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Extemporaneous Ointment with Salicylic Acid for Mild Psoriasis of Proven Quality

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Abstract:
Background: To improve the quality of pharmacy services by providing a proof of quality of the extemporaneous ointment, Ointment against psoriasis 2.
Materials and Methods: The extemporaneous Ointment against psoriasis 2, for patients with mild psoriasis was made, and its organoleptic properties, physical stability by centrifuge test, pH, salicylic acid content, microbiological quality, presence of heavy metals were examined. The amphiphilic properties of Belobaza® cream, e.g. the ability of this ointment's base to emulsify purified water and oils, were tested.
Results: Ointment against psoriasis 2 maintained its homogeneity, semisolid consistency, unchanged odor, color, application and sensory properties for 60 days at 25°C±3°C. Its pH corresponds to the therapeutic effect of salicylic acid which is to remove dead cells from the surface of psoriatic skin. Salicylic acid content in Ointment against psoriasis 2, determined by validated UV-VIS spectrophotometric method, remained almost unchanged even 10 days after the preparation. Belobaza® cream can emulsify 100% purified water and 25% oil mixture. Their pH values were acceptable for topical semisolid dosage forms. The tested samples (Ointment against psoriasis 2, samples Belobaza® cream) met the limits of acceptability for microbiological quality of non-sterile pharmaceutical preparations for cutaneous use, in the period of patients' individual needs, up to 10 days. In all tested samples, the presence of lead and cadmium were well below the allowed values.
Conclusion Ointment against psoriasis 2 retained its organoleptic properties, during the period of 60 days after preparation, while there were no significant changes in pH, salicylic acid and heavy metals content, and microbiological quality 10 days after preparation. Proven amphiphilic properties of Belobaza® cream can help pharmacists in preparation of extemporaneous liquid or other semisolid dosage forms and cosmetic preparations.
Key Word: Psoriasis; Extemporaneous preparation; Salicylic acid; Belobaza® cream, Stability.

I. INTRODUCTION

Psoriasis is a chronic, noncommunicable, inflammatory skin disease with a strong genetic predisposition, caused by triggers such as unhealthy diet and lifestyle habits, exposure to stress and various autoimmune processes[1,2]. Its characterized by skin lesions which are localized or generalized, mostly symmetrical, sharply demarcated, red papules and plaques, and usually covered with white or silver scales. This phenomenon occurs due to the accelerated multiplication and maturation of skin cells[1]. Mild psoriasis is usually treated topically[2,3-5] progressing to phototherapy[2] in the case of insufficient response (more than 10% of body surface area affected)[2,6]. In severe forms of psoriasis, systemic therapy is used[2] but topical pharmaceutical formulations remain an important adjunct to therapy[6]. Extemporaneous compounding is an important segment of pharmacy activity in many countries. Examples of semisolid extemporaneous preparations for topical therapy of mild psoriasis from a pharmacy practice in Sarajevo, Bosnia and Herzegovina, containing salicylic acid are: a) salicylic acid 2.5 g, betamethasone ointment 30.0 g and Belobaza® cream up to 50.0 g; b) salicylic acid 10.0 g, ammonium sulfogyrodal 10.0 g, lanolin 40.0 g and white petroleum 40.0 g; c) salicylic acid 5.0 g, castor oil 10.0 g, olive oil 10.0 g and Belobaza® cream up to 100.0 g. The components listed under c) are of extemporaneous preparation called Ointment Against Psoriasis 2, the preparation and testing of which is presented in this paper. 10 days are a period that satisfies the needs of the patient until

preparation and dispensing of the next required amount to continue treatment. Salicylic acid has been extensively used in dermatologic therapy as a keratolytic agent in concentrations of 2% to 6%, as it may solubilize cell surface proteins that keep the *stratum corneum* intact, resulting in desquamation of keratotic debris[3,5]. Its long-term use is not recommended, especially in children under the age of three, due to side effects[3,5,7]. One of the adopted documents in the European Union defining individual therapy is *Resolution of the Committee of Ministers CM/Res (2016)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients*. This document confirms the importance of medicines prepared in pharmacy and that this process, in addition to pharmacopeial prescriptions, is carried out using appropriate quality assurance systems[8].

