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STUDY OF THE SOLUBILITY OF BETAMETHASONE DIPROPIONATE AND THE CONDITIONS FOR THE FORMATION OF THE STABLE SUSPENSIONS

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The aim. *To study the solubility of betamethasone dipropionate (BD) in mixed solvents water – propylene glycol (PG) and liquid paraffin, as well as to identify the conditions necessary for the formation of stable BD suspensions.*
Materials and methods. *The solubility of BD in solvents water – PG was studied using spectrophotometry. The particle size distribution of BD in suspensions was analysed by laser diffraction. The suspensions and creams were subjected to optical microscopy for additional evaluation. Thermogravimetric analysis was conducted to explore the potential formation of BD crystallosolvates with PG, while differential scanning calorimetry was utilised to assess the characteristics of the dissolution processes. Additionally, the study employed the spin probe method, using a steroid spin-label.*
Results. *The solubility of BD in water – PG solvents was found to increase with rising temperature and to increase sharply with increasing PG concentration, provided that the PG structure dominated the system. The deviations of BD solubility from additivity at 20–35°C were negative, passing through a minimum at a PG concentration of ~35% mol, above which the transition to the structure of a nonaqueous solvent occurred. An elevation in temperature to 45–55°C resulted in a positive deviation of the BD solubility from additive values at specific PG concentrations. It has been demonstrated that PG and BD do not form crystallosolvates. The process of dissolving BD in PG is exothermic, while in liquid paraffin, it is endothermic. The steroid spin probe was found to be localized in the oil phases of creams. Suspensions in which BD particles recrystallize were formed when BD crystallized from solution in PG as a result of lowering the temperature and adding water. When BD was suspended in a water – PG solvent, where the water structure predominates, or in liquid paraffin (oil phase of creams), the BD particle size increased slightly, or there was no recrystallization.*
Conclusions. *The solubility of BD in solvents water – PG is contingent upon the temperature and concentration of PG; it exhibits a marked increase when the structure of a nonaqueous solvent predominates in the system. It has been demonstrated that BD with PG does not form crystallosolvates. When BD suspensions were obtained by crystallization from a solution in PG, suspensions were formed in which BD particles recrystallized over time. In the case of BD suspensions in solvent water – PG, where the water structure predominates, or in liquid paraffin, recrystallization was practically not observed*

Keywords: *betamethasone dipropionate (BD), solubility, crystallization, propylene glycol (PG), water, solvent, liquid paraffin*

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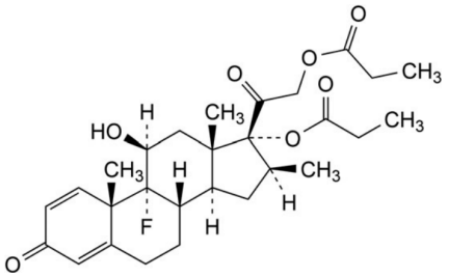
1. Introduction

Betamethasone dipropionate (BD) is a synthetic fluorinated corticosteroid with a chemical structure of 9-fluoro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate [1]. The BD substance is subject to standardization in Ph. Eur., USP, and BP [1–3].



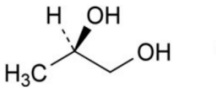
$C_{28}H_{37}FO_7$ M_r 504.6 CAS [5593-20-4]

BD is a white or almost white, crystalline powder. It is a hydrophobic substance that is practically insoluble in water, freely soluble in acetone and methylene chloride, and sparingly soluble in ethanol (96%) [1, 3].

Semi-solid and liquid preparations containing 0.064% BD are widely administered in dermatology [4]. According to the World Health Organization's ATC classification system, betamethasone is categorised in group D07A C «Corticosteroids, potent (group III)» [5]. BD is a corticosteroid that exerts a potent anti-inflammatory, anti-allergic, and antipruritic action when applied topically [4]. A number of pharmacopoeial monographs have been published for preparations with BD in various dosage forms for topical use. The following monographs are available in the USP: «Betamethasone Dipropionate Cream», «Betamethasone Dipropionate

Ointment», «Betamethasone Dipropionate Lotion», and «Clotrimazole and Betamethasone Dipropionate Cream». The BP includes several monographs on preparations containing betamethasone in combination with calcipotriol (ointment, gel, and cutaneous foam) [3]. It is noteworthy that none of the monographs for preparations with BD or betamethasone, where these active substances may be present in the form of a suspension, specify requirements for their particle size [2, 3], a characteristic that could potentially affect the efficacy and quality of the medicinal products.

A plethora of semi-solid preparations containing BD in the form of suspension are available on the global pharmaceutical market and in Ukraine [4, 6]. Of particular relevance are suspension-type creams with BD, whose bases are visco-plastic o/w emulsions. The dispersion medium of these creams is water or a mixed solvent *water – propylene glycol* (PG)



and enantiomer

$C_3H_8O_2$ M_r 76.1 CAS [57-55-6]

Propylene glycol is widely used as an antimicrobial preservative, disinfectant, humectant, plasticizer, solvent, stabilizer for vitamins, and water-miscible cosolvent in a variety of parenteral and nonparenteral pharmaceutical formulations [7]. It is a better solvent than glycerin and dissolves a wide variety of materials, for example, corticosteroids [7]. It was demonstrated that, in terms of antimicrobial preservation, PG is less efficacious than ethanol [8]. In experiments *in vitro*, PG is rapidly and completely released through a semipermeable membrane [9]. As demonstrated by [10], PG acted as both a solvent for hydrophobic corticosteroids and an enhancer of their penetration. Using an artificial lipid acceptor and excised human skin *in vitro* experiments, it was ascertained that PG functioned as a penetration enhancer for betamethasone 17-valerate and hydrocortisone 17-butyrate. The penetration mechanism of the corticosteroids due to PG at PG content levels of up to 40% m/m and 60–80% m/m was found to be different [10].

PG was studied by Carrer V. and co-authors [11] in the capacity of a co-solvent and penetration enhancer. The results indicated the enhancer properties of PG for all the studied compounds, especially for the hydrophilic ones. As demonstrated in [11], PG, at high concentrations, exerted a disordering effect on the lipid structure of the skin.

Numerous studies have been conducted by various authors on the physicochemical properties of mixed solvents *water – PG*. The surface tension of the system is known to decrease with increasing PG concentration and temperature [12, 13]. The values of density and excess density of mixed solvents *water – PG* are maximal at a PG concentration of approximately 35–36% mol. An increase in temperature results in a decrease in both density and excess density while maintaining their maximum values at the same PG concentration [12, 14]. The molar volumes increase with increasing PG concentration, and the excess molar volumes are minimal at a PG concentration of about 35–36% mol [12, 15]. The dynamic viscosity of binary solvents has been observed to increase with increasing PG concentration and decrease with decreasing temperature. The excess dynamic viscosity is minimal at PG concentrations of approximately 35–50% mol [12, 16].

The polythermal determination of the physical and chemical characteristics of mixed solvents (in particular, dynamic viscosity and molar volumes) provides the opportunity to calculate the thermodynamic functions of activation for viscous flow [17] and to gain insight into their structure depending on the composition. The determination should be carried out over the entire range of mole fractions, with excessive parameters being calculated [12, 14, 18]. The results of their analysis can be used to assess intermolecular interactions between components in the system.

The thermodynamic parameters and excess thermodynamic parameters of the activation for viscous flow at temperatures ranging from 293.15 K (20°C) to 313.15 K (40°C) were calculated, based on the determined values of the dynamic viscosity and molar volumes for the solvents *water – PG* [12]. Based on their isotherms at 298.15 K, assumptions were made about the change in the structure of binary solvents with increasing PG concentration (water structure → mixed structure → non-aqueous solvent structure). The structure of a mixed solvent exerts a significant influence on its functional properties, particularly its capacity to facilitate the dissolution of active pharmaceutical ingredients.

Raman spectroscopy and stimulated Raman scattering were used to investigate the hydrogen bonding network in binary solvents *water – PG* [18]. It was demonstrated that the ice-like structures appeared near the methyl group of PG, and the hydrogen bonds weakened. The structure of hydrogen bonds in this binary system underwent a transition from H_2O–H_2O to H_2O–PG when the volume fraction of PG was 0.4, as PG content increased [18].

The microstructure of the system *PG – water*, depending on the PG concentration, was studied by NMR [19]. *PG – water* solution system has an apparent critical concentration of PG when its mole fraction is around 0.3. PG alkyl protons form weak C–H···O hydroxyl bonds with surrounding water, and PG hydroxyls form strong O–H···O hydroxyl bonds with water, which results in the stronger hydrogen bond network. At the PG-rich region, the solution forms regions enriched in either hydrocarbons or hydroxyl groups, resulting in the formation of a microheterogeneous solution, where water is expelled from the alkyl tail and accumulated in the region of PG hydroxyl groups [19].

The ability to dissolve active pharmaceutical substances is probably the most significant performance characteristic of mixed solvents. The majority of solubility

studies employ a similar methodological approach. The authors conducted an experimental study to ascertain the solubility of a particular substance, with the variables of solvent composition and temperature. A subsequent thermodynamic analysis of the results was performed, and the solubility of the substance in a mixed solvent was predicted. Utilising a range of models, they have correlated the experimental data with the calculations.

The system *water – PG* was the subject of research on the dissolution of various active substances, including fluphenazine decanoate [20], daidzein [21], sodium phenytoin [22], mesalazine [23], several sodium sulfonamides [24], and sildenafil citrate [25], etc.

Many other studies focused on the system *water – PG*. For example, the investigation of solubility and *in vitro* release of acyclovir [26]; or the study of localization of diclofenac in the skin tissue depending on PG concentration [27], amongst others.

It is evident that the system *water – PG* has attracted significant interest from researchers, particularly in the field of studying the solubility of various active substances. However, a survey of the extant literature failed to yield any data concerning the solubility of BD in mixed solvents *water – PG*. The relevance of this issue is evidenced by the fact that certain creams intended for cutaneous application contain water, PG, and BD concurrently [4, 6].

