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Original Article

Influence of Base Type on the Physical Stability of Dermatological Preparations with Vitamins A and C

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ABSTRACT

The formulation base plays a critical role in the physicochemical stability and therapeutic efficacy of dermatological creams. Vitamins A and C are widely used in skincare due to their anti-aging and antioxidant properties, yet they are chemically unstable and highly sensitive to environmental conditions. This study aimed to evaluate the impact of different pharmaceutical and dermocosmetic cream bases on the physical stability and rheological behavior of formulations containing selected forms of vitamin A (retinol, retinyl palmitate, solubilized form of retinyl palmitate) and vitamin C (ascorbic acid). Methods: Creams were prepared using four bases: two traditional (Lekobaza, Eucerin) and two modern dermocosmetic bases (Versatile, Emolivan). Physical stability parameters including centrifuge test, spreadability, droplet size in optical microscopy, and rheological properties were assessed at days 1, 7, 14, and 30. Droplet size changes were analyzed statistically using the Friedman test and Kendall's W. Results: Creams formulated on Lekobaza and Eucerin maintained stability throughout 30 days. Versatile formulations showed good short-term stability (up to 14 days), but decreased viscosity and signs of destabilization by day 30. Emolivan was stable for retinol and solubilized vitamin A but showed rheological anomalies when combined with retinyl palmitate or ascorbic acid. Rheological analysis confirmed pseudoplastic flow behavior and time-dependent viscosity changes, particularly in Versatile and Emolivan systems. Conclusion: The choice of formulation base significantly affects the physical stability and usability of creams containing unstable vitamins. Traditional pharmaceutical bases provided superior long-term stability, while modern cosmetic bases may require formulation adjustments to maintain vitamin integrity.

KEYWORDS: vitamin A, vitamin C, cream formulation, dermocosmetic base, physicochemical stability

1. Introduction

Modern dermatological and cosmetic products constitute an essential component of skin therapy and care. Their effectiveness depends not only on the presence of active ingredients but also to a large extent on the type of base used, which influences the release of active substances, the stability of the formulation, and patient acceptance [1, 2]. Ready-to-use pharmaceutical bases are intended for the immediate preparation of magistral formulations. A properly selected base improves the sensory properties of the product [2, 3]. Available options include hydrophobic bases (paraffin, petrolatum), absorptive bases (those capable of incorporating water and forming water-in-oil [W/O] emulsions, e.g., eucerin), W/O pre-prepared emulsions such as cold cream (e.g., Emolivan), and oil-in-water [O/W] emulsions, also called hydrophilic or washable bases (e.g., Lekobaza) [4]. W/O-type bases leave a protective lipid film on the skin and promote occlusive effects, while O/W-type bases are lighter, easy to rinse, and preferred when good absorption and a non-greasy feel are desired [5, 6]. Recently, innovative dermocosmetic cream bases have been introduced to the market, combining the advantages of pharmaceutical and cosmetic formulations. One example is the VERSATILE base—an O/W emulsion capable, according to the manufacturer, of maintaining stable formulations for both hydrophilic and lipophilic ingredients [1, 7]. It is also available in a richer version (Versatile Rich), allowing adjustment of the cream's oiliness to meet individual skin needs [8]. Emolivan is a ready-to-use W/O emulsion base (cold cream) characterized by a greasy consistency, which reduces water evaporation from the stratum corneum [9]. Such bases are commonly used in pharmaceutical

compounding when prolonged activity of active substances or protection against external factors is required [7–9]. Literature reports confirm the use of Emolivan as an effective and stable vehicle for dexamethasone and urea solutions [1].

Vitamin A is a group of compounds (retinoids) essential for proper skin function and cellular renewal [10, 11]. Major representatives include all-trans-retinol (alcohol form), its esters (e.g., retinyl palmitate), and active metabolites such as retinal and retinoic acid. Retinol penetrates the epidermis and oxidizes into retinoic acid, which exerts biological effects by activating RAR/RXR (retinoic acid/rexinoid) receptors [10, 11]. Topical retinol use effectively improves skin structure, stimulates type I collagen and glycosaminoglycan synthesis, contributing to wrinkle reduction and increased skin firmness. Retinol, retinyl acetate, and retinyl palmitate are used in cosmetics at maximum concentrations of 0.05 % (retinol equivalents) in body lotions and up to 0.3 % in face and hand creams or other products such as sunscreens and anti-aging formulas [12].

In a clinical study involving elderly participants (mean age 87), 0.4 % retinol used for 24 weeks significantly reduced fine wrinkles and increased the expression of procollagen I and GAGs(glycosaminoglycans) [10]. Unfortunately, retinol is a highly unstable molecule prone to oxidation, isomerization, and photodegradation. Studies indicate that pure retinol undergoes considerable degradation under exposure to light and oxygen, especially in the presence of water, metal ions, and elevated temperatures [3, 13, 14]. To enhance chemical stability and reduce irritation, more stable derivatives like retinyl esters (e.g., retinyl palmitate) are commonly used [11]. Formulation-wise, both retinol and its esters are lipophilic, which complicates their incorporation into aqueous phases of creams. Commercially, vitamin A is available in several forms. Besides pure retinol dissolved in neutral oils [15] and retinyl palmitate oil concentrates (e.g., 1 million IU/g, corresponding to ~0.344 g of palmitate per 1 g of solution) [16], water-soluble solubilizates are also used. These are transparent aqueous solutions of retinyl palmitate stabilized with solubilizing agents (e.g., macrogolglycerol derivatives) [5]. Although convenient for dosing, they pose formulation challenges, particularly with W/O bases. O/W emulsifiers within solubilizates can destabilize W/O systems such as eucerin or Emolivan, causing phase separation. Therefore, it is advised to avoid combining solubilized vitamin A with W/O bases and instead use oil-based forms [5]. Moreover, solubilizates, mainly designed for oral use, often contain excipients like preservatives, fragrances, and synthetic solubilizers not intended for skin contact. Their presence in topical formulations may increase the risk of adverse effects, including irritation or allergic reactions [14]. Additionally, water content significantly reduces vitamin A stability. Retinyl palmitate is prone to hydrolysis and oxidation in aqueous environments, especially when exposed to light, oxygen, and heat [3]. According to SCCS (Scientific Committee on Consumer Safety) stability studies, even under refrigeration (4° C), the content of retinoids in creams decreases significantly, with substantial loss observed after six months [12]. When stored at room temperature and exposed to light, degradation may reach nearly 100 % [17, 18]. Retinol and its acetate can also strongly adsorb onto PVC (polyvinyl chloride) materials used in packaging [12]. Therefore, to ensure safety and efficacy, vitamin A formulations should be stored in appropriate packaging (e.g., aluminum tubes) [12], protected from light and oxygen, preferably refrigerated, and used within 1–2 months [3, 14].