II. Materials and Methods

Olive oil, purified water and standard lead and cadmium solution were obtained from Pharmamed d.o.o. (Travnik, Bosnia and Herzegovina). Castor oil was purchased from Olvea Group (Saint Léonard, France). Salicylic acid was purchased from Novacyl Sas (Lyon, France). Tryptone soy agar (TSA) (CASO-A, Casein soya bean digest), tryptone soy broth (TSB) (CASO-B, Casein soy bean digest broth), buffered sodium chloride peptone broth with polysorbate 80 and sabouraud dextrose agar (SDA) were purchased from Oxoid (Basingstoke, UK). Methanol and 2% nitric acid were purchased from Sigma Aldrich GmbH (Taufkirchen, Germany). Belobaza® cream was purchased from Belupo Pharmaceuticals and Cosmetics, Inc. (Koprvnica, Croatia). Mannitol salt agar (MSA) and Baird Parker agar (BPA) were purchased from Remel (Lenexa, USA). Cetrimide agar (CA) was purchased from Conda (Madrid, Spain). All chemicals were of analytical reagent grade or higher purity and were used without further purification.

Preparation of Ointment against psoriasis 2

The components of Ointment Against Psoriasis 2 were: salicylic acid 5% w/w, castor oil 10% w/w, olive oil 10% w/w and Belobaza® cream 75% w/w. Belobaza® cream contained: purified water (70%), petrolatum, liquid paraffin, cetostearyl alcohol (cetearyl alcohol), polyoxyl 20 cetostearyl ether (ceteareth 20), benzyl alcohol, sodium phosphate, phosphoric acid, sodium hydroxide[9]. Salicylic acid was weighed (Analytical balance XS 205DU, Mettler Toledo GmbH, Germany) and pulverized in ceramic mortar with pestle, and sieved through sieve N°170 (Gramed d.o.o., Serbia)[7]. Salicylic acid powder was incorporated by levigation („wet grinding“) in the mixture of castor and olive oil using mortar and pestle[4,10] after which Belobaza® cream was added gradually up to 100% w/w. Since salicylic acid is slightly soluble in fatty oils[11] resulting ointment was a suspension. Obtained preparation was white, uniform in appearance without signs of granular structure, and substantially greasier than the base. Ointment Against Psoriasis 2 (sample 10) was packed in plastic containers and stored at 25°C±3°C for 60 days.

Preparation of Belobaza® cream samples with purified water and oils

To test the ability of Belobaza® cream (sample 11) to emulsify water and oils, samples of different ratios of Belobaza® cream and purified water were made (sample 1 - 1:0.11, sample 2 - 1:0.25, sample 3 - 1:0.43, sample 4 - 1:0.67, sample 5 - 1:1), and Belobaza® cream and oils (sample 6 - 1:0.11, sample 7 - 1:0.25, sample 8 - 1:0.43, sample 9 - 1:0.67). All samples were packed in plastic containers and stored at 25°C±3°C for 60 days.

Organoleptic observations

Organoleptic observations were used to evaluate color, shine, consistency and homogeneity of samples 1-10. These observations were performed visually every five days for 60 days. Homogeneity was evaluated by observing the spread on a microscope plate against light, whereat the granular structure of the test samples should not be observed. The odor of the samples was tested, as one of the sensory/organoleptic properties of the preparation/base. The application properties of the samples and tactile perception of skin were evaluated after application of samples on skin surface.

Physical stability testing

Determination of physical stability of the samples was carried out in a centrifuge MIKRO 22 R (Hettich, Germany). The centrifuge test was performed 24 hours after samples preparation and repeated 10 days after, at 3000 rpm, after 15 and 30 minutes at 25°C by placing 3 g of each sample in centrifuge tubes. At the end of each cycle, tubes were investigated for the presence of any phase separation[12].

pH determination

The pH of samples was measured using digital pH meter Seven compact pH/JonS220 (Metler Toledo, Germany). 2 g of tested samples were weighed into laboratory beakers. 10 mL of purified water was added. The test

samples were stirred and heated to boiling and allowed to cool to room temperature[13]. After cooling the aqueous layer was separated and used to measure the pH. Measurements were made in triplicate, 24 hours and 10 days after samples preparation.