Numerous research results have been published in scientific papers on the solubility of active substances in systems *water – PG*, indicating an increase in drug solubility with increasing PG concentration and temperature. However, no research findings have been reported on the crystallization of the active substances during the reverse processes. During the production processes, the structure of the dispersion medium changes when the cream is cooled or a solution of the active substance in PG is introduced into water. This can result in the crystallization of a hydrophobic drug substance. In the case of crystallization, it is essential to ensure the stability of the resulting suspension and a more or less uniform size distribution of the suspended particles. The sedimentation and recrystallization have the potential to induce changes in the microstructure of the cream and result in an ununiform distribution of the drug substance. Consequently, this can have a negative impact on the biopharmaceutical properties and efficacy of the medicinal product.

The solubility of beclomethasone-17–21-dipropionate in acetone, methanol and ethanol was studied, followed by the crystallization of this corticosteroid. However, the purpose of the study was to produce micronised powder of this substance [28].

The aim. To study the solubility of betamethasone dipropionate (BD) in mixed solvents *water – propylene glycol* (PG) and liquid paraffin, as well as to identify the conditions necessary for the formation of stable BD suspensions.

2. Planning (methodology) of the research

The experimental design encompassed an investigation of the solubility of BD in solvents *water – PG* across the entire mole fraction range, within the temperature range of 293.15 K to 328.15 K, and in liquid paraffin. In this regard, it was necessary to develop an analytical procedure for the quantitative determination of BD in solutions and to validate it. The results of the study on the solubility of BD dependent on the PG content should have formed the basis for the calculation of the deviation of solubility from the additive values. In addition, the aim was to correlate them with the thermodynamic activation parameters of the viscous flow for binary solvents *water – PG* [12].

The subsequent stage of the research was to investigate the effect of isohydric crystallisation with a solvent change on the size distribution of BD particles in suspensions, and to identify the conditions under which the size of BD particles does not increase during storage. Conducting a thermogravimetric analysis was a rational approach to studying the possibility of forming crystallosolvates of BD with PG. In addition, the enthalpy of dissolution of BD in PG and liquid paraffin was planned to be determined using differential scanning calorimetry.

It was planned to investigate the localization and behavior of a hydrophobic steroid spin probe in systems *water – PG* and some dispersed systems with a liquid dispersion medium. The findings of these studies should provide the opportunity to predict the solubility of BD in liquid paraffin, the stability of BD suspensions in liquid paraffin and creams, and to recommend the techniques for introduction of BD into creams.

3. Materials and methods

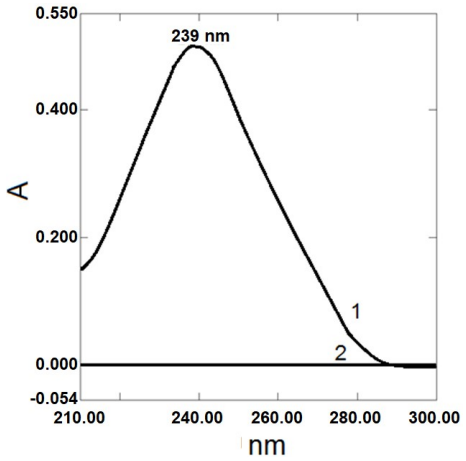
The betamethasone dipropionate micronized (Chemo Ibérica, S.A.), which met the requirements of the Ph. Eur. and the USP [1, 2] (hereinafter referred to as BD), was studied. In the experiment, water for injections (hereinafter referred to as water; conductivity 1.0 $\mu S \cdot cm^{-1}$ at 20°C) and propylene glycol (PG) (The Dow Chemical Company), both of pharmaceutical grade (Ph. Eur. [1]), were used. The water content of the propylene glycol was preliminarily determined by the semi-micro method using Metrohm 870 KF Titrino plus automatic titrator (Metrohm AG, Switzerland). The water content of propylene glycol was found to be 0.08%.

Binary solvents over the whole mole/mass fraction range were prepared gravimetrically using an analytical balance (AUW 120D, Shimadzu). The water content of the PG, as determined to be 0.08% m/m, was considered in the formulation of the mixed solvents.

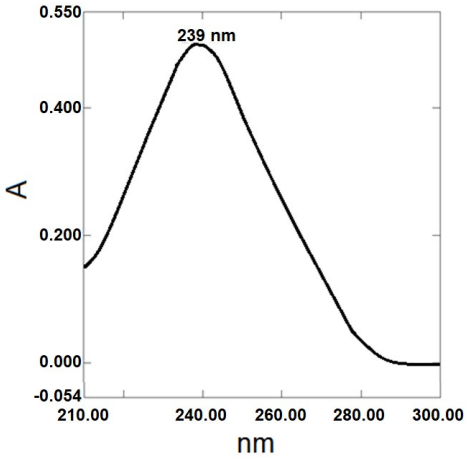
The solubility of BD in solvents *water – PG,* and in liquid paraffin, was studied by the isothermal method, and the concentration of BD in saturated solution was determined by absorption spectrophotometry (UV and visible) (2.2.25) [1]. BD was added in surplus to the specific solvent, and then the suspension was kept at a certain temperature (with an accuracy of ±0.1°C) with periodic stirring. The attainment of thermodynamic equilibrium was confirmed by the consistent absorbance values across several consecutive samples. Sub-

sequently, the solutions were maintained at a constant temperature for 3–4 hours before filtration. Following filtration, samples were collected for analysis. The filtration and analysis were both conducted at the same temperature as the solubility determination. The saturation time ranged from 10 to 100 hours, depending on the PG content. The experiment was conducted at temperatures ranging from 20°C to 55°C.

The absorbance was measured at 239 nm, which is the absorption maximum of BD (Fig. 1), using a «Shimadzu PharmaSpec UV 1700» spectrophotometer (Shimadzu; UVProbe software version 2.21), with the samples being diluted with ethanol (96%).



a



b

Fig. 1. UV absorption spectra of solutions in ethanol (96%): *a* – test solution of BD (1) and placebo solution (15 mg/ml PG) (2); *b* – solution of *Betamethasone dipropionate EP CRS*

The Bouguereau-Lambert-Beer law is applicable to BD solutions in *ethanol* (96%) *P* at concentrations ranging from 6.42 μg/ml to 22.48 μg/ml (Fig. 2). In the case of solutions in liquid paraffin, BD was previously extracted with *ethanol* (96%) *P* on three occasions.

The concentration of BD (C_{BD}) in solution was calculated by the equation

$$C_{BD} = (A_{BD} : A_{CRS}) \cdot C_{CRS} \cdot b, \quad (1)$$

where A_{BD} – absorbance of the test solution of BD; A_{CRS} – absorbance of the solution of *Betamethasone dipropionate EP CRS*; C_{CRS} – concentration of *Betamethasone dipropionate EP CRS* in the solution, which was 16 μg/ml; *b* – dilution.

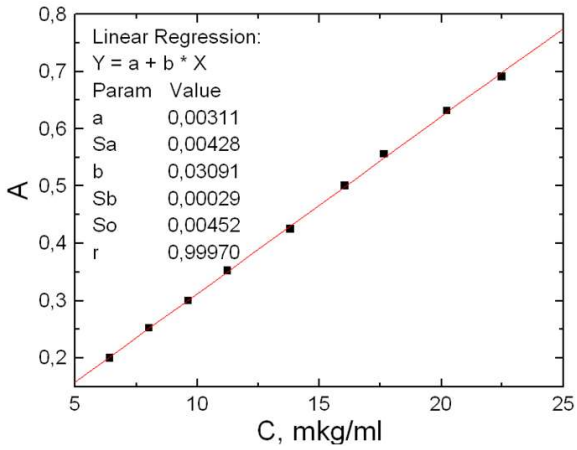


Fig. 2. The linear dependence of absorption (A) and the concentration of BD in solution

In accordance with the commonly accepted methodological approach [29], the analytical procedure for quantitative determination of BD was validated by evaluating such criteria as specificity, accuracy, repeatability, and linearity.

The analytical procedure is specific (Fig. 1), since the absorption maximum at the wavelength of 239 nm for the test BD solution in *ethanol* (96%) *P* coincided with the absorption maximum for the solution of *Betamethasone dipropionate EP CRS* in *ethanol* (96%) *P*. It was demonstrated that both *ethanol* (96%) *P* and PG exhibited no absorption at 239 nm (Fig. 1, *a*).

The procedure for the quantitative determination of BD is characterized by sufficient repeatability (precision) in the range of BD concentrations from 6.42 μg/ml to 22.48 μg/ml, since the relative confidence interval was 1.48%, which did not exceed the acceptance criterion of 1.60% for the tolerances of ±5% (Table 1) [29]. The procedure is characterized by appropriate accuracy since the systematic error of 0.09% did not exceed the established criteria for statistical and practical insignificance (Table 1) and was not statistically different from zero [29].

The linearity of the relationship between the added and found amount of BD in the range from 6.42 to 22.48 μg/ml was confirmed by the high value of the correlation coefficient $r = 0.99997$, as well as by the fact that in the regression equation ($Y_i = a + b \cdot X_i$) the constant term (*a*) did not exceed the confidence interval and was not statistically different from zero (Fig. 3) [29]

$$a = -0.27001 \le t(95\%, n-2) \cdot S_a = |1.8946 \cdot S_\alpha| = |1.8946 \cdot 0.23738| = |0.45|.$$

Moreover, the parameter S_0/b was found to be equal to 0.34736 (Fig. 3), and did not exceed the acceptance criterion of |0.84| [29].