L-ascorbic acid is a hydrophilic antioxidant widely used in dermatology and cosmetics [19–21]. Its primary mechanisms include scavenging free radicals, stimulating collagen synthesis, and reducing pigmentation by inhibiting tyrosinase activity [19, 20]. Consequently, it is employed in skin aging prevention, treatment of hyperpigmentation, post-inflammatory acne, and as a photoprotective agent [20]. Due to its regenerative and anti-inflammatory properties, ~~vitamin C~~ it supports skin healing and is used in scars and barrier-impairment conditions [19].

However, it presents significant formulation challenges due to its poor chemical stability. Ascorbic acid is highly water-soluble, forming solutions with a very low pH (~2–3), which can destabilize emulsions by deactivating emulsifiers or thickeners such as polyacrylates [20–24]. It also reacts with heavy metal ions (iron, copper), which catalyze degradation, hence the need for chelating agents [22]. Various stabilization strategies are employed in cosmetic and pharmaceutical products, including antioxidants (e.g., vitamin E, ferulic acid) [25], oxygen exclusion, and protective delivery systems like W/O/W multiple emulsions, which encapsulate the aqueous phase in lipid shells [24]. Even simple W/O emulsions offer better oxidation protection than classic O/W systems due to the oleophilic barrier. Refrigerated storage improves product longevity [23]. Nonetheless, ascorbic acid stability remains limited. A typical sign of degradation is color change (yellowing/browning), which correlates with reduced bioactivity [21, 26]. Therefore, compounded ascorbic acid preparations should have a short shelf life, be stored in airless or light-resistant packaging, and kept refrigerated [26]. To date, no comparative study has systematically evaluated the influence of both classical pharmaceutical and modern dermocosmetic bases on the physical stability of compounded creams containing unstable vitamins A and acorbic acid, which represents a significant gap in practical formulation research.

The aim of the present study was to compare the influence of different dermatological bases (Lekobaza, Eucerin, Emolivan, Versatile) on the physical stability and physicochemical properties of formulations containing various forms of vitamin A (solubilized and lipophilic retinyl palmitate, retinol) or ascorbic acid.

2. Materials and Methods

Four dermatological cream bases commercially available in pharmacies were used in the study. Two of them were traditional pharmaceutical bases commonly used in compounding: Lekobaza (Lekobaza®; Fagron) composed of (White petrolatum, Glyceryl monostearate, Cetyl alcohol, Miglyol 812, Macrogol-20-glyceryl monostearate, Propylene glycol, Water), Eucerin (Unguentum Eucerini I, Galfarm) consists of (Cetostearyl alcohol 0.5 %, Sterol alcohols from lanolin 6.0 %, and White petrolatum 93.5 %.), as well as two modern dermocosmetic bases: Versatile™ (Fagron, Spain) composed of (Cetearyl alcohol, PEG-150 Stearate, Polysorbate 60, Steareth-20, Glyceryl monostearate, PEG-75 stearate, Dicaprylyl carbonate, Simethicone, Isohexadecane, Isododecane, C13-15 Alkane, Tocopheryl acetate, Aqua, Disodium EDTA, Benzoic acid, Sorbic acid, Propanediol, Lecithin, Sodium hydroxide) and Emolivan™ (Fagron, Spain) composed of (Helianthus Annuus Seed Oil, Cera Alba, Aqua Purificata, Olus Oil, Cetearyl Olivate, C30-45 Alkyl Methicone, C30-45 Olefin, Tocopheryl Acetate,

Phenoxyethanol). The active substances included: vitamin A in aqueous solution (water-soluble retinyl palmitate solubilizate, Hasco, 45,000 IU(International Unit)/ml) composed of (retinyl palmitate stabilized with tocopherol, all-rac-α-tocopherol, natural vitamin E, butylated hydroxyanisole (BHA), citric acid monohydrate, disodium phosphate dodecahydrate, sodium saccharin, macrogolglycerol hydroxystearate, glycerol, lemon flavor, purified water)(retinyl palmitate sol.), retinol - 10% retinol in Caprylic/Capric Triglyceride (e-naturalne, Poland), corresponding to 0.1 g of pure retinol per 1 g of oil, retinyl palmitate (Zielony klub) (retinyl palmitate concentrate, 1.7 million IU/g composed of Retinyl Palmitate, Arachis Hypogaea (Peanut) Oil, Tocopherol) (retinyl palmitate), and ~~vitamin C~~ L-ascorbic acid (POCH, Gliwice), pure analytical grade, (ascorbic acid).

2.1 Cream preparation

Each formulation was prepared in 200 g batches. Into the bases Lekobaza, Eucerin, Versatile, and Emolivan, the following active substances were individually incorporated: 5 % of the vitamin A water solubilizate, 3 % retinol, 2 % retinyl palmitate, and 3 % of a 20 % ascorbic acid aqueous solution. The appropriate amount of base was weighed and transferred to the mortar, followed by the weighed amount of the active substance (solution or concentrate), and mixed using a pestle until a uniform consistency was obtained. Creams were prepared by manual trituration at room temperature (~22°C) for 5–7 min until homogeneous, without high-shear homogenization. All samples were stored in opaque 200 mL polypropylene jars filled nearly to the top to minimize headspace. The formulations were kept at 2–8°C, protected from light, for 30 days.

