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Influence of Technological Parameters on the Size of Benzocaine Particles in Ointments Formulated on Selected Bases

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Abstract: Compounding formulations, including semi-solid medication forms, must meet criteria related to specific stability and quality, during a period of their use. In suspension-type ointments, one of the criteria for assessment of their correct manufacturing is particle size, which in the compounding preparation cannot exceed 90 µm. An appropriate level of particle disintegration can be achieved via a selection of technological parameters and qualitatively compatible excipients. In this study, benzocaine ointments were prepared using a levigation process. The time of its application on the particle size of API in suspension ointments was evaluated. In parallel, the effect of mixing parameters and the co-solvent used on the precipitation of active substance crystals in emulsion ointments during the storage of these formulations for 28 days was investigated. Forty suspension and emulsion ointments were prepared using selected ointment bases: Pentravan®, Lekobaza, Lekobaza LUX, Eucerin Ointment I, Nourivan™ Antiox, Fitalite™, containing 2% benzocaine. Based on the results of the stability test, four formulations were selected to study the release kinetics of benzocaine *in vitro*. These formulations were characterized by the rate of release consistent with the Higuchi model, and the fastest rate of release occurred from the Eucerin-based emulsion ointment.

Keywords: benzocaine; particle size; ointments; levigation process; suspension ointment; emulsion ointment; mixing in a recipe mixer; stability of semi-solid formulations; grinding in a mortar; *in vitro* release

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1. Introduction

Semi-solid formulations represent one of the most commonly prescribed compounding drug substances in Poland [1]. Similarly to all other medical products, they should fulfil some specific requirements of stability and quality, during their use by a patient. These parameters are dependent on, among others, the type and quality of the utilized raw materials, drug substances manufacturing technique, as well as appropriate storing and application of the medical product.

In the compounding practice, various types of ointments can be encountered that represent multiphase formulations, in which an active substance is disintegrated, suspended or dissolved in the base. In particular, suspension-type ointments are characterized by the highest stability, compared to some other dispersive systems [2]. In such formulations, particle size cannot exceed 90 µm, so the introduction of an active substance into the base often requires its proper grinding, which can be achieved using a levigation [3]. The grinding process is facilitated by the addition of small amounts of a levigating liquid (*e.g.*, liquid paraffin, glycerol, or melted base), which wets the ground solid particles and thus facilitates even mixing with the base and prevents possible secondary reaggregation. It is also acceptable to use, instead of the levigating liquid, some small amounts of base, considering that it is plastic.

In addition, applied excipients—and in particular, a base—have a crucial impact on the stability of the manufactured compounding drug substances. During storage, hydrophilic

bases are often at risk of a gradual loss of solvents that can influence changes in the consistency of the formulation and may lead to the precipitation of crystals of the active pharmaceutical ingredient (API). Lipophilic bases are sensitive to oxidation, particularly the ones that contain fats with unsaturated carbon bonds.

Pentravan® as a hydrophilic base is a new cream-like basis of emulsion type (oil-in-water, o/w) that has transdermal properties, due to the presence of liposomes [4,5]. In addition, relatively new hydrophilic bases include Fitalite™—based on a hydrogel structure [6], and Nourivan™ Antiox—which is a cream-like base, containing emulsifiers, type o/w, and emollients [7].

Lekobaza LUX is a lipophilic base, based on oleogel [1]. Eucerine is an ointment base that is most often used in compounding formulations in Poland, due to its absorptive properties. It contains an emulsifier of the water in oil (w/o) type and creates stable emulsions after hydration [8]. In Monography of Polish National Pharmacopeia (FP) XII, this base is differentiated into Eucerin Ointment I, which contains alcohols from lanoline, and Eucerin Ointment II, which is a cholesterol-cethyl ointment [9].

Benzocaine is a local anaesthetic used in the treatment of pain and belongs to the ester class of local anaesthetics [10]. Its mechanism of action is shown in Figure 1. The interactions of the nonionized and ionized forms of benzocaine are associated with blocking the permeation of sodium ions within the voltage-gated sodium channels [11]. Nerve conduction arrest is easier in nerve fibres without a myelin sheath than in fibres with a myelin sheath. First, the sensation of pain is eliminated, followed by the sensation of temperature, touch and pressure.