Table 1

Results of the analysis of model solutions containing BD in concentrations ranging from 40% to 140% of the content in the reference solution, their statistical processing, and evaluation

No.	Added as a percentage of the concentration in the reference solution (X_i, %)	Found as a percentage of the concentration in the reference solution (Y_i, %)	Found *vs* added, % $Z_i = 100 \times (Y_i / X_i)$
1	40.14	40.08	99.86
2	50.17	50.50	100.65
3	60.21	60.12	99.86
4	70.24	70.47	100.33
5	86.30	85.17	98.69
6	100.35	100.40	100.06
7	110.38	111.42	100.94
8	126.44	126.65	100.17
9	140.48	138.54	98.62
Mean value, Z_{av}			99.91%
Relative standard deviation (RSD_z)			0.7964%
Relative confidence interval $\Delta_z\% = t\,(95\%, 9-1) \times RSD_z = 1.8595 \times 0.7946\% =$			1.4776%
Critical value for repeatability of results (Δ_{As})			1.60%
Evaluation of repeatability:			1.48% < 1.60%
Evaluation of accuracy:			
Systematic uncertainty $\delta\% = \lvert Z_{av} - 100\rvert =$			0.09%
Criterion of non-significance of systematic uncertainty:			
1) statistical insignificance: $\delta < \Delta_z : \sqrt{9} = 1.4776\% : 3 = 0.49\%$			0.09% < 0.49%
2) practical insignificance: $\delta \le 0.32 \times 1.60\% = 0.51\%$			0.09% < 0.51%

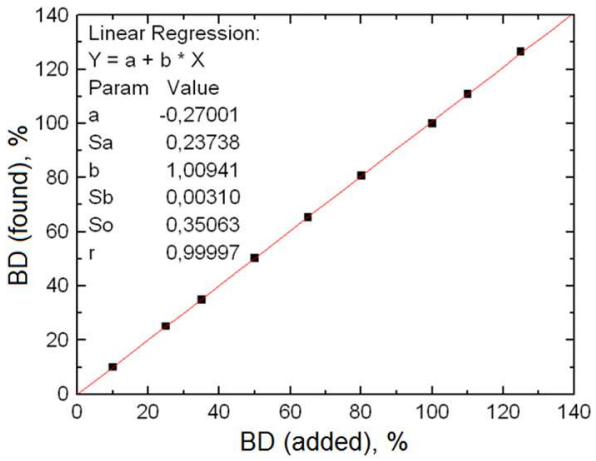


Fig. 3. The linear dependence of the found amount of BD and the added amount of BD

The research results demonstrate the validity of the analytical procedure for the quantitative determination of BD in solutions within its concentration range from 6.42 μg/ml to 22.48 μg/ml.

Based on the results of determining the solubility of BD (L) at different PG concentrations, the excess solubility (L^E) was calculated according to the equation

$$L^E = L - \left(L_1 \cdot X_1 + L_2 \cdot X_2\right), \qquad (2)$$

where L – experimentally determined value of BD solubility; L_1 і L_2 – BD solubility in water and PG, respectively; X_1 і X_2 – mole fractions of water and PG, respectively.

The particle size distribution in the BD substance and BD suspensions was determined by laser diffraction (2.9.31) [1] using a Shimadzu SALD-2201 laser diffraction particle size analyser (Shimadzu; WingSALD II software version 2.1.0). The BD content in the test samples was approximately 0.1 mg/ml.

The dispersed state of BD in suspensions and creams was also determined by optical microscopy (2.9.37) [1] using a microscope with an ocular micrometer «Krüss MBL-2100» (A. Krüss Optronic). In the course of the study, suspensions and creams were not diluted.

The suspension of BD in liquid paraffin [1] was prepared by stirring with a «Polytron PT-MR 3100» mixer (Kinematica AG) for 3 min. The suspensions of BD in the binary solvent *water – PG* (90 : 10 m/m) were obtained using two different techniques: crystallisation and suspending.

The crystallisation technique combined isohydric crystallisation and solvent exchange. BD (0.064 g) was dissolved in PG (10 g) at 60°C with stirring. The resultant solution was then cooled to 40°C, after which 90 g of water at 40°C was added. This resulted in the formation of BD suspension, which was then cooled to 25 °C with stirring. Before the measurements, the suspension was treated using an ultrasonic bath UZM-003/N for 3 min.

In the case of the suspending process, a binary solvent (*water – PG* (90 : 10 m/m)) was prepared and heated to 40°C, BD was suspended in it, and then cooled to 25°C with stirring. The mixture was stirred with a Polytron PT-MR 3100 mixer for 15 min, which was necessary due to the poor wettability of the BD powder.

The particle size distribution in the prepared suspensions was measured immediately after prepara-

tion and after 48 hours. Before measurement, the samples stored for 48 hours were treated for 3 min in an ultrasonic bath and then stirred for 3 min using a Polytron PT-MR 3100 mixer, in accordance with the method of suspension preparation.

Investigations by means of thermogravimetry and differential thermogravimetry analysis (TGA-DTG) were performed using a thermoanalytical system «Mettler TA 3000» (Mettler, Switzerland). To examine the possibility of BD-PG crystallosolvates formation, 25–35 mg samples were placed into 150 μL corundum crucibles with perforated lids. Thermal scans were performed within 30°C to 300°C temperature range at a scanning rate of 0.5°C/min in the air atmosphere. To explore BD thermostability, 70 μL corundum crucibles with perforated lids were used, the sample weight was 3–4 mg, and thermal scans were performed at a scanning rate of 10°C/min in the air atmosphere. Sample weight data were collected every 1 s. Each system was subjected to at least three independent thermal scans.

Based on the collected data, temperature dependences were plotted for relative mass loss (TGA curve) and mass loss rate (DTG curve). Relative mass loss (Δm) was determined as

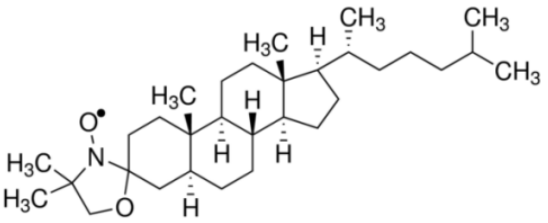
$$\Delta m = \frac{m - m_0}{m_0} \cdot 100\%, \quad (3)$$

where m is the current sample weight, m_0 is the initial sample weight.

In order to obtain the total mass loss (Δm_{fin}) from eq. (3), the final value of sample weight was used, $m = m_{fin}$, which was obtained after completing an experiment and further cooling of a sample to room temperature. Mass loss rate was determined as dm/dt [mg/s], where t is the measurement time. Experimental error of sample weight determination was 0.05 mg; the accuracy of temperature determination was 1°C.

Determination of BD solvation enthalpy in different solvents was performed by means of differential scanning calorimetry (DSC) using a microcalorimeter «Mettler DSC 1» («Mettler-Toledo», USA). Dry BD was placed into a 40 μL aluminum crucible, then the necessary amount of a solvent was added, and the crucible was hermetically sealed with a lid. A similar sealed crucible with a corresponding solvent was used as a reference. Measurement was started immediately after sealing without any additional sample treatment (stirring, shaking, etc.). Thermal scans were performed within a temperature range from 30 to 85°C at a scanning rate of 1°C/min in the air atmosphere. The total sample weight was 10 to 20 mg. Data processing was performed by means of the original software STARe v. 11.00. Experimental error of enthalpy determination was 0.8 kJ/mol.

The distribution and behaviour of a hydrophobic steroid in dispersed systems with a liquid dispersion medium were studied by means of the spin probe method. The 4',4'-dimethylspiro(5α-cholestane-3,2'-oxazolidin)-3'-yloxy free radical (M_r 473.77; CAS No. [55569-61-4]) was used as a spin probe to model a corticosteroid.



By contrast with BD, the molecule of this spin probe does not contain hydroxyl and carbonyl groups, and thus it is more hydrophobic than BD.

The spin probe was added to the systems under study at a concentration of 10^{-4} mol/l. The EPR spectra were recorded using the «ESR Spectrometer CMS8400» («Adani»; software EPRCMD). The type of EPR spectra (triplet, anisotropic spectrum, superposition spectrum, etc.), the peak heights at the low-field (h_{+1}), central (h_0), high-field (h_{-1}) components, and the linewidth at the low-field (ΔH_{+1}) and central (ΔH_0) components of the EPR spectra were determined. The rotational correlation times of the spin probe (τ_{+1}, τ_{-1}, $\tau_{\pm 1}$) and the anisotropy parameter (ε) were calculated using the equations:

$$\tau_{+1} = \left(\sqrt{\frac{h_0}{h_{+1}}} - 1 \right) \cdot \Delta H_0 / 2 \cdot 10^8; \quad (4)$$

$$\tau_{-1} = \left(\sqrt{\frac{h_0}{h_{-1}}} - 1 \right) \cdot \Delta H_0 / 3.6 \cdot 10^9; \quad (5)$$

$$\tau_{\pm 1} = \left(\sqrt{\frac{h_{+1}}{h_{-1}}} - 1 \right) \cdot \Delta H_{+1} \cdot 6.65 \cdot 10^{-10}; \quad (6)$$

$$\varepsilon = \frac{\sqrt{h_0/h_{+1}} - 1}{\sqrt{h_0/h_{-1}} - 1}. \quad (7)$$

The A_N constant, which characterises the polarity of the radical's environment, was determined as the distance (in mT) between the central and high-field components in the case of triplet spectra.

Table 2

Compositions for research by the spin probe method

Ingredients [1]	Content, % m/m				
	No. 1	No. 2	No. 3	No. 4	No. 5
Paraffin, liquid (PL)	20	–	–	–	–
Isopropyl myristate (IPM)	–	–	–	20.0	–
Macrogol 20 cetostearyl ether	3.0	10.0	3.0	3.0	–
Cetostearyl alcohol (CSA)	7.0	–	7.0	7.0	–
Propylene glycol (PG)	7.0	9.0	9.0	7.0	99.92
Water	63.0	81.0	81.0	63.0	0.08

4. Research results

Study of BD solubility in systems water – PG.

The solubility and particle size of BD are physicochemical properties that can influence the performance of the finished medicinal products. It is therefore recommended that particular attention be paid to the study of these physicochemical properties, with due consideration given to the influence of excipients, manufacturing process options, and process parameters [30].