The choice of these storage conditions was based on the ICH Q1A (R2) Guideline: Stability Testing of New Drug Substances and Products, which provides internationally harmonized recommendations for pharmaceutical stability studies. According to this document, storage at 2–8°C corresponds to the *refrigerated storage conditions* recommended for products sensitive to temperature and light [27].

The present study focused exclusively on assessing the short-term physical stability (viscosity, droplet size, and spreadability changes) of the formulations; therefore, accelerated and chemical stability tests were not performed. The evaluation of physical properties was conducted based on established literature guidelines [27–37]. Tests were carried out on each sample at defined time intervals: 1, 7, 14, and 30 days after preparation to monitor changes indicative of potential destabilization.

2.2 Centrifugation test for physical stability

One gram of cream was placed into an Eppendorf-type test tube. The samples were centrifuged in a laboratory centrifuge (Eppendorf 5418R) at 8600 rpm for 15 minutes. After centrifugation, visual assessment was conducted to check for phase separation (appearance of a distinct fluid layer or loss of uniformity). This test simulates accelerated aging of emulsions under centrifugal forces and reveals tendencies toward coalescence and phase separation in a short time frame [28–30].

2.3. Spreadability test

Spreadability was assessed using an extensometer, which measures the cream's ability to spread under applied load [29–32]. One gram of the cream (accurately weighed) was placed in the center of a circular measurement plate. The sample was compressed from above with a flat piston, upon which successive weights were applied: 200 g, 400 g, 600 g, 800 g, and 1000 g. Each load was maintained for one minute, after which the radii of the spread cream circle were measured (four directions at 45° intervals, and the average was calculated). This procedure was repeated three times for each sample. Based on the average diameters, the spread area was calculated (for each load), and the spreadability index (Ip) was determined, defined as the area under the curve describing the relationship between spread area and load [30]. The values of Ip (cm^2/g) were used for quantitative comparison of the ease of spreading between formulations. Each sample was tested in triplicate. Results are presented as the arithmetic mean ± SD (standard deviation) in Tables 1–4.

2.4 Particle Size Evaluation

To monitor changes in the droplet size of the dispersed phase in the emulsions, microscopic observations were performed using an optical microscope (Leica ICC 50 HD, bright-field mode) at 10× magnification and air objective [29, 30]. A thin uniform layer of the tested cream was spread on a clean microscope glass slide and covered with a coverslip to prepare the sample. For each formulation and each time point, observations were made in three randomly selected fields of view, from which a total of 100 randomly chosen oil-phase droplets were measured using LAS EZ software (Leica Microsystems, Germany). Representative micrographs were taken with automatic scale calibration (scale bar = 200 µm). A representative microscopic image of the emulsion structure is shown in Figure 1. From these measurements, the average droplet diameter for each sample was calculated. The mean droplet sizes were then chronologically compared (1, 7, 14, and 30 days) for each series of creams to assess, using statistical tests, whether coalescence and thus emulsion destabilization occurred over time. The results of the droplet size evaluation for each formulation are presented as mean ± SD in Tables 1–4. A representative microscopic image of the emulsion droplets is shown in Figure 1. Figure 2 presents a histogram illustrating the droplet size distribution for the Emolivan + retinyl palmitate formulation (day 1), while Figure 3 shows the droplet size changes over time with corresponding trend lines for two selected formulations.

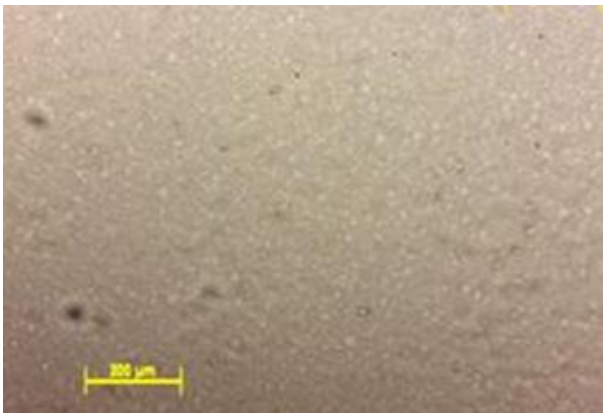

Figure 1. Microscopic image of Emolivan cream containing retinyl palmitate (day 1, 10× magnification), scale bar = 200µm .

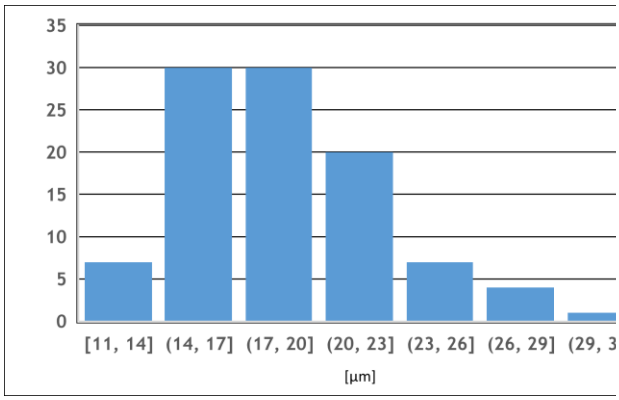

Figure 2. Histogram showing the droplet size distribution for the Emolivan + retinyl palmitate formulation (day 1).

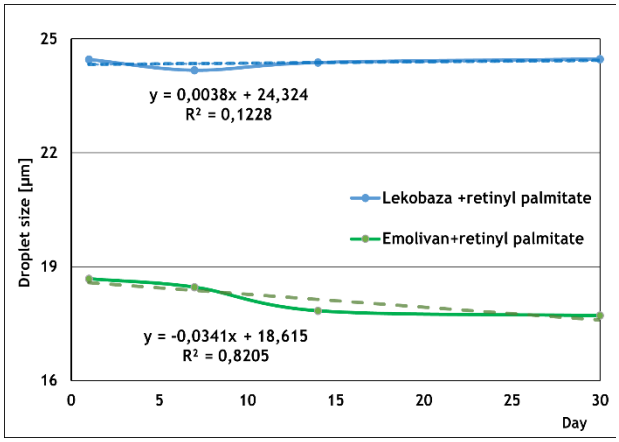

Figure 3. Changes in the mean droplet size (µm) of the oil phase over time in creams containing retinyl palmitate, prepared on Lekobaza and Emolivan bases and stored at 2–8°C.