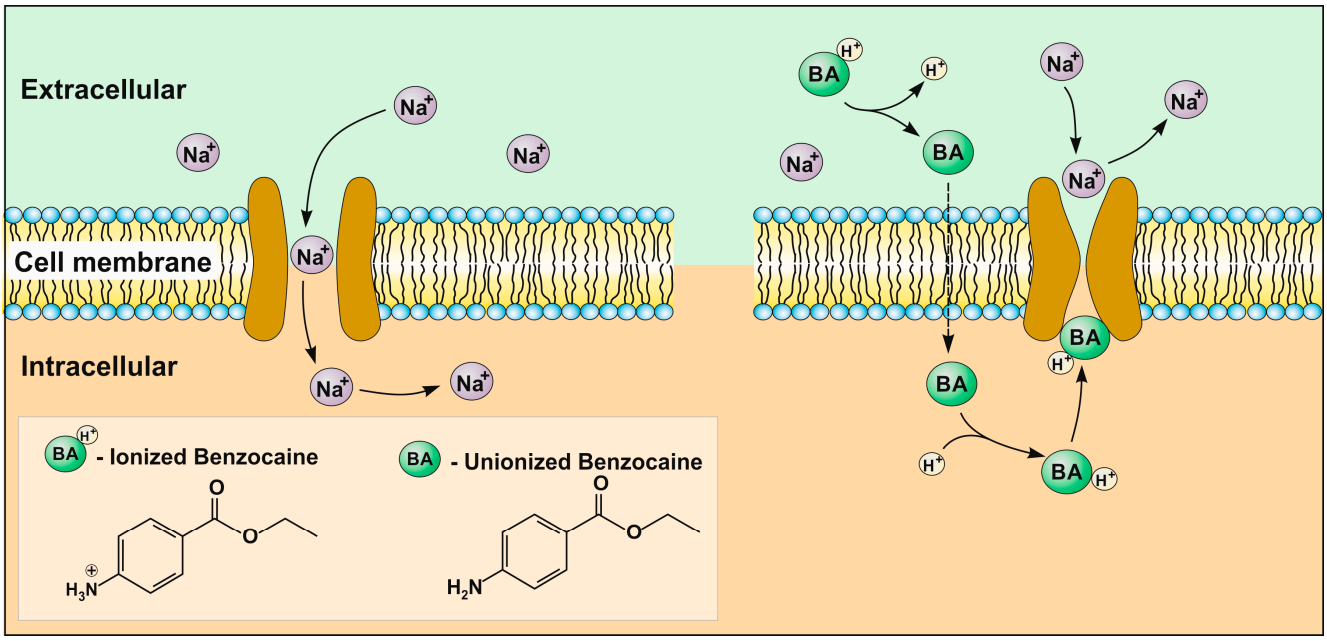

Figure 1. A mechanism of action of benzocaine.

Benzocaine is an anaesthetic, widely applied in numerous medical and surgical subspecialities, such as ophthalmology, otorhinolaryngology, dentistry, and urology [12–17]. It is used in spray form, liquid, creams, gels, and throat lozenges [12,18,19]. When applied topically, it is classified as a low-risk drug, although some patients may experience allergic reactions [20–22]. Overdose of these oxidizing agents may lead to methemoglobinemia [23–26]. Benzocaine spray is the most commonly reported formulation to cause methemoglobinemia. Due to differences in absorption and metabolism, it should be used with caution, especially in children and the elderly. Its topical use is not recommended in patients with deep wounds, lesions, or severe burns.

Due to its low solubility in water (1 part of benzocaine to 2500 parts of water), and good penetration of the skin barrier, it is mostly used as a local anaesthetic, which can be applied on the skin in the form of suspension or ethanol solution (1 part of benzocaine is dissolved in 8 parts of ethanol 96○ [27,28]. The Polish Pharmacopoeia XII recommends the external use of benzocaine, in concentrations of 1.0–3.0%—for solutions, and up to 10%—for ointments [9]. In compounding formulations, it is commonly recommended to prepare benzocaine on hydrated ointments, or rarely—on a water-free basis. Most often, benzocaine is prescribed in combination with Eucerine or Soft paraffin: yellow, white, and hydrophilic [28]. As a raw material *pro receptura,* it is available in form of relatively large crystals (up to a few mm in diameter).

