± 10.2 |
| O4 | 192.9 ± 2.5 | 298.8 ± 26,5 | -276.7 ± 63.1 |
| B3 | 62.8 ± 0.4 | 131.6 ± 1.1 | -140.8 ± 1.9 |
| B4 | 72.5 ± 0.3 | 146.7 ± 1.6 | -144.4 ± 0.6 |

### *In vitro* KET release

The release of KET was measured through natural cellulose membrane (Cuprophan®, Medicell, London, UK) using an enhancer cell with surface area of 3.80 $cm^2$. The enhancer cell consisted of a teflon load ring, a cap, a membrane and a drug reservoir. This study was performed using the USP dissolution apparatus 2 (Agilent 708-DS, Agilent Technologies, Cary, NC, USA) with mini vessels (250 mL) and mini paddles. Samples, each of about 3 g, were placed in the enhancer cell which was then immersed in the dissolution vessel containing 100 mL of the release medium (acetic buffer pH 5.5 with 1% SDS to provide the *sink* conditions), previously warmed and maintained at 32°C ± 0.5°C. Agitation was provided by mini paddles at 75 rpm and aliquots each of 2 mL were withdrawn at different time intervals (0.5, 1, 2, 3, 4, 5 and 6 h). Withdrawn samples were replaced by equal volumes of fresh release medium (26). The samples were assayed by HPLC method as described above.

### *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 choice of an optimal base for semisolid dosage forms depends on many factors, such as the nature of the active compound, desired therapeutic effect and stability of the final product. The vehicle should

neither irritate nor sensitize the skin, it should be smooth, inert, odorless, physically and chemically stable and compatible with both the skin and active ingredient. Moreover, it should be of a such consistency that spreads and softens easily when stress force is applied. In the last few years, new types of gels have been reported for dermal application, such as oleogels and bigels. The possibility of transforming liquid oils into soft, viscoelastic gels opens up a number of opportunities for their applications as transdermal or topical drug delivery systems for poorly water soluble drugs.

The prepared oleogels and bigels with KET were inspected visually for their color, homogeneity, consistency and phase separation. Oleogels were white or yellow in color, depending on the type of oil used in the formulation. No phase separation was noticed, formulations showed suitable homogeneity and consistency. In the case of formulations O1, O2 and O3, KET was suspended in the oleogel base, while in O4 formulation it was completely dissolved, owing to the addition of ethanol.

Stable and homogeneous bigels (formulations composed of sodium alginate hydrogel and oleogels) were obtained only from oleogels containing castor oil (O3 and O4) and using oleogel to hydrogel weight ratio 30 : 70. Prepared bigels (B3 and B4) were smooth, homogenous, white in color, creamy in appearance and they were not greasy in touch. In bigels formulated with 50 : 50 weight ratio, 24 h after preparation phase separation was observed.

The average KET content was in the acceptable pharmacopoeial limit (27) and was in the range from 94.7 to 106.0 % (Table 2), what indicated that drug during preparation process was homogenously dispersed and not degraded.

The pH of a product can influence not only the solubility and stability of a drug in the formulation, but may also affect its skin irritation potential. The pH values of oleogels and bigels were in the range from 6.1 to 7.0 (Table 2). The pH of prepared formulations provides a safe application to the skin without the risk of irritation problems (28-30). Moreover, pH values of all prepared formulations do not affect degradation of KET, which is stable at pH 6 – 8 (31).

Microscopy imaging revealed the presence of KET crystals in oleogels O1, O2 and O3 (Fig. 2). The particles size of suspended KET in oleogels was below 90 μm and ranged from 26.0 to 31.6 μm (Table 2). The droplets size of the dispersed phase in bigels was in the range of 13.2 – 17.2 μm and it was lower in case of formulation B4 containing ethanol (Table 2, Fig. 2).