2.4.1 Statistical Analysis of Droplet Size

The results of droplet size measurements were statistically analyzed using MS Office 2021 (Excel) and Statistica 13.1 software. The normality of the data distribution was assessed using the Shapiro–Wilk test. Due to a lack of normal distribution ($p < 0.05$), the non-parametric Friedman ANOVA test was applied to evaluate changes in the size of the oil phase droplets over time. To assess the strength of ordinal agreement between consecutive time points, Kendall's coefficient of concordance (W) was also calculated. The analysis included four time points: 1 day, 7 days, 14 days, and 30 days for each tested formulation. In cases where the Friedman test indicated significant differences, a post hoc analysis was performed using the Wilcoxon signed-rank test. The results of this analysis are summarized in Table 5.

2.5 Rheological Testing

The consistency and flow properties of the creams were evaluated using an Anton Paar RheolabQC rotational rheometer equipped with a coaxial cylinder measuring system (cylinder CC27/S (coaxial cylinder measuring system) with Peltier temperature control) [28–29]. Each sample was placed in the measuring cylinder and thermostated for 10 minutes before rheological testing. The measurement protocol consisted of increasing the shear rate from 0.1 s^{-1} to 300 s^{-1}, followed by a decreasing phase from 300 s^{-1} back to 0.1 s^{-1}. This measurement cycle allowed the evaluation of thixotropy, i.e., reversible structural breakdown under shear stress. From the resulting flow curves, dynamic viscosity (η) values at selected shear rates (5 s^{-1} and 50 s^{-1}) were determined, and the hysteresis loop area, a measure of thixotropy, was calculated. The rheological data were fitted to the Ostwald-de Waele model (pseudoplastic fluid model) to obtain the consistency coefficient K (in Pas) and the flow behavior index n (dimensionless). Comparison of K and n values over time enabled assessment of the effect of aging on the sample's consistency and flow behavior [29]. Each formulation was tested once. The values of absolute viscosity at shear rates of 5 s^{-1} and 50 s^{-1}, as well as the Ostwald-de Waele model parameters, are presented in Tables 1–4. Representative rheological curves illustrating shear stress (flow curves) and viscosity behavior of the selected formulation (Lekobaza + retinyl palmitate) are shown in Figures 4 and 5, respectively.

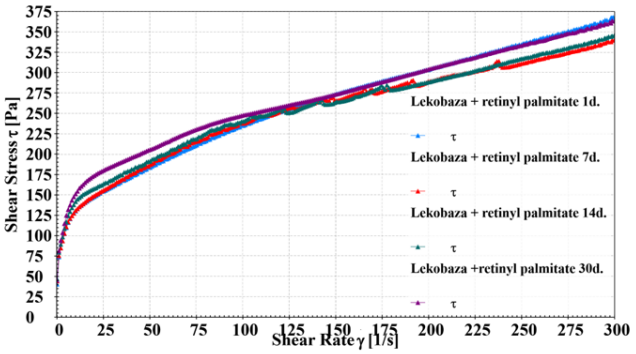

Figure 4. Flow curves (shear stress vs. shear rate) for the formulation Lekobaza + retinyl palmitate at different time points (1, 7, 14, and 30 days). Measurements were performed using an Anton Paar rotational rheometer (CC27/S SN60412) at 25°C.

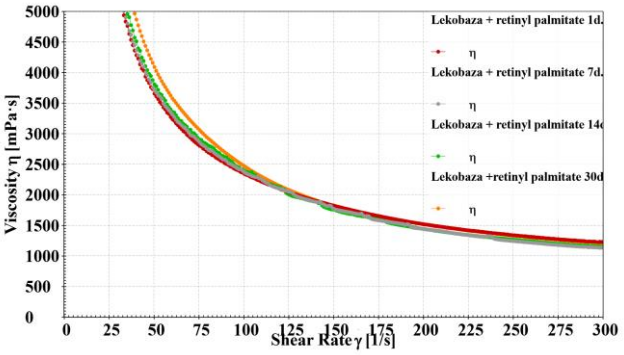

Figure 5. Viscosity curves (viscosity vs. shear rate) for the formulation Lekobaza + retinyl palmitate at different time points (1, 7, 14, and 30 days). Measurements were performed using an Anton Paar rotational rheometer (CC27/S SN60412) at 25°C.

Table 1. Summary of results for formulations prepared using Lekobaza

Day	T	Ip	f	η $_{5s^{-1}}$	η $_{50s^{-1}}$	Ostwald-de Waele parameters		A
						K	p [-]	
Lekobaza + retinyl palmitate sol.								
1	+	123 ± 1.11	23.66 ± 4.61	13.5	2.4	37.3	0.32	6640
7	+	127 ± 1.68	23.46 ± 5.76	14.54	2.8	45.6	0.29	9771