In this study, we analyzed the effects of using levigation, and the time of its application on the size of benzocaine particles, in suspension-type ointments. Simultaneously, we examined the influence of mixing parameters, and the applied solvent on the precipitation of crystals of the active substance in the emulsion-type ointments, during storing process of these formulations, for a four-week time period. For the formulation of semi-solid forms of the API, the traditional bases most frequently prescribed by physicians were selected: Eucerin I ointment (hydrated lipophilic base), Lekobaza LUX (absorbent lipophilic base), and Lekobaza (amphiphilic base). In addition, new bases undergoing research were also used, i.e., multicomponent bases (Fitalite™, Nourivan™ Antiox) and Pentravan®, which enables deeper penetration of the active substance [29–32].

Technological solutions have been sought for the preparation of the ointments of suspension or emulsion type for individual patient needs that are stable not only on the day of formulation. The set goal of the study was carried out by organoleptic analysis of changes in the formulations of the prescription drug, the evaluation of the selection of partial technological processes during their preparation: the method of introducing substances into the bases, the mixing parameters used and their impact on the durability and quality of the obtained formulations.

2. Materials and Methods

2.1. Materials

Pentravan® (Fagron, Cracow, Poland)—an oil-in-water emulsion base (o/w), ingredients: cetyl alcohol, stearyl alcohol, butylhydroxytoluene, EDTA, glycerol monostearate, carbomer 980, benzoic acid, sorbic acid, potassium sorbate, hydrochloric acid, hydrochloric acid 35% v/v, stearic acid 50, soy lecithin, isopropyl myristate, urea, simethicone, polyoxyethylene stearate, purified water; Nourivan™ Antiox (Fagron, Olomouc, Czech Republic)—an oil-in-water emulsion base (o/w), ingredients: purified water, cetearyl alcohol, polysorbate 60, C13–C16 isoparaffin, C12–C14 isoparaffin, C13–C15 alkane, glyceryl stearate, PEG-75 stearate, polyacrylate 13, polyisobutate, polysorbate 20, polyurethane-39, stearyl behenate, cetyl alcohol, ascorbic acid, benzoic acid, sodium bisulfite, sorbic acid, tocopheryl acetate); Fitalite™ (Fagron, Olomouc, Czech Republic)—a hydrophilic gel-cream base, ingredients: purified water, safflower oleosomes, polyacrylate 13, polyisobutene, polysorbate 20, benzoic acid, sodium carbomer, sorbic acid, tocopheryl acetate; Lekobaza (Pharma Cosmetic, Cracow, Poland); Lekobaza LUX (Pharma Cosmetic, Cracow, Poland); Eucerin Ointment I (Pharma Cosmetic, Cracow, Poland); benzocaine (Pharma Cosmetic, Cracow, Poland); and ethyl alcohol 96% v/v (Avantor Performance Materials, Gliwice, Poland). All materials used in the study were of the analytical grade and satisfy the requirements of standards and certificates.

2.2. Methods

2.2.1. Formulation of the Ointment

Ointment formulations with benzocaine (2% wt/wt) were prepared on a total of six ointment bases, including three new, multiphase (Pentravan®, Nourivan™ Antiox, and Fitalite™) and three known (Lekobaza, Lekobaza LUX, and Eucerin Ointment I) used in pharmacies, using the prescription mixer (Unguator® E/S; Gako GmbH, Scheßlitz,

Germany). Benzocaine was introduced into the base in two combinations: by grinding it in a mortar with an equivalent small amount of the base (levigation) or by dissolving it in ethanol.

Formulation of ointments of the suspension type

The composition of suspension-type ointments and their methods of formulation are shown in Table 1.

Table 1. The composition of suspension-type ointments with benzocaine and technical parameters of their preparation methods.