UV-VIS spectrophotometric method for salicylic acid determination

Stock solution: About 10.0 mg of salicylic acid was dissolved in 100 mL of methanol using an ultrasonic bath (Sonorex Digitec DT 512 H, Bandelin, GmbH, Germany) for 10 minutes. *Reference solution:* 1 mL of stock solution was diluted to 5 mL with methanol (concentration of 0.02 mg/mL). UV spectrum (UV-VIS spectrophotometer, UV-1601, Shimadzu, Japan) of reference solution in the range of 200 to 400 nm was recorded to determine the absorption maximum of test substance. The wavelength of maximum absorption (figure 1) was be used to determine its content in the Ointment Against Psoriasis 2.

The method for the determination of salicylic acid was validated according to ICH guideline Q2 (R1) for linearity, precision (repeatability), accuracy (recovery study) and specificity[14].

Linearity was determined in the concentration range of 0.005-0.05 mg/mL of salicylic acid, by calculating the parameters of the linear regression equation and the correlation coefficient (R^2). Linear regression equation (figure 2) was used to quantify salicylic acid content.

Precision (repeatability) was statistically estimated by standard deviation (SD) and relative standard deviation (%RSD) of individual results obtained by performing the same analytical procedure on samples belonging to the same homogeneous series. Method repeatability was determined by analyzing 100% solution of salicylic acid (0.02 mg/mL) six times without changing the measurement parameters.

Samples containing 80%, 100% and 120% of salicylic acid and placebo mixtures (castor oil, olive oil and Belobaza® cream) were prepared in triplicate. Salicylic acid was extracted from 1 g of test samples using 50 mL of methanol and an ultrasonic bath, at 50°C. After extraction, solutions were filtered (cellulose nitrate filter, pore size 0.45 μm, Sartorius AG, Germany). 1 mL of these solutions was diluted to 50 mL with methanol. The solutions were prepared in triplicate and measured using UV-VIS spectrophotometric method.

Accuracy (recovery study) was determined at three different concentration levels of salicylic acid in the base/placebo mixture. Recovery (%R) was calculated using the following equation:

$$\%R = \frac{c_c}{c_d} \times 100 \qquad [1]$$

where c_c is calculated concentration of salicylic acid (mg/mL) and c_d is declared concentration of salicylic acid (mg/mL). The tolerance (%SD), which indicates the interaction of salicylic acid with excipients (placebo mixture), may be ±2%.

Accurately weighed 1 g of placebo mixture was dissolved in 50 mL of methanol in Erlenmeyer flask in the ultrasonic bath at 50°C (placebo stock solution). From placebo stock solution having concentration of 20 mg/mL, five dilutions of placebo working solutions in the concentration range 0.2-2.0 mg/mL were prepared, each in triplicate and measured at 304.0 nm. The dependence of the absorbance on the concentration of placebo solution, and linear regression equation, is shown in figure 3. Interference of placebo (0.4 mg/mL) with salicylic acid absorbance (0.02 mg/mL) was calculated:

$$\%\text{interference} = \frac{\text{A (placebo mixtures)}}{\text{A (salicylic acid)}} \times 100 \qquad [2]$$

where A is absorbance. UV spectrum of placebo solution (0.4 mg/mL), in the wavelength range of 200 to 400 nm, was recorded. Methanol was used as a blank (figure 4).

Accurately weighed 1 g of Ointment Against Psoriasis 2 was dissolved in 50 mL of methanol (1 mg salicylic acid/mL) in Erlenmeyer flask using ultrasonic bath at 50°C. Samples were prepared in triplicate, filtered and diluted with methanol to obtain concentration of 0.02 mg/mL. The solutions were prepared in triplicate. Salicylic acid content was determined from the linear regression equation twice, 24 hours and 10 days after ointment preparation.