14	+	127 ± 2.08	23.71 ± 4.95	14.2	2.3	40.6	0.28	6886
30	+	101 ± 1.88	23.79 ± 5.71	12.1	2.1	35.1	0.28	4983
Lekobaza + retinol								
1	+	104 ± 4.12	24.66 ± 5.44	18.8	3.68	59.2	0.29	6166
7	+	100 ± 2.24	23.28 ± 6.86	23.7	4.0	73.6	0.26	8531
14	+	112 ± 3.32	24.91 ± 5.95	22.1	3.7	64.2	0.28	6204
30	+	93 ± 1.59	23.29 ± 6.91	21.7	3.7	67.4	0.26	7057
Lekobaza + retinyl palmitate								
1	+	90 ± 2.34	24.46 ± 6.51	21.8	3.7	59.8	0.31	5789
7	+	101 ± 1.98	24.18 ± 6.46	22.0	3.7	65.8	0.28	5973
14	+	107 ± 1.54	24.38 ± 7.65	23.2	3.8	71.4	0.27	7420
30	+	96 ± 3.45	24.47 ± 6.31	24.8	4.1	76.8	0.26	6065
Lekobaza + sol. 20% ascorbic acid								
1	+	110 ± 3.34	23.86 ± 5.61	17.5	3.0	48.1	0.31	5537
7	+	115 ± 2.21	23.66 ± 7.31	18.8	3.1	51.9	0.3	4322
14	+	124 ± 1.54	23.78 ± 8.22	16.3	2.6	47.2	0.28	5217
30	+	113 ± 1.69	23.85 ± 6.31	19.8	3.5	59.5	0.29	8120

T – centrifugation test; + – positive; Ip – spreadability index (cm^2/g) $x10^3$ ± SDx10^3;f - mean droplet size (μm), $\eta_5 s^{-1}$— viscosity measured at a shear rate of 5 s^{-1} (Pa·s), $\eta_{50} s^{-1}$ — viscosity measured at a shear rate of 50 s^{-1} (Pa·s), K – consistency coefficient ($Pa \cdot s^n$), n - flow behavior index (-), A – thixotropy area (Pa·s)

Table 2. Summary of results for formulations prepared using Eucerin

Day	T	Ip	f	$\eta_5 s^{-1}$	$\eta_{50} s^{-1}$	Ostwald-de Waele parameters		A
						K	p [-]	
Eucerin + retinyl palmitate sol.								
1	+	110 ± 1.05	18.02 ± 3.41	11.8	3.0	32.7	0.38	10172
7	+	107 ± 1.28	18.03 ± 3.21	12.3	2.9	33.9	0.37	9704
14	+	118 ± 2.43	18.01 ± 3.51	11.2	2.4	30.3	0.36	5986
30	+	110 ± 2.56	18.12 ± 3.12	12.2	2.5	35.6	0.32	6421
Eucerin + Retinol								
1	+	97 ± 2.16	-	11.7	2.3	31.7	0.33	6265
7	+	103 ± 2.43	-	11.3	2.2	30.7	0.33	5769
14	+	114 ± 3.45	-	11.9	2.2	32.7	0.32	5709
30	+	104 ± 2.87	-	13.8	2.3	32.7	0.32	5700
Eucerin + retinyl palmitate								
1	+	88 ± 2.39	-	10.4	2.5	26.0	0.4	9445
7	+	109 ± 1.28	-	11.7	2.6	29.7	0.38	8727
14	+	137 ± 1.49	-	11.2	2.5	29.6	0.37	8267
30	+	125 ± 1.69	-	11.4	2.4	31.2	0.36	7652
Eucerin + sol. 20% ascorbic acid								
1	+	91 ± 1.79	2.52 ± 0.71	11.4	3.3	34.1	0.39	13187
7	+	92 ± 2.68	2.50 ± 0.67	14.2	3.3	41.6	0.35	11216
14	+	116 ± 4.68	2.42 ± 0.79	12.8	2.8	36.7	0.35	9493
30	+	109 ± 2.68	2.41 ± 0.67	12.1	2.6	37.0	0.33	8427

Legend as in Table 1

Table 3. Summary of results for formulations prepared using Versatile

Day	T	Ip	f	$\eta_5 s^{-1}$	$\eta_{50} s^{-1}$	Ostwald-de Waele parameters		A
						K	p	
Versatile + retinyl palmitate sol.								
1	+	94 ± 1.68	5.53 ± 1.43	16.6	2.8	58.1	0.22	5602
7	+	107 ± 2.24	4.47 ± 1.51	16.2	2.6	53.9	0.23	4363
14	+	94 ± 1.98	4.23 ± 1.78	10.9	1.9	36.7	0.25	2529
30	+	95 ± 2.65	4.48 ± 1.52	6.2	0.7	21.4	0.17	1706
Versatile + Retinol								
1	+	84 ± 4.43	6.64 ± 2.00	15.6	2.8	66.2	0.18	7527
7	+	105 ± 1.19	5.61 ± 1.87	17.6	2.7	61.6	0.2	6155
14	+	97 ± 2.21	7.04 ± 2.82	10.2	1.5	36.3	0.2	2707
30	+	103 ± 4.43	4.73 ± 1.87	17.8	2.6	56.1	0.24	4178
Versatile + retinyl palmitate								
1	+	94 ± 2.67	5.14 ± 1.74	19.6	2.5	69.8	0.17	3889
7	+	105 ± 3.67	4.25 ± 1.47	15.2	2.1	47.5	0.22	1013
14	+	100 ± 1.98	4.19 ± 1.36	16.4	2.3	50.5	0.23	2250
30	+	95 ± 2.73	4.48 ± 1.12	11.2	1.7	34.2	0.25	1020
Versatile + sol. 20% ascorbic acid								
1	+	106 ± 2.48	5.11 ± 1.83	15.3	2.6	50.3	0.24	3116
7	+	124 ± 4.81	4.61 ± 1.43	12.9	2.3	40.6	0.27	4598
14	+	120 ± 4.42	4.59 ± 1.42	15.4	2.4	49.1	0.24	3562
30	+	115 ± 1.54	4.53 ± 2.05	13.2	2.3	39.6	0.28	2508