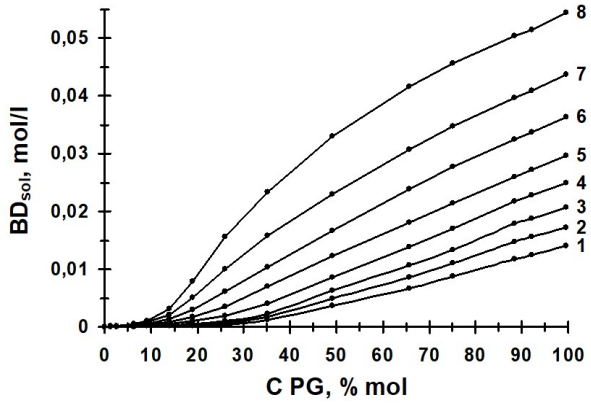
The solubility of BD in the binary solvents *water – PG* increased significantly with increasing temperature and even more so with increasing PG concentration (Table 3 and Fig. 4). At 55°C, 2.725% m/v of BD can be dissolved in PG. This provides an opportunity for the dissolution of 0.064 g BD in a small amount of PG, facilitating its incorporation into a cream base.

The solubility of BD was not a linear function of the composition of the mixed solvents (Fig. 4). At 298.15 K, the deviation of BD solubility from additivity was negative, with a minimum at PG concentration of approximately 35% mol (~70% m/m) (Fig. 5).

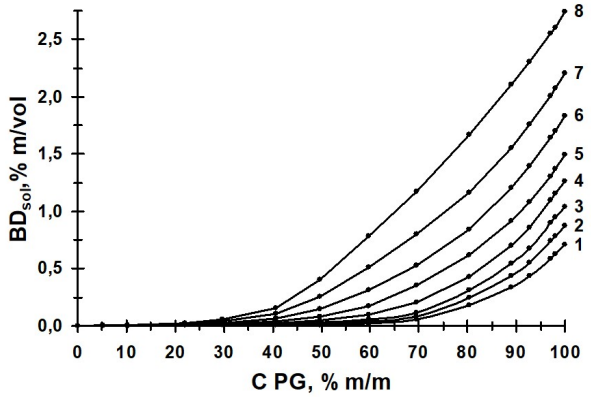
It has been demonstrated that at a PG concentration of more than ~35% mol at 298.15 K, a transition to the structure of the nonaqueous solvent (PG) occurred. This transition was evidenced by a decrease in the values of the thermodynamic activation parameters of the viscous flow for mixed solvents *water – PG* (Fig. 6) [12].

As the temperature rises above 40°C, a significant increase in BD solubility was evident at lower PG concentrations (Fig. 4). This phenomenon was likely attributable to a change in the structure of the mixed solvent. The nature of the isotherms of excess solubility of BD in the binary solvents *water – PG* also underwent alteration (Fig. 7); at certain concentrations of PG, the excess solubility of BD became positive.

At 55°C (328.15 K), the minimum for deviation from additivity shifted from ~35% mol PG to ~14% mol PG. Furthermore, a positive maximum for deviation was observed at PG concentration of approximately 50% mol (~80% m/m) (Fig. 7).



a



b

Fig. 4. Solubility of BD (*a* –% mol/l; *b* –% m/vol) in solvents *water – PG* as a function of PG concentration at: 1 – 293.15 K (20°C); 2 – 298.15 K (25°C); 3 – 303.15 K (30°C); 4 – 308.15 K (35°C); 5 – 313.15 K (40°C); 6 – 318.15 K (45°C); 7 – 323.15 K (50°C); 8 – 328.15 K (55°C)

Table 3

Solubility of BD in solvents *water – PG,* at various temperatures

% PG		Concentration of BD in solution (mol/l) at temperatures (T/t):							
m/m	mole	293.15 K 20°C	298.15 K 25°C	303.15 K 30°C	308.15 K 35°C	313.15 K 40°C	318.15 K 45°C	323.15 K 50°C	328.15 K 55°C
0	0	$3.98\cdot10^{-5}$	$4.48\cdot10^{-5}$	$4.99\cdot10^{-5}$	$5.42\cdot10^{-5}$	$5.93\cdot10^{-5}$	$6.56\cdot10^{-5}$	$7.22\cdot10^{-5}$	$8.14\cdot10^{-5}$
5.04	1.24	$5.01\cdot10^{-5}$	$5.81\cdot10^{-5}$	$6.47\cdot10^{-5}$	$7.03\cdot10^{-5}$	$7.94\cdot10^{-5}$	$9.05\cdot10^{-5}$	$1.03\cdot10^{-4}$	$1.18\cdot10^{-4}$
10.25	2.63	$6.13\cdot10^{-5}$	$7.17\cdot10^{-5}$	$8.30\cdot10^{-5}$	$9.37\cdot10^{-5}$	$1.07\cdot10^{-4}$	$1.26\cdot10^{-4}$	$1.52\cdot10^{-4}$	$1.75\cdot10^{-4}$
22.08	6.29	$8.71\cdot10^{-5}$	$1.07\cdot10^{-4}$	$1.34\cdot10^{-4}$	$1.67\cdot10^{-4}$	$2.18\cdot10^{-4}$	$2.97\cdot10^{-4}$	$3.89\cdot10^{-4}$	$4.90\cdot10^{-4}$
29.63	9.07	$1.10\cdot10^{-4}$	$1.43\cdot10^{-4}$	$2.00\cdot10^{-4}$	$2.62\cdot10^{-4}$	$3.88\cdot10^{-4}$	$5.62\cdot10^{-4}$	$7.91\cdot10^{-4}$	$1.10\cdot10^{-3}$
40.66	13.96	$1.41\cdot10^{-4}$	$2.14\cdot10^{-4}$	$3.39\cdot10^{-4}$	$5.37\cdot10^{-4}$	$8.88\cdot10^{-4}$	$1.35\cdot10^{-3}$	$2.13\cdot10^{-3}$	$3.16\cdot10^{-3}$
49.63	18.92	$2.04\cdot10^{-4}$	$3.61\cdot10^{-4}$	$5.84\cdot10^{-4}$	$1.04\cdot10^{-3}$	$1.68\cdot10^{-3}$	$2.97\cdot10^{-3}$	$5.03\cdot10^{-3}$	$7.94\cdot10^{-3}$
59.73	25.99	$4.38\cdot10^{-4}$	$7.41\cdot10^{-4}$	$1.12\cdot10^{-3}$	$1.95\cdot10^{-3}$	$3.47\cdot10^{-3}$	$6.23\cdot10^{-3}$	$1.01\cdot10^{-2}$	$1.56\cdot10^{-2}$
69.57	35.12	$1.15\cdot10^{-3}$	$1.71\cdot10^{-3}$	$2.35\cdot10^{-3}$	$4.03\cdot10^{-3}$	$7.01\cdot10^{-3}$	$1.04\cdot10^{-2}$	$1.59\cdot10^{-2}$	$2.33\cdot10^{-2}$
80.35	49.19	$3.63\cdot10^{-3}$	$4.88\cdot10^{-3}$	$6.25\cdot10^{-3}$	$8.53\cdot10^{-3}$	$1.23\cdot10^{-2}$	$1.67\cdot10^{-2}$	$2.31\cdot10^{-2}$	$3.31\cdot10^{-2}$
89.05	65.82	$6.72\cdot10^{-3}$	$8.66\cdot10^{-3}$	$1.08\cdot10^{-2}$	$1.39\cdot10^{-2}$	$1.81\cdot10^{-2}$	$2.39\cdot10^{-2}$	$3.08\cdot10^{-2}$	$4.17\cdot10^{-2}$
92.72	75.10	$8.70\cdot10^{-3}$	$1.10\cdot10^{-2}$	$1.34\cdot10^{-2}$	$1.70\cdot10^{-2}$	$2.14\cdot10^{-2}$	$2.77\cdot10^{-2}$	$3.48\cdot10^{-2}$	$4.57\cdot10^{-2}$
97.01	88.48	$1.17\cdot10^{-2}$	$1.47\cdot10^{-2}$	$1.79\cdot10^{-2}$	$2.18\cdot10^{-2}$	$2.59\cdot10^{-2}$	$3.25\cdot10^{-2}$	$3.97\cdot10^{-2}$	$5.05\cdot10^{-2}$
98.01	92.10	$1.25\cdot10^{-2}$	$1.56\cdot10^{-2}$	$1.88\cdot10^{-2}$	$2.29\cdot10^{-2}$	$2.72\cdot10^{-2}$	$3.37\cdot10^{-2}$	$4.10\cdot10^{-2}$	$5.15\cdot10^{-2}$
99.92	99.66	$1.41\cdot10^{-2}$	$1.73\cdot10^{-2}$	$2.07\cdot10^{-2}$	$2.50\cdot10^{-2}$	$2.97\cdot10^{-2}$	$3.63\cdot10^{-2}$	$4.37\cdot10^{-2}$	$5.44\cdot10^{-2}$

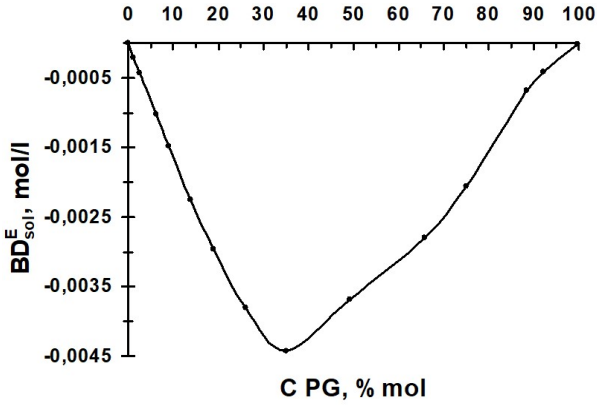


Fig. 5. Excess solubility of BD (mol/l) in binary solvents *water – PG* as a function of PG concentration (C, % mol) at 298.15 K (25°C)

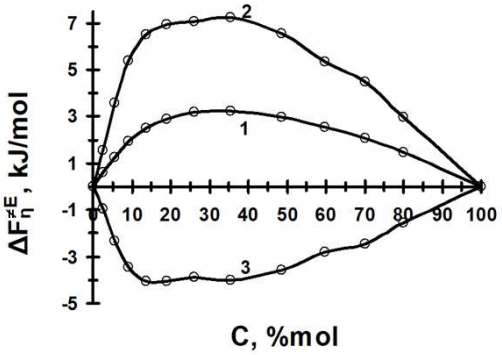


Fig. 6. Excess thermodynamic activation parameters of viscous flow (1 – $\Delta G^{\neq E}_{\eta}$, 2 – $\Delta H^{\neq E}_{\eta}$, 3 – $-T\Delta S^{\neq E}_{\eta}$) for binary solvents *water – PG* as a function of PG concentration (C,% mol) at 298.15 K (25°C) [12]

Study of crystallization and particle size distribution. The distribution of BD particles in suspensions under study is illustrated in Fig. 8 and detailed in Table 4.