Microbiological testing

The samples 1, 5, 6, 7 and 10 were subjected to microbiological examination using 2.6.12. Microbial enumeration tests, 2.6.13. Test for specified micro-organisms and 5.1.4. Microbiological quality of non-sterile pharmaceutical preparations for cutaneous use, 24 hours and 10 days after their preparation[13,15]. Under aseptic conditions, 10 g of samples were weighed and transferred into bottle containing sterile sodium chloride peptone

solution with the addition of polysorbate (Laminar chamber model HPH12 L, Kendro-Heraeus, Germany). The mixture was stirred to dissolve the samples and homogenize them with sodium chloride buffer solution. From the homogenized solution, 1 mL of 10^{-1} dilution and 1 mL of 10^{-2} dilution were pipetted onto the surface of TSA, TSB and two SDAs. After absorption, the plates were left for incubation (Incubator model B6, Kendro-Heraeus, Germany) (TSA at 30-35°C/3-5 days to determine the number of aerobic bacteria and SDA at 20-25°C/5-7 days to determine aerobic fungi). 10 mL of 10^{-1} dilution was transferred into 100 mL TSB and incubated for 18-24 hours at 30-35°C (presence/absence test for *Staphylococcus aureus* and *Pseudomonas aeruginosa* in 1 g or 1 mL). In the sample bottle with TSB, there was no turbidity after 1 day, so incubation was continued for the next 24 hours. After 2 days, the contents of the bottle with TSB, were subcultured on a plate with MSA or alternatively BPA (*Staphylococcus aureus*) and incubated at 30-35°C/18-72 hours. The sample was subcultured on a plate with CA and tested for *Pseudomonas aeruginosa*. After 3 days, there was no increase in colonies number on either growth media. Incubation was continued for the next 24 hours, and again there was no increase in colonies number on either growth media. If growth of black glossy colonies on BPA with a translucent zone was observed, it would indicate the presence of *Staphylococcus aureus*. The growth of yellow or white colonies surrounded by yellow zone on MSA, indicates the presence of *Staphylococcus aureus*, where it is further treated according to the instructions for identification of this micro-organism. The growth of Gram-negative bacilli colonies, usually with greenish fluorescence, indicates the presence of *Pseudomonas aeruginosa*, and it is necessary to do an oxidase test, or follow the instructions for identification of this micro-organism. If there was no growth of micro-organisms, the sample would meet the test conditions. In case of colony growth after fifth day, the total number of colonies on TSA and on SDA is recorded. Acceptance criteria for microbiological quality of non-sterile preparations for cutaneous use are: total aerobic microbial count (TAMC) - up to 10^2 CFU (colony forming units) per g or mL, total combined yeasts/molds count (TYMC) - up to 10^1 CFU per g or mL, absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* in 1 g or 1 mL. Described procedure was performed twice, 24 hours and 10 days after test samples were made (1, 5, 6, 7 and 10).

Heavy metals determination

Samples were analyzed by atomic absorption spectroscopy (AAnalyst 400, Perkin Elmer, USA) for lead (Pb) and cadmium (Cd). 50 mL of 2% nitric acid (HNO_3) was added to 10 g of samples 1, 5, 6, 7 and 10. The mixtures were heated to boiling, cooled to room temperature and filtered. Wavelengths for lead were set at 283.31 nm and for cadmium at 228.80 nm[13,16]. The tube of the apparatus was immersed in the prepared standard solutions of 1, 3 and 5 ppm, then in the blank and the test sample. The flame to test these two metals was air/acetylene mixture[13]. The analysis of samples for heavy metals in was done 24 hours and 10 days after preparation.