The viscosity of the formulation may affect mechanical characteristics (firmness, adhesiveness, compressibility) and the release of the drug. Prepared oleogels were found to have significantly different viscosities values (the range from 4207 mPa·s to 11754 mPa·s, Table 2), which was caused by the type of oils used in formulations and the addition of ethanol. When colloidal silicon dioxide is dispersed in the non-polar vehicle (mineral oil or

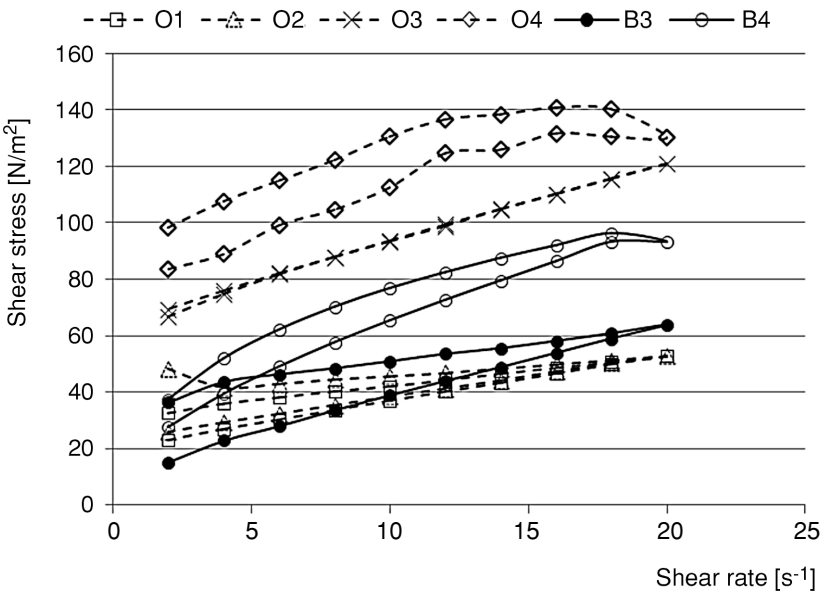


Figure 3. Rheograms of oleogels (O1 – O4) and bigels (B3 and B4) containing KET

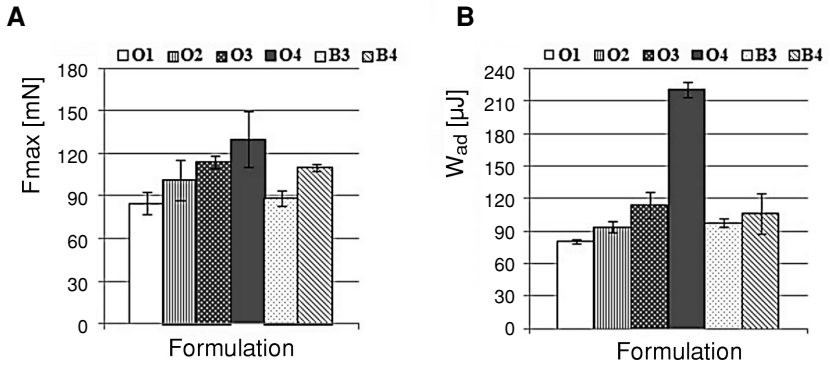


Figure 4. *Ex vivo* bioadhesive properties of oleogels (O1 – O4) and bigels (B3 and B4) containing KET determined as the maximum detachment force $F_{max}$ (A) and the work of adhesion $W_{ad}$ (B)

vegetable oil), the available silanol groups can easily interact with each other *via* hydrogen bonding with a visible formation of three-dimensional structure and thus imparting semisolid consistency depending on polarity of the oil. Nonpolar oils are hydrocarbons such as mineral oil (liquid paraffin), and typical polar oils are fatty alcohols, esters and triglycerides (8, 9). The highest viscosity was noticed in the case of oleogels containing castor oil or castor oil with ethanol (9339 mPa·s and 11754 mPa·s for O3 and O4, respectively), the lowest viscosity possessed oleogel with liquid paraffin (O1; 4207 mPa·s). Viscosity values of prepared bigels B3 and B4 (5093 mPa·s and 7686 mPa·s, respectively; Table 2), were significantly lower than viscosities of corresponding oleogels O3 and O4.

Figure 3 shows the rheograms of prepared oleogels and bigels with KET. From the rheograms it was deducted that most of the formulations were non-Newtonian, pseudoplastic systems and they exhibited a shear-thinning behavior. Moreover, they possessed thixotropic properties, as evidenced by the hysteresis loops formed on rheograms. It appears that under shearing stress, the hydrogen bonding between silica particles and other components are broken down with a more fluid-like low viscosity system, while in the absence of mechanical forces, silica particles rejoin again and the three-dimensional network rebuilds fairly quickly, resulting in a rapid recovery of the structure (8, 9). However, different rheogram of oleogel O3 presented in Fig. 3 shows almost linear relationship between shear rate and shear stress which is not typical for pseudoplastic flow but rather for Bingham model. The Bingham model concerns a viscoplastic material that behaves as a rigid body at low stress and flows as a viscous fluid at the higher stress. Moreover, the hysteresis loop recorded for oleogel O3 indicates that the thixotropy is negligible. High value of viscosity and mechanical parameters indicate rigid structure of O3 oleogel created with using fumed silica and castor oil, resulting from a strong particle-particle interaction leading to a firm network formation. It might be affected by the gelling agent and also by the type of oil used in the formulation.