The D_{50} value for the sample of BD substance used in the experiments was 5.690 μm (Table 4). During the process of crystallization, a suspension was formed, with the BD particles being significantly smaller than those of the reference suspension (reference sample No. 1). In particular, the D_{50} value was found to be 2.73 times lower (Fig. 8 and Table 4). However, when this suspension was stored for a mere 48 hours, a recrystallisation process ensued, leading to a substantial increase in the size of BD particles across all fractions, ranging from 10- to 20-fold. The different sizes of particles are evidenced by the micrographs in Fig. 9.

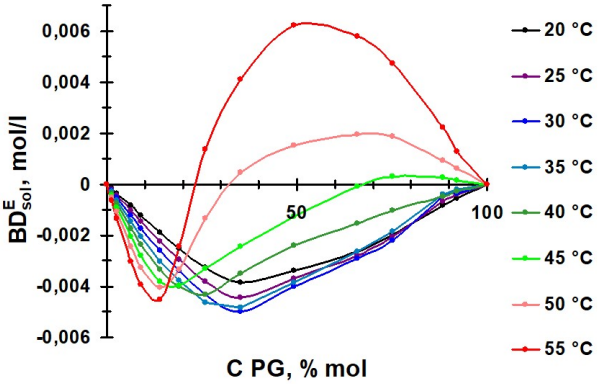


Fig. 7. Excess solubility of BD in binary solvents *water – PG* as a function of PG concentration (C) at temperatures ranging from 20°C to 55°C

The suspensions of BD were prepared by suspending the substance in the solvent *water – PG* (90 : 10 m/m), in which the water structure predominates [12]. The histograms of the reference suspension, suspensions after preparation, and after 48-hour storage were very similar (Fig. 10). When the suspensions were prepared through suspending process, a slight increase in the BD particle size was observed after 48 hours of storage, although the composition of the dispersion medium (10% m/m PG and 90% m/m water) was the same for both the crystallization and suspension methods.

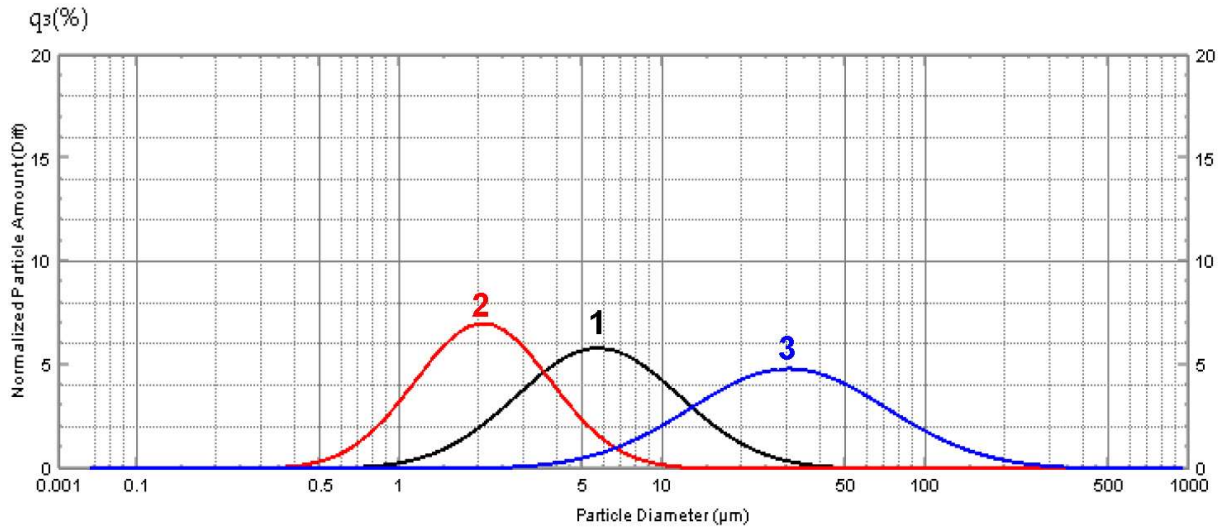
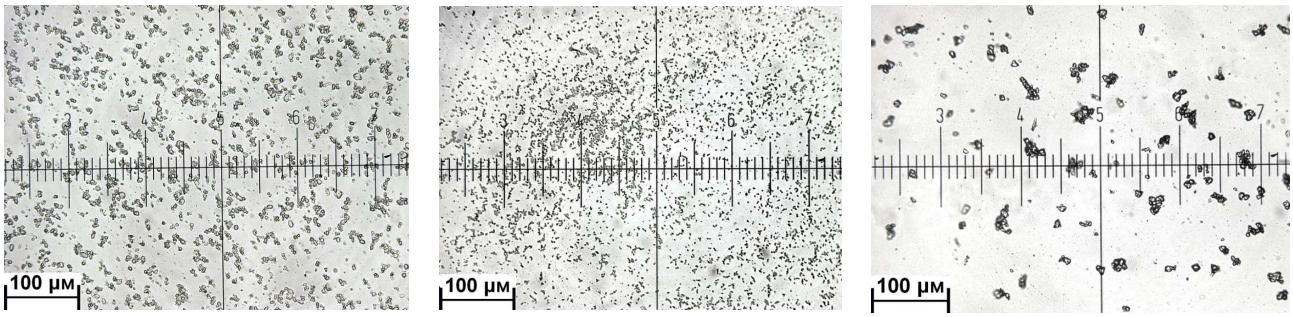


Fig. 8. Particle size distribution (D_{max}) in suspensions of BD: 1 – suspension of BD micronized in liquid paraffin (reference sample); 2 – suspension of BD obtained by crystallization, immediately after preparation; 3 – suspension of BD obtained by crystallization, 48 hours after preparation



a *b* *c*

Fig. 9. Micrographs of suspensions: *a* – No. 1; *b* – No. 2; *c* – No. 3; magnification ×150

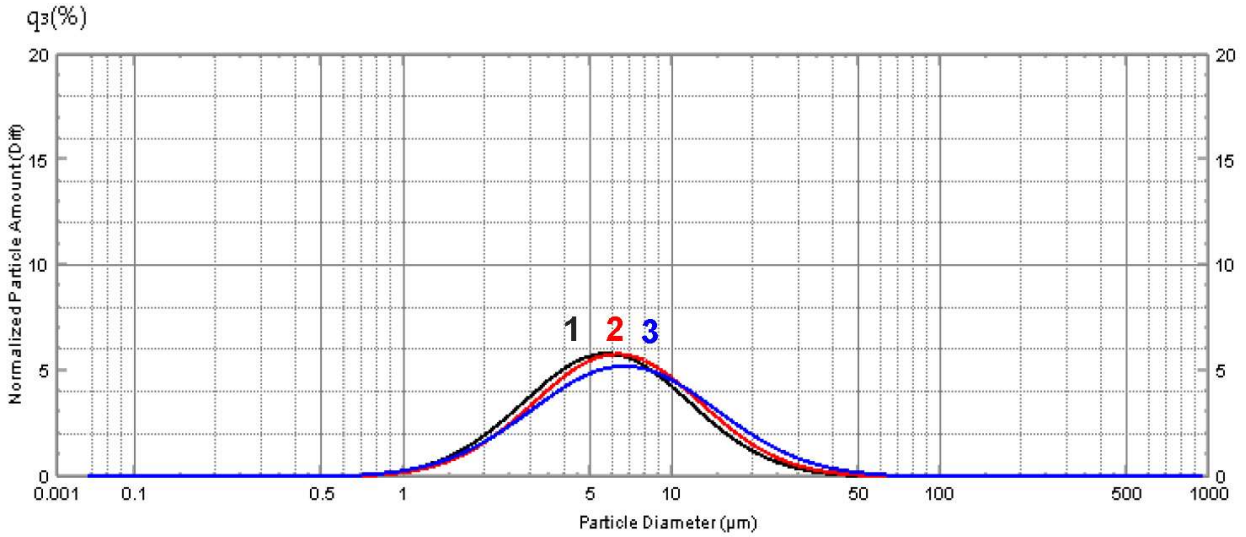


Fig. 10. Particle size distribution (D_{max}) in suspensions of BD: 1 – suspension of BD micronized in paraffin liquid (reference sample); 2 – suspension of BD obtained by suspending, immediately after preparation; 3 – suspension of BD obtained by suspending, 48 hours after preparation

Table 4

Particle size distribution in suspensions of BD

Sample number*	D_{max} (μm)								
	D_{10}	D_{20}	D_{30}	D_{40}	D_{50}	D_{60}	D_{70}	D_{80}	D_{90}
1	2.269	3.131	3.920	4.746	5.690	6.826	8.277	10.374	14.275
2	0.975	1.268	1.524	1.788	2.082	2.417	2.848	3.441	4.480
3	10.074	14.603	19.222	24.262	30.158	37.509	47.363	62.048	91.097

Note: The numbers of the suspensions correspond to the numbers in Fig. 8.