III. Results

Organoleptic observations

Ointment Against Psoriasis 2 was odorless, white, semisolid, without shine and traces of granular structure (homogeneous). It easily spreads, leaving non-greasy, non-sticky film on the skin, with a subjective feeling of skin hydration. During 60 days of storage at 25°C±3°C unchanged appearance, odor, application and sensory properties were confirmed. Samples 6 and 7 were odorless, white, semisolid, greasier structure compared to samples 1-5. In samples 1-7, these properties remained unchanged for 60 days. All creams were easily spreadable. Samples 1-5 left non-greasy, non-sticky film on the skin with a subjective feeling of skin hydration. In samples 8 and 9 complete separation of the oil and water phases, the presence of a cheesy consistency and traces of yellow color from the separated oils were observed after 60 days. Belobaza® cream (sample 11) could emulsify 100% water and only 25% oils. It could not emulsify 42.86% of a castor-olive oil mixture. A higher proportion of oil phase caused significant structural changes of Belobaza® cream.

Physical stability testing

After the centrifuge test, samples 1-6, 11 were physically stable since there was no phase separation, oil phase on the surface (cremation) or aqueous phase on the bottom of the cuvette (sedimentation) 24 hours and 10 days after preparation. An oil phase separated on the surface of the samples tested 7-9. Samples 8 and 9 were not further analyzed. The Ointment Against Psoriasis 2 (sample 10) was physically unstable, which is significant from the aspect of possible longer storage.

pH determination

The initial pH of samples 1, 5, 6, 7 were 5.27-5.36 at 22°C±2°C, 24 hours after preparation. 10 days after preparation, the pH of samples 1 and 6 were almost unchanged (5.35/5.31, 5.27/5.13), while pH of sample 5 decreased

from 5.36 to 4.17, and pH of sample 7 from 5.29 to 3.81. Ointment Against Psoriasis 2 (sample 10) contained salicylic acid in concentration of 5%, so its initial pH was 2.54. The pH of the preparation was almost unchanged (2.50), 10 days after its preparation.

UV-VIS spectrophotometric method for salicylic acid determination

Figure 1 shows the UV spectrum of salicylic acid.

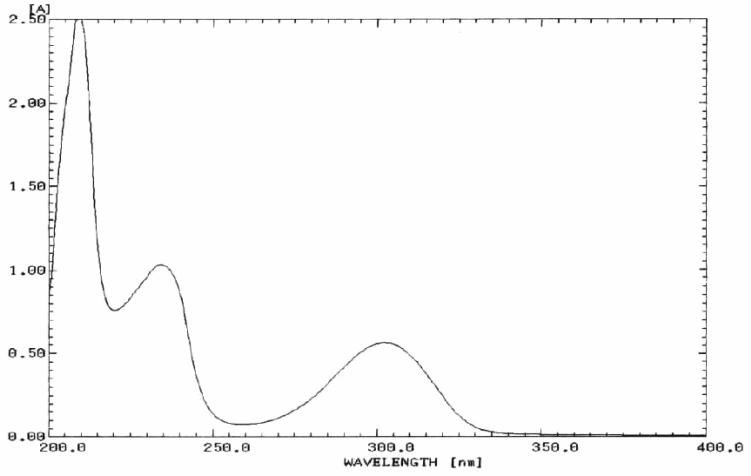

Figure 1: UV spectrum of salicylic acid.

The maximum absorption of 0.02 mg/mL salicylic acid in methanol, at 304.0 nm was used to construct calibration curve to determine salicylic acid content in Ointment Against Psoriasis 2[17]. The calibration curve of salicylic acid, and linear regression equation, is shown in figure 2.

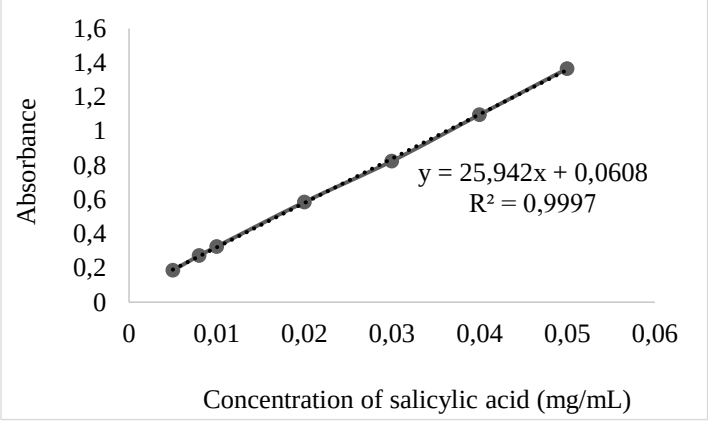

Figure 2: Calibration curve of salicylic acid.