Legend as in Table 1

Table 4. Summary of results for formulations prepared using Emolivan

Day	T	Ip	f	$\eta_5 s^{-1}$	$\eta_{50} s^{-1}$	Ostwald-de Waele parameters		A
						K	p	
Emolivan + retinyl palmitate sol.								
1	+	55 ± 1.02	20.16 ± 4.21	51.9	9.1	153.1	0.29	15963
7	+	51 ± 0.69	18.26 ± 3.44	43.4	8.0	120.6	0.32	10993
14	+	43 ± 1.11	17.47 ± 3.12	32.4	5.9	95.4	0.3	9576
30	+	49 ± 1.32	19.37 ± 3.10	44.4	8.0	122.9	0.31	14107
Emolivan + Retinol								
1	+	43 ± 1.91	20.66 ± 3.91	74.5	10.7	236.8	0.23	30307
7	+	41 ± 1.15	17.46 ± 2.86	78.0	10.7	251.3	0.2	27439
14	+	35 ± 0.89	17.19 ± 3.23	76.3	10.2	240.2	0.2	23791
30	+	37 ± 1.26	19.11 ± 3.41	63.0	8.8	195.7	0.21	12976
Emolivan + retinyl palmitate								
1	+	39 ± 1.53	18.68 ± 3.21	87.9	12.4	295.8	0.2	26921
7	+	34 ± 1.29	18.46 ± 3.23	73.4	11.6	233.0	0.24	24694
14	+	34 ± 1.98	17.84 ± 2.92	62.3	8.5	183.4	0.23	12540
30	+	37 ± 0.67	17.71 ± 4.37	49.4	7.9	139.0	0.29	6179
Emolivan + sol. 20% ascorbic acid								
1	+	36 ± 0.81	20.92 ± 3.91	95.4	16.9	417.6	0.16	45540
7	+	36 ± 0.89	18.47 ± 3.14	72.5	13.2	231.1	0.27	17912
14	+	32 ± 0.99	18.07 ± 3.01	87.0	14.6	332.2	0.19	48066
30	+	33 ± 1.05	18.61 ± 3.42	56.9	10.2	171.4	0.29	10022

Legend as in Table 1

Table 5. Summary of statistical analysis results for the size of dispersed phase droplets in the tested formulations

Formulation	Chi²	df	p	Kendall's W	Post-hoc significance
Lekobaza + retinyl palmitate sol.	20.61	3	0.001	0.068	1–7***/not significant
Lekobaza + retinol	5.74	3	0.125	0.019	not significant
Lekobaza + retinyl palmitate	3.25	3	0.354	0.011	not significant
Lekobaza + sol.20% ascorbic acid	10.4	3	0.015	0.035	1–7*/not significant
Eucerin + retinyl palmitate sol.	17.72	3	0.000	0.059	not significant
Eucerin + sol. 20% ascorbic acid	31.01	3	0.000	0.103	not significant
Emolivan + retinyl palmitate sol.	53.46	3	0.000	0.178	1–7***, 1–30***
Emolivan + retinol	90.86	3	0.000	0.303	1–7***, 1–14***, 1–30**
Emolivan + retinyl palmitate	162.58	3	0.000	0.542	1–7***, 1–14***, 1–30***
Emolivan + sol.20% ascorbic acid	38.21	3	0.000	0.127	1–7***, 1–14***, 1–30***
Versatile + retinyl palmitate sol.	95.45	3	0.000	0.318	1–7***, 1–14***, 1–30**
Versatile + retinol	53.46	3	0.000	0.178	1–7**, 1–30***
Versatile + retinyl palmitate	95.65	3	0.000	0.319	1–7***, 1–14***, 1–30**
Versatile + sol 20% ascorbic acid	40.48	3	0.000	0.135	1–7*, 1–14*, 1–30**

Explanation of post-hoc significance symbols (Wilcoxon test): *** $p < 0.001$ – highly significant difference; ** $p < 0.01$ – significant difference; * $p < 0.05$ – moderately significant difference; no star – not statistically significant ($p \geq 0.05$).

3. Results

All tested formulations passed the centrifugation test positively on day 1 after preparation. No signs of phase separation were observed. During further testing (up to day 30), none of the creams prepared using commercial bases (Lekobaza, Eucerin, Emolivan, Versatile) showed phase separation in the centrifugation test. The absence of phase separation indicates their stability and appropriate structure [28, 30].

The mean diameters of dispersed phase droplets in freshly prepared emulsions depended on the type of base used. For O/W bases such as Lekobaza, the average droplet size was approximately 20 µm, while for Versatile, it was about 5.5 µm. In formulations prepared on Eucerin —i.e., with retinyl palmitate sol. the droplet size was around 18 µm, and for the formulation with a 20% ascorbic acid solution, it was ~2.5 µm. In Eucerin based preparations with retinol or retinyl palmitate, no distinct dispersed phase was observed, as the lipophilic substances dissolved in the lipophilic base, forming a single-phase system. Therefore, droplet size analysis was not performed for these formulations. In the case of the Emolivan base, a W/O emulsion, the droplet size of the aqueous phase was approximately 20 µm for all tested formulations.

Statistical analysis of the droplet size in the dispersed phase revealed some discrepancies. The Friedman test showed statistically significant differences between time points in most of the tested systems. Non-significant results were obtained for Lekobaza with retinol and Lekobaza with retinyl palmitate, with p-values of 0.125 and 0.354 respectively (significance level $\alpha = 0.05$). In these cases, the absence of significant changes in droplet size over time indicates high physical stability. These systems maintained stable droplet sizes throughout the 30-day observation period, confirming good physical stability.

For the remaining formulations, the Friedman test indicated statistical significance ($p < 0.05$), suggesting changes in droplet size over time. However, the strength of the rank-order relationship, assessed using Kendall's coefficient, was low to moderate in many cases ($W < 0.2$), indicating slight changes of limited practical significance. An exception was the Emolivan system with retinyl palmitate ($W = 0.542$), which showed a strong and systematic decrease in droplet size over time, potentially indicating a distinct emulsification stabilization process.