Texture can be regarded as a manifestation of the rheological properties of a product. Textural analysis is widely used for the mechanical characterization of semisolids, especially in pharmaceutical and cosmeceutical field (22). The textural properties are important to determine the ease of sample removal from the container or its spreadability at the application site. Textural parameters, e.g. firmness, adhesiveness and compressibility provide information on the response of a formulation to the external force. Firmness is defined as the maximal force required to attain a given deformation and samples with higher firmness are more difficult to remove from the container or to spread on the skin. Adhesiveness is helpful in predicting the topical residence time and is defined as the work necessary to overcome attractive forces between the investigated sample and the model adhesive layer. Compressibility (calculated from the positive area under the force-time curve) defines the work required to deform the product during the compression of probe and it is correlated with the spreadability on the skin surface (22-24). Texture profile parameters obtained for the investigated samples are presented in Table 3.

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 Fig. 4.

It was observed that all formulations were characterized by bioadhesive properties which might be explained by the formation of hydrogen bonds between the proteins present in the skin and the polymer chain. The greater values of $F_{max}$ and $W_{ad}$ were noticed in case of oleogels O3 and O4, characterized by high viscosity and high values of parameters of mechanical properties.

***In vitro KET release and mathematical models of release profile***

From the *in vitro* dissolution studies it is possible to determine how the composition of the formulation affects the drug release. The drug release from dermatological preparations depends on several parameters such as the nature of the vehicle and its viscosity, the solubility of the active compound in the vehicle and acceptor medium, as well as drug partition coefficient between the vehicle and water. Generally, it is considered that the release rate increases in the following order: lipophilic ointment < cream oil/water < gel. The release of KET from oleogels and bigels is demonstrated in Fig. 5. It was shown that KET was released significantly slower from commercially available product than from prepared formulations. The release of KET can be ranked in the following descending order: O4 ≈ B4 > B3 > O3 > O2 > O1 > C (control formulation). The largest amount of released KET was observed for oleogel O4 (after 6 h, cumulative amount of released KET was 104.8 μg/cm$^2$). It might be due to the improved solubility of KET caused by ethanol present in this formulation. Interestingly, KET was faster released from bigels B4 and B3 (after 6 h, cumulative amount of released KET was 98.6 μg/cm$^2$ and 79.4 μg/cm$^2$, respectively) than from oleogels O1, O2 and O3. These results are due to the increase of hydrophilicity of bigel which facilitated the penetration of the release medium into the vehicle and diffusion of the drug. Oleogel O1 showed the slightest drug release (after 6 h, cumulative amount of released KET was only 32.2 μg/cm$^2$). Oleogel O1 was characterized by relatively low viscosity, but in this formulation KET was mainly suspended in the vehicle. The lower drug release from commercially available product might be due to its relatively high viscosity. The increased viscosity of the vehicle may negatively affect the drug diffusion rate. Moreover, excipients used in the preparation, in contact with dissolution medium might cause increase in the viscosity of the

Table 4. Models of KET release from designed formulations and commercially available product (C).

| Formulation code | Kinetic models | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Zero order kinetics | | First order kinetics | | Higuchi model | | Korsmeyer-Peppas model | | |
| | $R^2$ | $K_0$ | $R^2$ | $K_1$ | $R^2$ | $K_H$ | $R^2$ | $K_{KP}$ | n |
| C | 0.564 | 0.139 | 0.791 | 0.0005 | 0.939 | 0.233 | 0.911 | 1.079 | 0.158 |
| O1 | 0.850 | 0.356 | 0.971 | 0.0021 | 0.986 | 0.855 | 0.972 | 1.201 | 0.315 |
| O2 | 0.930 | 0.830 | 0.901 | 0.0053 | 0.986 | 2.285 | 0.963 | 1.382 | 0.367 |
| O3 | 0.915 | 0.973 | 0.858 | 0.0062 | 0.987 | 2.763 | 0.956 | 1.480 | 0.460 |
| O4 | 0.960 | 1.328 | 0.951 | 0.0092 | 0.996 | 3.792 | 0.989 | 1.521 | 0.458 |
| B3 | 0.882 | 1.003 | 0.852 | 0.0062 | 0.989 | 2.683 | 0.971 | 1.340 | 0.345 |
| B4 | 0.963 | 1.299 | 0.925 | 0.0090 | 0.990 | 3.769 | 0.976 | 1.534 | 0.483 |