UV-VIS spectrophotometric method was precise method for determining the content of salicylic acid (99.36%±0.17%) in Ointment Against Psoriasis 2 since the obtained RSD is less than 2%. Results of accuracy study are shown in table 1.

Table no 1: Accuracy study data.

Declared salicylic acid concentration (mg/mL)	A	Calculated salicylic acid concentration±×10^{-4} (mg/mL)	%R±SD
0.016	0.4833	0.0163±2.86	101.85±1.54
0.020	0.5702	0.0197±1.35	98.26±0.68
0.024	0.6908	0.0243±3.71	101.30±1.55

[A]absorbance n=3, [R]recovery, [SD]standard deviation

Figure 3 shows the dependence of the placebo mixture absorbance on the concentration (0.2 mg/mL, 0.4 mg/mL, 0.8 mg/mL, 1 mg/mL, 2 mg/mL) measured at 304.0 nm, and the linear regression equation.

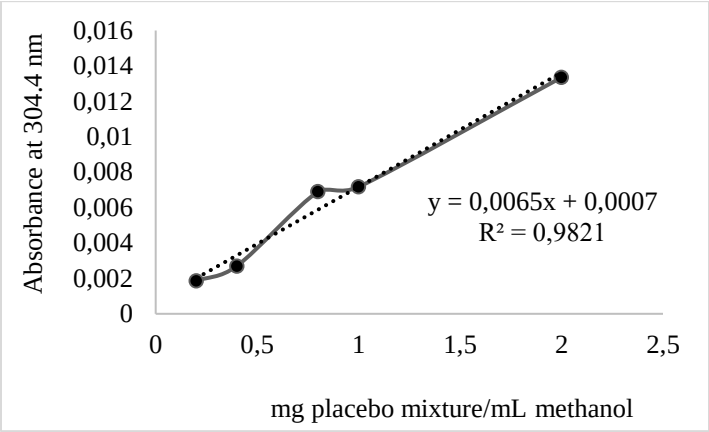

Figure 3: Dependence of the placebo mixture absorbance on the change of its concentration.

The interference of the placebo mixture (concentration 0.4 mg/mL, A=0.0027) with the salicylic acid absorbance (concentration 0.02 mg/mL, A=0.585) was 0.4615%. Figure 4 shows the UV spectrum of 0.4 mg/mL placebo mixture in methanol.

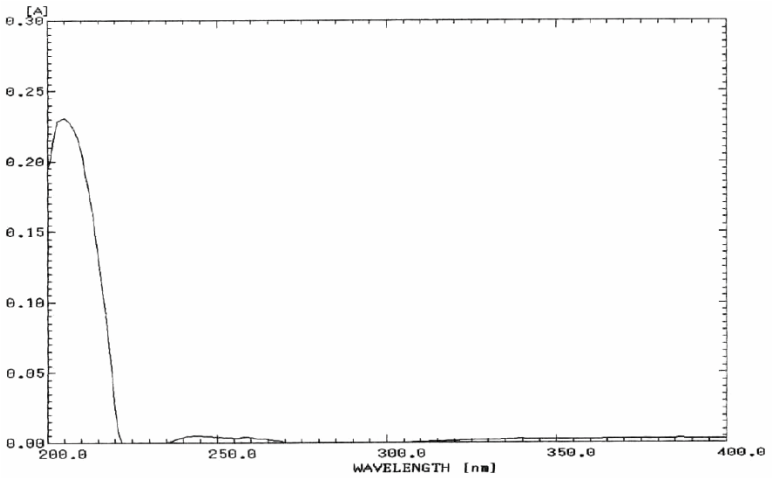

Figure 4: UV spectrum of placebo mixture.

The salicylic acid content in Ointment Against Psoriasis 2 determined 24 hours and 10 days after preparation was 98.26%±0.68% and 98.02% ± 0.95%, respectively.