These analyses made it possible to identify specific days between which statistically significant differences occurred. Table 5 highlights the time points where significant differences in droplet size were noted. Most commonly, significant differences were observed between day 1 and day 7. These typically reflected a reduction in droplet size within the first week of storage, indicating an early stage of stability loss. Differences between day 1 and day 14 suggest a progressive change continuing over time. In the Emolivan + retinyl palmitate and Emolivan + retinyl palmitate sol., these changes were particularly pronounced and statistically strong, indicating a substantial reorganization of the emulsion structure in the second week. Differences between day 1 and day 30 for Versatile + retinol and Versatile + 20% ascorbic acid solution were more distinct than at earlier time points, suggesting ongoing destabilization. A particularly strong and systematic decrease in droplet size was observed in the Emolivan + retinyl palmitate system, confirmed by extremely low p-values ($p < 0.000001$) in all pairwise day comparisons. It should be noted that advanced techniques for droplet-size distribution analysis, such as laser diffraction (LD) or dynamic light scattering (DLS), were not employed in this study. Nevertheless, the applied microscopic evaluation provided a reliable assessment of physical changes over time and enabled the detection of possible coalescence in the tested emulsions, which was the main objective of the work.

The spreadability coefficient (Ip), expressing the surface area covered by 1 g of cream under load, varied noticeably depending on the cream base used. The best spreadability was observed for creams prepared on Lekobaza. They exhibited desirable sensory properties, including smooth application and high spreadability. Similarly, the Versatile-based cream demonstrated a high Ip, indicating ease of spreading. The poorest spreadability was noted in creams prepared with Emolivan and Eucerin. These had the lowest Ip values among all tested creams. This results from the nature of these bases—O/W emulsions (Lekobaza, Versatile) are inherently easier to spread and absorb quickly, while W/O (Eucerin, Emolivan) formulations form a lasting lipophilic film on the skin.

Ip values were measured on days 1, 7, 14, and 30. Changes in the spreadability coefficient over time were minimal, indicating the preservation of consistent texture in these formulations [30]. The creams did not undergo noticeable liquefaction or thickening during storage at 2–8°C over the testing period.

All tested creams exhibited pseudoplastic flow behavior (flow index $n < 1$). No yield stress was observed, indicating that they will dispense easily from the packaging and spread well on the skin [29, 30]. Thixotropy was recorded for the tested formulations; the area between the upward and downward shear stress curves indicated a reversible breakdown of structure under shear, meaning that the creams temporarily liquefy during application (e.g., during spreading) and gradually return to their original consistency after the stress is removed.

Analysis of rheological parameters over time confirmed high stability of preparations made on Lekobaza and Eucerin. The consistency coefficient K and the flow index n for these preparations remained relatively unchanged from day 1 to day 30. No decreases in apparent viscosity were observed, indicating that the structure of these preparations did not undergo significant degradation.

Formulations based on dermocosmetic bases behaved differently. In the case of Versatile, two formulations—with retinyl palmitate and with retinyl palmitate sol. —showed a systematic decrease in viscosity over time. The K value for the Versatile base with retinyl palmitate decreased from approximately 58 Pas to 21 Pas over 30 days, and for the Versatile base with retinyl palmitate sol., from approximately 70 Pas to 34 Pas, with the most marked changes observed between days 14 and 30. This suggests that rheological properties remained stable during the first two weeks, but began to degrade after longer storage, as reflected by a decline in viscosity. The 14-day mark appears to be the stability threshold for these formulations, which aligns with the shelf-life recommended by pharmacopeias for compounded topical preparations [4].

Emolivan with ascorbic acid solution and Emolivan with retinyl palmitate displayed rheological anomalies from day 1 of testing. Viscosity measurements were highly scattered, varied between replicates, and K and n values fluctuated erratically. It was observed that immediately after measurement, under high shear rates, samples lost homogeneity and visible textural changes occurred. This led to inconsistent rheological readings and lack of repeatability, indicating reduced physical stability of these two formulations. It is presumed that the strongly acidic environment in the ascorbic acid formulation destabilized the system either through reactions with emulsion components or by altering the properties of thickeners in the base. This is supported by literature reports on the impact of low pH on certain W/O emulsions [20, 22]. In contrast, Emolivan formulations with retinol and with retinyl palmitate sol. remained stable in terms of K and n values.

4. Discussion

The obtained results confirm how crucial the choice of cream base is for the physical stability of preparations containing vitamins A and ascorbic acid ~~C~~. Differences in the composition and characteristics of the bases affected the aging process of the studied emulsions. Recent findings by Majchrzak et al. [38] demonstrated that the physicochemical properties and stability of emulsions depend not only on the antioxidant form but also on the nature of the continuous phase. Their study showed that emulsions containing hydrophilic ascorbic acid and lipophilic ascorbyl palmitate exhibited uniform droplet sizes (~200 nm) and negative zeta potential values below −30 mV, indicating good kinetic and electrostatic stability. The authors also observed that the addition of dextrose increased viscosity and improved internal structural integrity, which contributed to enhanced emulsion stability. These findings are in agreement with our observations, where the type of base significantly affected viscosity and droplet size behavior over time, confirming that both compositional and physicochemical parameters play a crucial role in maintaining physical stability in vitamin-containing emulsions. The traditional pharmaceutical bases, Lekobaza and ~~Eucerya~~ Eucerin proved to be highly effective in maintaining the physical stability of creams with these sensitive and formulation-challenging vitamins. Lekobaza, as an O/W emulsion, ensured good physicochemical compatibility with both retinoids and ascorbic acid. Its hydrophilic nature facilitated even dispersion of ingredients and maintenance of homogeneity. No destabilization or deterioration of application properties was observed in creams based on Lekobaza, even after 30 days of storage, and the low Kendall's coefficient ($W < 0.2$) recorded during statistical analysis suggests that despite minor variations in droplet size, the system remained stable. The absence of a mechanical homogenizer may have contributed to minor variations in droplet size [37]; however, this reflects the practical conditions of manual compounding in a pharmacy setting, where such equipment is not routinely used.