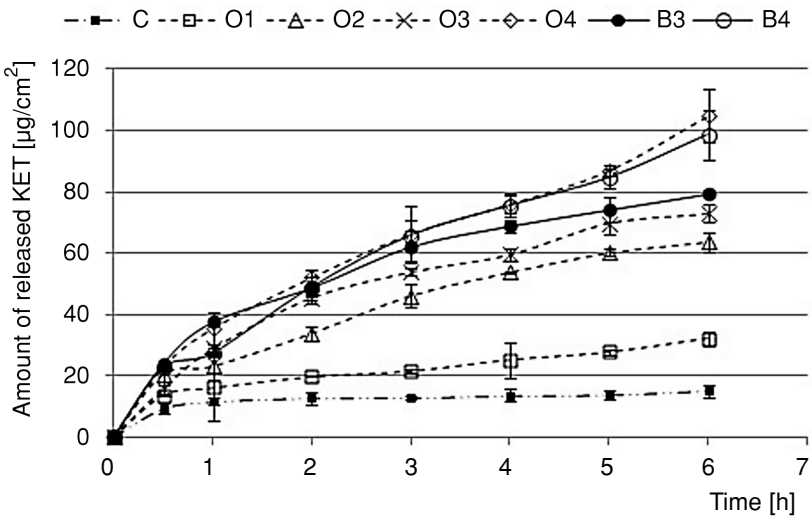


Figure 5. *In vitro* KET release from oleogels (O1 – O4) and bigels (B3 and B4) comparing with commercially available product (C)

formulation and in the consequence impede the diffusion of the drug substance.

The mechanism of KET release from obtained formulations was analyzed according to various mathematical models: zero order kinetic, first order kinetic, Higuchi model and Korsmeyer-Peppas equation to find out the coefficient of correlation ($R^2$) and the values of the release exponent (n) (14, 33, 34). Zero-order kinetics describes process independent of the existing or initial concentrations. First-order kinetic takes place at a constant proportion of the drug concentration available at that time so the process is depending on the initial concentration. In models of Higuchi and Korsmeyer-Peppas, release rate is variable in time and these models are based on the assumption of the conformity of the release of Fick's law.

Kinetic model that best describes the process of KET release from prepared oleogels and bigels was selected based on the highest values of the coefficient of determination $R^2$. The best model to describe the release of KET either from oleogels and bigels was Higuchi model (Table 4). The Higuchi kinetic plots were found to be fairly linear as indicated by their highest regression values and for all prepared formulations correlation coefficients values ($R^2$) were in the range of 0.939 – 0.996. Higuchi's model describes the diffusion of the drug in accordance with Fick's law, where the rate of diffusion through the membrane is affected by the difference in concentrations of the drug across the membrane. An important parameter describing the drug release is the diffusion exponent n, the value of which indicates the mechanism of release. If $n \leq 0.5$, the drug is released by diffusion in accordance with Fick's law, when n = 1.0, the release takes place with zero-order kinetics, in the case where the value of the exponent n is in the range of $0.5 < n < 1.0$, the release is governed by both aforementioned processes (33, 34). Exponents for KET diffusion from both oleogels and bigels were less than 0.5, which indicates that its release takes place by diffusion in accordance with Fick's law.

## 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. Most of the obtained oleogels and bigels were non-Newtonian systems, showing a shear-thinning behavior with thixotropic properties. Moreover, it was noticed that all formulations were characterized by beneficial bioadhesive properties. The oleogel to hydrogel weight ratio 30 : 70 was optimal combination for bigels, showing proper homogeneity and stability, good rheological and mechanical properties and high KET release. The designed formulations provided better release profile than commercially available product. The release of KET from the obtained oleogels and bigels demonstrated diffusion mediat-

ed release behavior. In this study, it was successfully proved that prepared oleogels and bigels may be used as drug delivery vehicles for lipophilic drug such as KET. Obtained formulations present promising potential for further investigations and development of vehicles for topical drug delivery.