Microbiological testing

The results of microbiological analysis 24 hours and 10 days after the preparation of Ointment Against Psoriasis 2 and samples 1, 5, 6 and 7 were negative and met the acceptability limits for non-sterile pharmaceutical preparations for cutaneous use, category 2[13]. The absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* was confirmed. TAMC and TYMC values were 0 CFU/g.

Heavy metals determination

Content of lead and cadmium (ppm) 24 hours and 10 days after preparation are presented in table 2.

Table no 2: The content of lead and cadmium in the samples tested.

Samples	Lead (ppm)		Cadmium (ppm)	
	After 24 h	After 10 days	After 24 h	After 10 days
1	0.370	0.500	0.002	0.020
5	0.408	0.107	0.006	0.049
6	0.404	1.475	0.056	0.189
7	0.758	1.359	0.138	0.178
10	0.139	0.328	0.168	0.232

IV. Discussion

After the centrifuge test, Ointment Against Psoriasis 2 showed physical instability. However, its use was safe during the treatment of psoriasis, which was confirmed by organoleptic observations. This extemporaneous preparation is made according to the physician's prescription. Since it is prescribed for 10-days therapy, its application can be considered safe for a period of 10 days.

Stability of samples tested depends on the stability of the crystalline gel phase consisting of two layers of nonionic emulsifier and fatty amphiphile separated by layers of interlamellar bound water[18]. Belobaza® cream contained ceteareth 20 (nonionic emulsifier) and cetostearyl alcohol (lipophilic co-emulsifier/co-stabilizer, fatty alcohol/amphiphile). In combination with ceteareth 20, cetostearyl alcohol forms physically stable hydrophilic cream with very complex microstructure in the form of liquid crystals, lamellar structures and gel phase[9]. This combined emulsifier densely packs on the interface of oil (petrolatum, liquid paraffin) and aqueous phases (70% purified water, benzyl alcohol, sodium phosphate, phosphoric acid, sodium hydroxide)[18,19]. Liquid-crystal gel structures of multiphase hydrophilic cream form stable networks responsible for consistency, stability, spreadability, cooling effect and skin feel, and for its possible interaction with skin lipids. Upon contact with the skin, free water is first released, which moisturizes the skin, but evaporates quickly. Subsequent release of interlamellar bound water (water molecules between two layers of cetostearyl alcohol and ceteareth 20) leads to prolonged effect of skin hydration[19].

Belobaza® cream and Ointment Against Psoriasis 2 contained a significant amount of water, up to 70%. The samples also contained the preservative benzyl alcohol, which was why the microbiological quality of the samples was preserved, even in the sample 5 with the highest water content. Benzyl alcohol achieves optimal microbiological activity at pH below 5 while its activity decreases only at pH above 8[9].

The pH of Belobaza® cream met the requirement for semisolid preparations for cutaneous use. The same applied for the samples obtained by adding up to one part of purified water or up to 0.11 parts of a mixture of castor and olive oil was added to one part of Belobaza® cream. The initial pH of Ointment Against Psoriasis 2 remained almost the same 10 days after preparation, which corresponded to the pharmacotherapeutic effect of the preparation: chemical exfoliation, that is, keratolytic action of salicylic acid to remove accumulated dead cells from the surface psoriatic skin.

UV-VIS spectrophotometric method was specific for the determination of salicylic acid in Ointment Against Psoriasis 2 since placebo mixtures did not show an absorption maximum at 304.0 nm (figure 4) nor interference.

The World Health Organization sets maximum permissible limit of 10.0 mg/kg (ppm) for lead, and 0.3 mg/kg (ppm) for cadmium[16,20]. Contents of lead and cadmium in samples tested were well below permissible limits.

V. Conclusion

Ointment Against Psoriasis 2 retained its organoleptic properties, during the period of 60 days after preparation, while there were no significant changes in pH, heavy metals and salicylic acid content and microbiological quality 10 days after preparation. The ointment showed physical instability, but that didn't affect its safety for the patients. All the above once again confirms the fact that extemporaneous compounding in pharmacies provides therapy tailored to one patient in case appropriate drug is not available on the market.

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