Table 5

Particle size distribution in suspensions of BD

Sample number*	D_{max} (μm)								
	D_{10}	D_{20}	D_{30}	D_{40}	D_{50}	D_{60}	D_{70}	D_{80}	D_{90}
1	2.269	3.131	3.920	4.746	5.690	6.826	8.277	10.374	14.275
2	2.503	3.402	4.275	5.199	6.230	7.473	9.090	11.425	15.559
3	2.391	3.387	4.359	5.412	6.623	8.094	10.018	12.902	18.391

Note: The numbers of the suspensions correspond to the numbers in Fig. 10.

Thermal analysis of BD suspensions and BD *dissolutions in PG.*

Thermogravimetry analysis of BD suspensions in PG aimed to ascertain the potential for the formation of crystallosolvates. To this end, BD thermostability limits should be previously determined. As it is evidenced by TGA data (Fig. 11), the onset temperature of BD thermodestruction (T_{onset}) was 224°C and the

maximum (T_{max}) corresponded to 280°C. Hence, under the experimental conditions, the upper limit of BD thermostability can be assessed as 224°C.

Based on the data obtained, a temperature range between 100°C and 120°C was chosen for subsequent experiments. These temperature limits provided solvent elimination with maintenance of BD structure, since it was well below both the BD thermodestruction onset (224°C) and the BD melting temperature (178°C). It is noteworthy that the TGA thermograms of dry BD evidenced mass loss ~1.5% m/m up to 120°C. Additional experiments have shown that this process is reversible, so it can be attributed to the adsorption/desorption of atmospheric gases.

The thermogram of desolvation of *BD – PG – water* suspension obtained after centrifugation (curves 1, 1′) is presented in Fig. 12. The thermogram displays distinctly the several stages of solvent elimination, namely, the first one, up to 107°C ($\Delta m = -86 \div -88\%$), and the second one, up to 118°C ($\Delta m = -97\%$). The attainment of a plateau at a temperature over 118°C indicates the complete desolvation of the sample under the experimental conditions. The value of the final sample mass, $m_{fin} = 3\%$, should correspond to the content of dry BD. A comparison of the thermograms obtained for the *BD – PG – water* suspension with those obtained for BD in the binary solvent *water – PG* (10% *w/w*) (Fig. 12, curves 2, 2′) demonstrates the same Δm limits, i.e., identical stages of the solvent elimination. These stages can be explained by the substantially higher rate of water desorption in comparison to that of PG, until the formation *PG – water* azeotropic mixture. These data, together with PG desorption data obtained from additional TGA experiments, provided a foundation for estimating the PG content in the azeotropic mixture as ~78% m/m (~45.64% mol).

An examination of additionally dried suspensions containing ~20% m/m BD enabled the determination of the BD – solvent weight ratio after the first desolvation stage to be 1:2. For these samples, the general shape of the TGA-DTG thermograms is similar to those represented in Fig. 12, and characteristic DTG peaks indicative of crystallosolvates decomposition are absent. Consequently, no evidence of BD – PG crystallosolvates was obtained using the TGA-DTG methods.

The process of BD solvation in PG occurs rather slowly under ambient conditions; consequently, it can be properly reproduced under controlled conditions of the DSC experiment. Using PG as a reference sample facilitated the isolation of the thermal events related to the solvation process. A typical DSC thermogram of the process is presented in Fig. 13 (the heat flow value is normalized by the sample weight, [W·g^{-1}]). One can trace a slow exothermal process starting around 40°C, reaching the maximum up to 60°C, and finishing to 85°C. The enthalpy of BD solvent in PG was determined as 40.0 ± 0.8 kJ/mol, using the value of the peak area and BD content in the sample. Fig. 13 also contains the thermogram of BD solvation in the binary solvent *water – PG* (10% m/m). In contrast to PG, no thermal events have been observed in this solvent up to a temperature of 80°C. This finding points to significant decrease in BD solubility in the binary solvent and is consistent with the data of Table 3 evidencing that BD solubility decreases drastically (by a factor of ~288 and ~311 at 50°C and 55°C, respectively) when replacing PG with solvent *water – PG* (10% m/m).

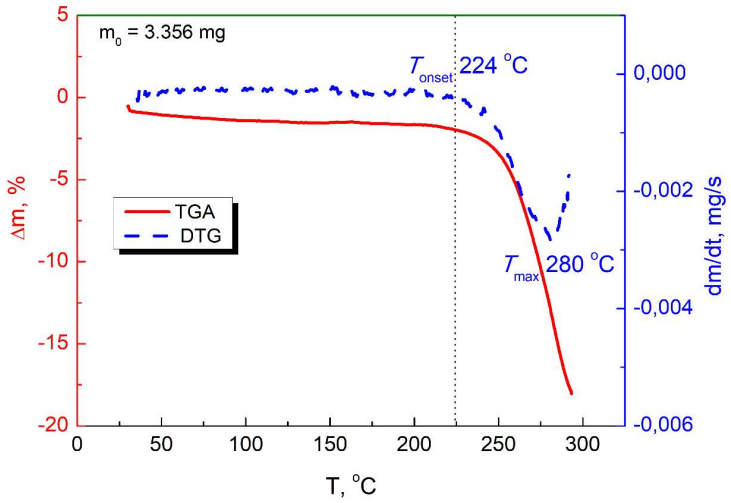


Fig. 11. Thermograms of dry BD sample: TGA (solid line) and DTG (dashed line). T_{onset} and T_{max} are the temperatures of BD thermodestruction onset and maximum, respectively. The vertical dotted line indicates the thermostability limit of BD under the experimental conditions. The initial sample weight (m_0) is specified on the plot

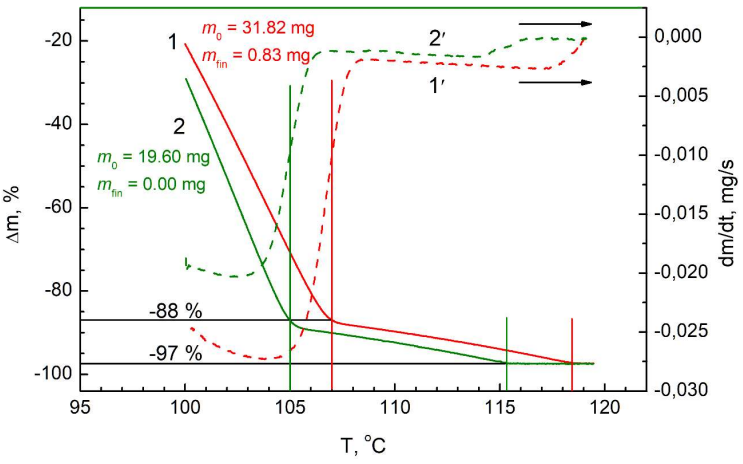


Fig. 12. Thermograms TGA (solid lines) and DTA (dashed lines) of the *BD – PG – water* suspension obtained after centrifugation (1, 1′) and BD dissolved in the binary solution *water – PG* (10% *m/m*). The straight lines mark the limits of desolvation stages. The initial and final sample weights (m_0 and m_{fin}, respectively) are specified on the plot

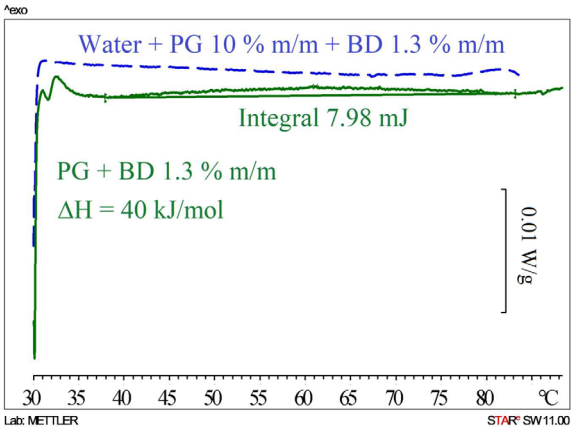


Fig. 13. Normalized DSC thermograms obtained during the process of BD solvation in PG (solid line) and the binary solvent *water – PG* (10% m/m) (dotted line) under heating. BD content in each system was 1.3% m/m. The peak area (Integral) and the solution enthalpy (ΔH) are specified on the plot

Studies by the spin probe method.

The spin probe method provides information on the localization and distribution of steroid probe molecules, as well as their state in the phases of dispersed systems with a liquid dispersion medium [31].

In a similar manner to BD, the steroid probe dissolved in PG, as illustrated by the EPR spectrum, which was triplet (Fig. 14) (composition No. 5, Table 2). When 20% m/m water is added to PG, the EPR spectrum changed, becoming a superposition of a triplet and a singlet (Fig. 14). Therefore, the solubility of the steroid probe decreased with the addition of water, even when the structure of a non-aqueous solvent dominated in the mixed solvent [12]. It has been demonstrated that the majority of the injected probe was in a dissolved state, with the remainder undergoing aggregation. In the case of a mixed solvent *water – PG* 40 : 60% m/m, the EPR spectrum of the steroid probe manifested as a singlet (Fig. 14). It is evident that, upon transitioning from a non-aqueous solvent to a mixed structure [12], the steroid-based probe lost its ability to dissolve at 25°C.

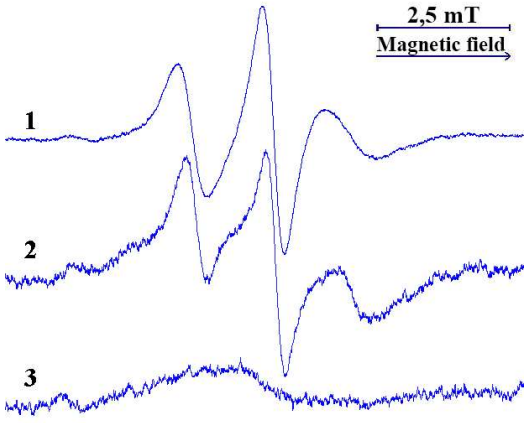


Fig. 14. EPR spectra of a steroid probe at 25°C in solvents: 1 – *PG*; 2 – *water – PG* (20 : 80 m/m); 3 – *water – PG* (40 : 60 m/m)

The steroid-based spin probe is more hydrophobic than BD; consequently, the presence of water is a more critical factor in determining its solubility. At 25°C, in the mixed solvent *water – PG* containing 40% m/m water, BD dissolved at a concentration of $7.41 \cdot 10^{-4}$ mol/l. The steroid probe did not dissolve under these conditions at its concentration of 10^{-4} mol/l. However, a comparison of the EPR spectra (Fig. 14) and the data in Table 3 reveals that the presence of water had the same effect on the solubility of steroids in systems *water – PG*; an increase in water content resulted in a decrease in the solubility of hydrophobic steroids.