Eucerin, a classic absorption base forming a W/O emulsion, guaranteed satisfactory stability across all formulations. Its high water absorption capacity [6] enabled permanent binding of aqueous solutions. The limited amount (3%) of aqueous ascorbic acid solution allowed the lanolin alcohols to maintain stability despite the lowered pH. Additionally, Eucerin, being a W/O emulsion, protected ascorbic acid from oxygen exposure, which aligns with literature data indicating that W/O emulsions provide better protection of ascorbic acid against oxidation than O/W emulsions [22]. This confirms that hydrophobic W/O bases are often an optimal choice for oxidation-sensitive vitamins. Restricted access to water and oxygen supports the stability of both retinoids [25, 26] and ascorbic acid [22, 25]. Retinol and retinyl palmitate, being lipophilic ingredients, dissolved in the base, forming ointments without a visible dispersed

phase, thus eliminating the risk of coalescence and ensuring system stability.

The modern dermocosmetic bases used to prepare the formulations turned out to be less effective in ensuring long-term physicochemical stability. The Versatile base initially provided excellent physical parameters, such as fine dispersion of the internal phase, light texture, and good spreadability. For the first two weeks of storage, formulations based on Versatile were stable. However, extending the storage period to 30 days revealed a progressive breakdown of structure. Particularly, Versatile with retinyl palmitate and with solubilized vitamin A showed significant decreases in viscosity, indicating emulsion degradation. It can be assumed that the contact of lipophilic vitamin A with the aqueous continuous phase of the base contributed to the gradual destabilization of the emulsion. Although these decreases were substantial, they occurred only after about two weeks, which often corresponds to the maximum recommended usage period for compounded preparations with sensitive ingredients [4].

None of the creams based on Emolivan showed phase separation during the 30-day study. However, rheological tests revealed that under shear stress, applied during rheological measurement, the structural integrity of the formulation was compromised. This effect was observed in the formulation with retinyl palmitate. It is possible that the oily concentrate was not fully evenly distributed in the thick base without stronger mixing. Literature emphasizes that the homogenization process is crucial for the stability of emulsions, as it reduces particle size and prevents phase separation [37].

There is no universal ideal base for vitamins A (retinol, retinyl palmitate and retinyl palmitate sol.) and ascorbic acid. Traditional pharmaceutical bases such as Lekobaza and Eucerin enable the development of more stable dermatological formulations. New dermocosmetic bases, although more convenient in use and more appealing sensorially, may require an individualized approach when incorporating vitamins [1]. The results for Versatile and Emolivan demonstrate that the addition of ingredients such as retinoids or ascorbic acid may necessitate formulation adjustments, e.g., the use of buffers to control the pH of ascorbic acid emulsions [22, 23], addition of antioxidants [24, 25], or avoiding mixing solubilized vitamin A with W/O bases [14, 17].

Emolivan may be a valuable base for retinoids, mainly due to its W/O emulsion structure, which promotes retinol penetration into the skin and limits its oxidation. In this study, the highest physical stability was observed in formulations containing retinyl palmitate sol. In contrast, the Versatile base, although it offered favorable sensory characteristics for 14 days, did not maintain long-term stability in formulations containing retinyl palmitate in oily form or ~~vitamin C~~ ascorbic acid solution.

In the case of solubilized vitamin A, combining it with an O/W-type base (e.g., Versatile or Lekobaza) is most advisable, as the additional surfactants present in solubilizates may destabilize W/O emulsions such as Emolivan or Eucerin. The obtained results clearly indicate that the stability of preparations containing different forms of vitamin A and ~~vitamin C~~ ascorbic acid largely depends on the type of base used. Traditional pharmaceutical bases, such as Lekobaza (O/W) and Eucerin (W/O), provided the highest physical stability for both lipophilic forms of vitamin A (retinol and retinyl palmitate) and aqueous solutions of ascorbic acid. The modern Versatile base (O/W) demonstrated good usability and initial stability, but the formulations deteriorated after 14 days, limiting its use to short-term therapy. Emolivan (W/O), in turn, proved effective only in selected systems with retinol and retinyl palmitate sol. but did not maintain stability for retinyl palmitate and ascorbic acid solution, confirming the need for careful selection of ingredients for this type of base.
Recent studies indicate that the stability of emulsions depends not only on viscosity and droplet size distribution but also on dynamic interfacial phenomena occurring during droplet formation and collision. The diffusion and adsorption of emulsifiers, as well as factors such as temperature and pH, determine the rate of coalescence and the overall physical stability of emulsion systems.
The development of new technologies, such as microfluidic systems, enables more precise examination of these parameters, providing new insights into the mechanisms of emulsion destabilization and supporting the optimization of formulation composition [39].

5. Conclusions

The selection of an appropriate base and correct preparation technique is essential to obtain a physical stable formulation containing vitamin A (retinol, retinyl palmitate and retinyl palmitate sol.) or ~~C~~ ascorbic acid.

The Lekobaza base (O/W) provides the highest physical stability for preparations with retinol, retinyl palmitate and retinyl palmitate sol. or ascorbic acid.; in all tested formulations, no changes in consistency or phase separation were observed during 30 days of storage.

The Eucerin base (W/O) is a physical stable carrier for retinol, retinyl palmitate, and ascorbic acid. All Eucerin - based formulations remained homogeneous and maintained their rheological properties throughout the 30-day study period.

The Versatile base (O/W) ensures the physical stability of creams with vitamins for up to 14 days. However, after 30 days, signs of destabilization (decrease in viscosity, partial loss of thixotropy) were observed, particularly in the presence of lipophilic forms of vitamin A.

The Emolivan base (W/O) was stable for 30 days in creams containing retinol and retinyl palmitate sol. However, in formulations with a 3% ascorbic acid 20 % solution and with retinyl palmitate, structural destabilization symptoms were observed as early as day 7.

Abbreviations:

O/W – oil-in-water

W/O – water-in-oil

GAGs - glycosaminoglycans

RAR/RXR -retinoic acid/rexinoid receptors

IU – international unit

sol. – solution

Ip – spreadability index

SD – standard deviation

η – dynamic viscosity

K – consistency coefficient

n – flow behavior index

f - ~~average~~ mean droplet size

A - thixotropy area

LD – laser diffraction

DLS - dynamic light scattering

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