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**REFERENCES**

1. Rehman K., Zulfakar M.H.: Drug Dev. Ind. Pharm. 40, 433 (2014).
2. Singh Malik D., Mital N., Kaur G.: Expert Opin. Ther. Pat. 26, 213 (2016).
3. Vintiloiu A., Leroux J.-Ch.: J. Control. Release. 125, 179 (2008).
4. Davidovich-Pinhas M.: Ther. Deliv. 7, 1 (2016).
5. Singh V.K., Pramanik K., Ray S.S., Pal K.: AAPS PharmSciTech. 16, 293 (2015).
6. Davidovich-Pinhas M., Barbut S., Marangoni A.G.: Carbohydr. Polym. 127, 355 (2015).
7. Osmałek T., Milanowski B., Froelich A., Górska S., Białas W. et al.: Pharm. Dev. Technol. 20, 1 (2016).
8. Patel A.R., Mankoc B., Bin Sintang M. D., Lesafferb A., Dewettinck K.: RSC Adv. 5, 9703 (2015).
9. Lu Z., Fassihi R.: AAPS PharmSciTech. 16, 636 (2015).
10. Almeida I.F., Fernandes A.R., Fernandes L., Pena Ferreira M.R., Costa P.C. et al.: Pharm. Dev. Technol. 13, 487 (2008).
11. Ibrahim M.M, Hafez S.A., Mahdy M.M.: Asian J. Pharm. Sci. 8, 48 (2013).
12. Singh V.K., Anis A., Banerjee I., Pramanik K., Bhattacharya M.K. et al.: Mater. Sci. Eng. C Mater. Biol. Appl. 44, 151 (2014).
13. Rehman K., Mohd Amin M.C., Zulfakar M.H.: J. Oleo. Sci. 63, 961 (2014).
14. Rehman K., Zulfakar M.H.: Pharm. Res. 33, 1 (2016).
15. Kauffman C.A., Carver P.L.: Adv. Pharmacol. 39, 143 (1997).
16. Gil C., Perez – Diaz R., Nombela C.: J. Med. Vet. Mycol. 32, 151 (1994).
17. Kovács K., Stampf G., Klebovich I., Antal I., Ludányi K.: Europ. J. Pharm. Sci. 36, 352 (2009).
18. Jacobs G.A., Gerber M., Malan M.M., du Preez J.L., Fox L.T. et al.: Drug Deliv. 23, 631 (2016).
19. Tannergren C., Knutson T., Knutson L., Lennernäs H.: Br. J. Clin. Pharmacol. 55, 182 (2003).
20. The European Pharmacopoeia 8.0, Council of Europe: Strasbourg, France, 2014.
21. Wróblewska M., Winnicka K.: Int. J. Mol. Sci. 16, 20277 (2015).
22. Hurler J., Engesland A., Poorahmary Kermany B., Škalko-Basnet N.: J. Appl. Polym. Sci. 125, 180 (2012).
23. Hurler J., Škalko-Basnet N.: J. Funct. Biomater. 6, 37 (2012).
24. Carvalho F.C., Calixto G., Hatakeyama I.N., Luz G.M., Gremião M.P. et al.: Drug Dev. Ind. Pharm. 39, 1750 (2013).
25. Sosnowska K., Szekalska M., Winnicka K.: POLIMERY-W. 61, 322 (2016).
26. Winnicka K., Wroblewska M., Wieczorek P., Sacha P.T., Tryniszewska E.: Molecules. 17, 4612 (2012).
27. The United States Pharmacopeia, USP 39–NF 34; The United States Pharmacopeial Convention: Rockville, MD, USA, 2015.
28. Zhai H., Chan H.P., Farahmand S., Maibach H.I.: Skin Res. Technol. 15, 470 (2009).
29. Worth A.P., Cronin M.T.: Toxicology. 169, 119 (2001).
30. Pandey M., Belgamwar V., Gattani S., Surana S., Tekade A.: Drug Deliv. 17, 38 (2010).
31. Skiba M., Skiba – Lahiani M., Marchais H., Duclos R., Arnaud P.: Int. J. Pharm. 198, 1 (2000).
32. Palacio M.L., Bhushan B.: Philos. Trans. A Math. Phys. Eng. Sci. 370, 2321 (2012).
33. Costa P., Sousa Lobo J.M.: Eur. J. Pharm. Sci. 13, 123 (2001).
34. Siepmann J., Siepmann F.: Int. J. Pharm. 453, 12 (2013).

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