The steroid spin probe was injected into the objects whose composition is shown in Table 2. The corresponding EPR spectra are illustrated in Fig. 14 and Fig. 15, while Table 6 presents the parameters of the EPR spectra.

In a 20% liquid paraffin emulsion (composition No. 1), the steroid probe was localized in the oil phase, where it was predominantly in a dissolved state. The free radical was localized in a hydrophobic non-polar environment, as evidenced by the low value of the isotropic constant ($A_N = 1.31$ mT). For composition No. 1, as well as for compositions No. 2 and No. 5, the values of τ_{+1} were not very accurate when calculated using equation (4). However, these conventional values provide a useful indication of the extremely slow rotation of the steroid probe around the long axis of the molecule.

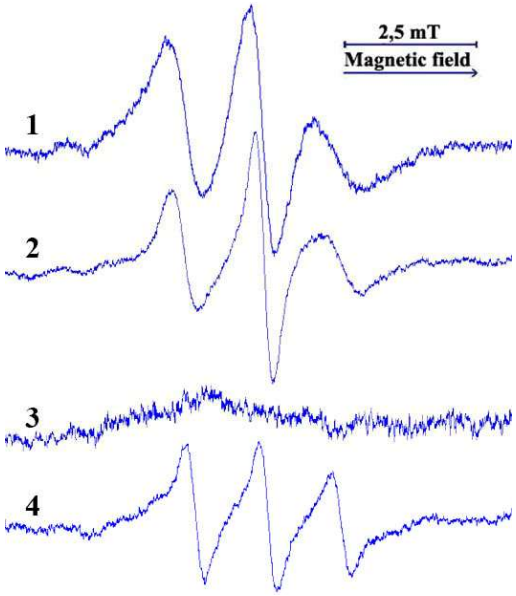


Fig. 15. EPR spectra of a steroid probe at 25°C in: 1 – composition No. 1; 2 – composition No. 2; 3 – composition No. 3; 4 – composition No. 4 (Table 2)

The steroid probe was solubilized by micelles of the nonionic surfactant macrogol 20 cetostearyl ether (composition No. 2), as evidenced by the EPR spectrum (triplet). In this instance, the free radical was localized in the polar part of the micelles, since the value of the isotropic constant $A_N = 1.51$ mT was quite high.

Table 6

Parameters of the EPR spectra of the steroid probe in different compositions at 25°C (Table 2, Fig. 14, 15)

Composition	A_N, mT	τ_{+1}, ns	τ_{-1}, ns	$\tau_{\pm1}$, ns	ε	Spectrum type
No. 1	1.31	**5.69**	1.14	2.38	0.28	triplet
No. 2	1.51	**8.53**	1.10	1.29	0.43	triplet
No. 3	–	–	–	–	–	singlet
No. 4	1.35	0.55	0.18	0.35	0.17	triplet
No. 5	1.44	**7.92**	1.50	2.40	0.29	triplet

In the case composition No. 3 without the oil phase, the EPR spectrum transformed into a singlet (Fig. 15), indicating that the probe was not dissolved in the dispersion medium and was not solubilized by the aggregates of the nonionic surfactant macrogol 20 cetostearyl ether and cetostearyl alcohol.

When IPM was used as an oil phase (composition No. 4), the steroid probe was localized in the IPM phase ($A_N = 1.35$ mT), and the EPR spectrum was once again transformed into a triplet. In this instance, the rotational correlation times (τ) and the anisotropy parameter (ε) were found to be significantly lower than when the probe was localized in the liquid paraffin phase (Table 6). In summary, the rotation of the steroid spin probe was significantly faster in IPM compared to its rotation in liquid paraffin. This phenomenon may be attributable to the enhanced solubility of the steroid probe in IPM. The determination of the solubility of BD in IPM and other emollients may be a subject of further research.

The values of the steroid spin probe EPR spectra parameters $\tau_{\pm1}$ and ε in liquid paraffin and PG were similar. The use of hydrophobic liquid paraffin as a dispersion medium for BD suspensions may be a reasonable option. The utilization of hydrophilic PG is a conceivable alternative, however, given the solubility of BD in PG (Table 3), there exists a potential risk of recrystallisation of BD particles. Therefore, it was of interest to investigate the solubility and crystallization of BD in liquid paraffin.

Study of the solubility and crystallization of BD in liquid paraffin.

The dissolution of 0.07 mg/g of BD in liquid paraffin was observed at 25°C. It was established that the solubility of BD in liquid paraffin increased at 60°C. In particular, 0.075 mg/g of the substance was dissolved in liquid paraffin at 40°C, while 0.27 mg/g of BD was dissolved at 60°C. No crystallization of BD was observed in the filtered saturated solutions in liquid paraffin obtained at 60°C after cooling to 25°C and during their subsequent storage.

Suspensions consisting of 0.064 g of BD and 20.0 g of liquid paraffin were stored for three days at 60°C, cooled to 25°C, and following a further three-day period, the particle size distribution was determined and compared with that of the reference BD suspension, which was not exposed to heat (Fig. 16, Table 7).

The micrographs in Fig. 17 further support the observation that the particle size in BD suspensions No. 1 and No. 2 was identical.

As demonstrated in Fig. 16, the histograms of the two suspensions are very similar, with minimal variation in the maximum size of BD particles across the different fractions. Specifically, an increase of 3.4% was observed for D_{50}, while a decrease of 2.3% was determined for D_{90} (Table 7). Following the crystallization of BD from its solution in PG after a storage period of two days, the D_{50} and D_{90} were found to be 30.158 μm and 91.097 μm, respectively (Table 4).

Table 7

Particle size distribution in suspensions of BD

Sample number*	D_{max} (μm)								
	D_{10}	D_{20}	D_{30}	D_{40}	D_{50}	D_{60}	D_{70}	D_{80}	D_{90}
1	2.269	3.131	3.920	4.746	5.690	6.826	8.277	10.374	14.275
2	2.515	3.348	4.146	4.974	5.885	6.984	8.371	10.334	13.952

Note: The numbers of the suspensions correspond to the numbers in Fig. 16.

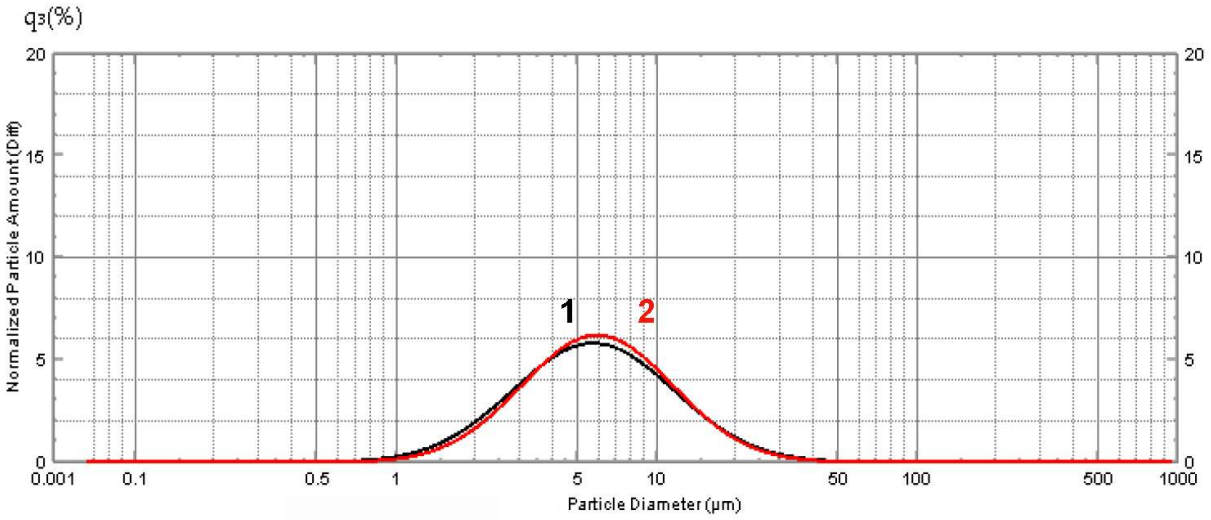
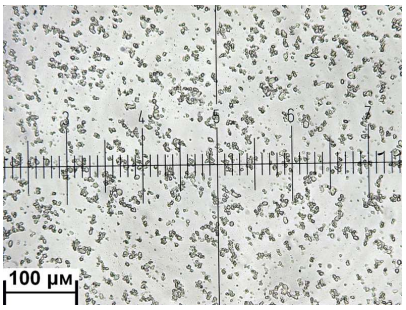
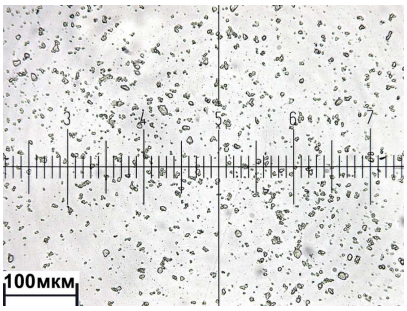


Fig. 16. Particle size distribution (D_{max}) in suspensions of BD: 1 – suspension of BD micronized in liquid paraffin (reference sample); 2 – BD suspension, which was exposed to heating to 60°C and subsequent cooling to 25°C, three days after the process

Determination of BD solvation enthalpy in paraffin liquid (PL) was performed using the DSC technique by the method described above, under heating from 30°C to 130°C. As can be seen from the obtained thermogram (Fig. 18), the solvation process spontaneously starts around 60°C, which is in good agreement with the above data on BD solvation in paraffin liquid (PL). The DSC peak is asymmetric, probably due to a significant increase in BD solubility with temperature. However, it has a completed shape, indicating total BD solvation under the experimental conditions. These data allowed us to establish that BD solvation in paraffin liquid is an endothermic process with an enthalpy of ~280 kJ/mol.



a



b

Fig. 17. Micrographs of suspensions: *a* – No. 1; *b* – No. 2; magnification ×150

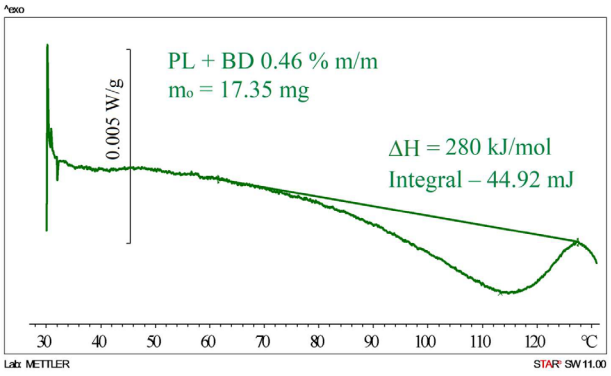
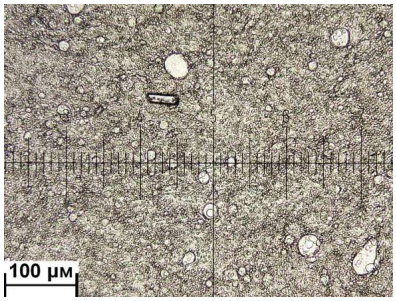


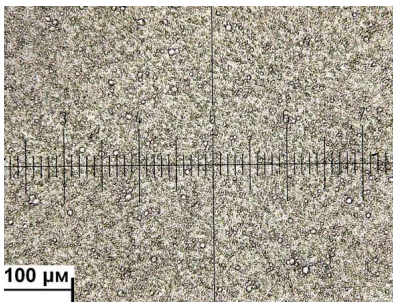
Fig. 18. Normalized DSC thermograms obtained during the process of BD solvation in paraffin liquid (PL) under heating. BD content corresponds to 0.46% m/m in the system. The sample weight, peak area (Integral), and the solution enthalpy (ΔH) are specified on the plot

Micrographs of two creams (cream base – composition No. 1, Table 2), which were produced through different techniques in a vacuum homogenizer and stored for six months at 25°C, are presented in Fig. 19.

In the cream produced using crystallization of BD, the corticosteroid recrystallized to form large crystals measuring approximately 40 μm (Fig. 19, *a*). In the cream obtained by suspending BD in paraffin liquid, large-sized BD particles were not observed (Fig. 19, *b*).



a



b

Fig. 19. Micrographs of the creams produced using the following processes: *a* – crystallization of BD from its solution in PG; *b* – suspending BD in liquid paraffin at 60°C; magnification ×150

5. Discussion of research results

The molecules of BD are hydrophobic with a relatively high molecular weight (M_r = 504.6) [1]. To dissolve in water at 20–25°C, these molecules must undergo hydrophobic hydration, which should result in the formation of ice-like water structures and a significant decrease in the system's entropy; however, it is impossible at this temperature. On the other hand, introducing PG into the system primarily results in interaction between its molecules and water molecules. According to paper [18], the methyl groups of PG molecules are surrounded by water molecules arranged in an ice-like structure. As the PG content increases, strong hydrogen bonds form between the water and the hydroxyl groups of the PG. The transition from *water – water* hydrogen bonds to *water – PG* hydrogen bonds occurs when the volume fraction of PG is ≥0.4. This is approximately equivalent to a PG concentration of 14% mol; such a mixed solvent lies at the boundary between solvents with a predominant structure of water and binary solvents with a mixed structure of water with PG [12]. When transitioning to mixed structures at 20–25°C, the solubility of the hydrophobic BD molecules increased only slightly (Table 3). The formation of mixed associates between molecules of water and PG in the binary

solvent presents an additional obstacle to the dissolution of BD, as demonstrated by the great minimum on the excess solubility of BD plot (Fig. 5, 7). The deviation of the BD solubility from additivity, depending on the PG content, was negative at temperatures of 20–35°C; the minimum was extreme at a PG concentration of ~35% mol (~70% m/m) (Fig. 7). This PG concentration marks the boundary between binary solvents with mixed structure of water with PG and binary solvents, where the structure of the non-aqueous solvent (PG) predominated (Fig. 6) [12].

At temperatures from 20°C to 35°C, the solubility of BD exhibited a substantial increase commencing at PG concentration of approximately 35% mol (~70% m/m) (Fig. 4). At this, an increase in PG concentration was observed to result in a decrease in the absolute values of the deviation of BD solubility from additivity (Fig. 5, 7), given the transition to the PG structure that occurred in the binary solvent [18]. This transition is evidenced by a decrease in the excess thermodynamic activation parameters of viscous flow in mixed solvents *water – PG* (Fig. 6) [12].

At 25°C, 0.873% BD can be dissolved in PG, which is 13.64 times higher than the BD content of 0.064% in a cream. At 55°C, 42.58 times the required amount of BD (0.064%) can be dissolved in PG. This provides an opportunity to dissolve 0.064 g of BD in 5–10 g of PG at a certain temperature and then mix this solution with the cream base.

As the temperature rises to 40°C and then above to 55°C, the minimum for deviation from additivity of BD solubility shifted towards lower PG concentrations (Fig. 7). At temperatures ranging from 45°C to 55°C, and under certain PG concentrations, the deviation of BD solubility from additivity became positive, with increase in the values with rising temperature (Fig. 7). This change occurred at specific PG concentrations, which decreased with increasing temperature. A positive maximum for deviation from additivity at 55°C was observed at PG concentration of approximately 50% mol (Fig. 7). Therefore, the excessive dissolution of BD during the heating of the system should result in crystallization of BD during the subsequent cooling.

Based on the results of the study, it can be concluded that the solubility of BD depends on the structure of the binary solvents *water – PG*. The solubility of BD in binary solvents *water – PG* increased significantly with rising temperature. This increase was even more pronounced at higher concentrations of PG (Fig. 4).

Therefore, depending on the PG concentration and the temperature, BD can be added to the cream base in either a dissolved state or as a suspension.

The suspensions obtained by the crystallization process were found to be thermodynamically unstable, undergoing recrystallization of BD particles (Fig. 8, 9, Table 4).

The TGA-DTG thermograms of the desolvation processes of the BD suspension in the temperature range of 100–120°C, in which BD was thermally stable, indicated the absence of BD crystallosolvates with PG in the system (Fig. 12). DSC thermograms obtained during the dissolution of BD in PG indicated that this process was exothermic with an enthalpy of ~40 kJ/mol (Fig. 13). A significant difference was identified between the thermograms of BD dissolution in PG and in the binary solvent *water – PG* (90 : 10 m/m), indicating a substantial decrease in the solubility of BD in the binary solvent compared to PG.

In the process of preparing suspensions in a mixed solvent *water – PG* (90 : 10 m/m), where the water structure predominated [12], the recrystallization of the particles of the dispersed phase was negligible due to the low solubility of BD (Fig. 10, Table 5). However, at such low concentrations of PG, the wetting of BD powder by the dispersion medium was unsatisfactory, complicating the suspending process. An increase in the content of PG resulted in an enhancement of the surface-active properties of the resulting aqueous solution [12], thereby facilitating the wetting of BD powder. However, the solubility of BD increased, especially at temperatures ≥ 45°C, and the risk of recrystallization of BD particles in the cream increased.

Studies employing a spin probe method demonstrated that the hydrophobic steroid spin probe was localized in the oil phase and was dissolved there (Fig. 15, Table 6). The solubility of BD in liquid paraffin was determined. According to the results of the study, liquid paraffin can be used for the preparation of BD suspension.

The DSC method was used to demonstrate that the dissolution of BD in liquid paraffin was an endothermic process with an enthalpy of ~280 kJ/mol (Fig. 18). At a temperature of 60°C, which is acceptable for the emulsification process, 0.27 mg/g BD dissolved in liquid paraffin. However, upon cooling the suspension to 25°C, no crystallization of BD in liquid paraffin and recrystallization of its particles in the cream were observed (Fig. 16, 17, Table 7).

In an o/w emulsion-based cream produced using a BD suspension in liquid paraffin, no recrystallisation of BD particles occurred. In a BD cream with the same formulation but made by crystallization of BD from a solution in PG, recrystallization was observed during storage with the formation of large-sized BD particles (Fig. 19).

The findings of the study indicate that, in manufacturing medicinal products with BD in the form of creams, it could be recommended that the production process include a stage of preparing a BD suspension in liquid paraffin, followed by emulsification at a temperature of approximately 60°C.

Practical relevance. The obtained results provide a theoretical basis for further research and development of production processes for BD creams.

Study limitations. The present study is constrained by the fact that the properties of only one corticosteroid, namely betamethasone dipropionate, its solubility and crystallization in the systems *water –*

PG and liquid paraffin were investigated. This is due to the purpose of the work and its applied significance.

Prospects for further research. Further research may be related to other corticosteroids, their solubility, and the process of crystallization from other hydrophilic and lipophilic solvents.

6. Conclusions

The solubility of BD in solvents *water – PG* is contingent upon the temperature and concentration of PG; it exhibits a marked increase when the structure of a nonaqueous solvent predominates in the system. It has been demonstrated that BD with PG does not form crystallosolvates. When BD suspensions were obtained by crystallization from a solution in PG, suspensions were formed in which BD particles recrystallized over time. In the case of BD suspensions in solvent *water – PG*, where the water structure predominates, or in liquid paraffin, recrystallization was practically not observed.

Conflict of interest

The authors confirm that they have no conflict of interest related to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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Data availability

Data will be made available upon reasonable request.

Use of artificial intelligence

The authors confirm that no artificial intelligence technology was used in the creation of this paper.

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