Formulation Code	Qualitative Composition of Prepared Ointment		Technical Parameters	
			Time Levigation (min)	Unquator: Mixing Time (min); Agitator Rotation (rpm)
P-1	Pentravan®	Benzocaine	1.5	2; 1260
P-2	Pentravan®	Benzocaine	1.5	4; 1630
P-3	Pentravan®	Benzocaine	5.0	2; 1260
P-4	Pentravan®	Benzocaine	5.0	4; 1630
P-5	Pentravan®	Benzocaine	10.0	2; 1260
P-6	Pentravan®	Benzocaine	10.0	4; 1630
P-7	Pentravan®	Benzocaine	15.0	2;1260
P-8	Pentravan®	Benzocaine	15.0	4; 1630
L-9	Lekobaza	Benzocaine	5.0	2; 1260
L-10	Lekobaza	Benzocaine	5.0	4; 1630
L-11	Lekobaza	Benzocaine	10.0	2; 1260
L-12	Lekobaza	Benzocaine	10.0	4; 1630
L-13	Lekobaza	Benzocaine	15.0	4; 1630
LLux-14	Lekobaza LUX	Benzocaine	5.0	2; 1260
LLux-15	Lekobaza LUX	Benzocaine	5.0	4; 1630
LLux-16	Lekobaza LUX	Benzocaine	10.0	2; 1260
LLux-17	Lekobaza LUX	Benzocaine	10.0	4; 1630
LLux-18	Lekobaza LUX	Benzocaine	15.0	4; 1630
E-19	Eucerin Ointment I	Benzocaine	-	2; 1260
E-20	Eucerin Ointment I	Benzocaine	-	4; 1630
E-21	Eucerin Ointment I	Benzocaine	5.0	2; 1260
E-22	Eucerin Ointment I	Benzocaine	5.0	4; 1630
E-23	Eucerin Ointment I	Benzocaine	10.0	2; 1260
E-24	Eucerin Ointment I	Benzocaine	10.0	4; 1630
N-25	Nourivan™ Antiox	Benzocaine	1.5	2; 1260
N-26	Nourivan™ Antiox	Benzocaine	1.5	4; 1630
F-27	Fitalite™	Benzocaine	1.5	2; 1260
F-28	Fitalite™	Benzocaine	1.5	4; 1630

Formulations in the form of suspensions were obtained after grinding the drug substance in a mortar with an equivalent amount of the vehicle. Various grinding times were used in the levigation process: 1.5, 5, 10, and 15 min. The remaining amount of the base

was added in portions to the thus obtained benzocaine concentrate and thoroughly mixed until a homogeneous consistency was obtained. Then the whole was transferred to the container, which was mounted in the Unguator® and the appropriate mixing parameters were set: mixing time/agitator rotation, respectively: 2 min/1260 rpm or 4 min/1630 rpm.

Formulation of emulsion-type ointments

Benzocaine was dissolved in ethanol 96% in a ratio of 1 to 8. After the API was completely dissolved, the solution was added to a container with a pre-weighed base. The whole was homogenized in a recipe mixer, setting the parameters described above.

The compositions of the emulsion ointments and the methods of their formulation are presented in Table 2.

Table 2. The composition of emulsion ointments with benzocaine and technical parameters of their formulation methods.

Formulation Code	Qualitative Composition of Prepared Ointment			Technical Parameters
				Unquator: Mixing Time (min); Agitator Rotation (rpm)
P-E-29	Pentravan®	Benzocaine	Ethanol	2; 1260
P-E-30				4; 1630
L-E-31	Lekobaza	Benzocaine	Ethanol	2; 1260
L-E-32				4; 1630
LLX-E-33	Lekobaza LUX	Benzocaine	Ethanol	2; 1260
LLX-E-34				4; 1630
E-E-35	Eucerin Ointment I	Benzocaine	Ethanol	2; 1260
E-E-36				4; 1630
N-E-37	Nourivan™ Antiox	Benzocaine	Ethanol	2; 1260
F-E-39	Fitalite™	Benzocaine	Ethanol	2; 1260
F-E-40				4; 1630

2.2.2. Visual Inspection of Formulation Appearance

The organoleptic evaluation was carried out by applying a small amount of the test formulations to the watch glasses. The changes in colour, consistency, and, after 15 min, also in their smell were examined.

2.2.3. Stability Studies of Semi-Solid Formulations

The ointments were stored in polyethylene containers at a temperature of 20 –22 °C for 4 weeks. Throughout this period, visual changes were observed weekly and the particle size of the drug substance was checked.

Particle size observation

In order to test the stability of the formulated semi-solid preparations, the particle size of benzocaine in the collected samples was measured at the following time intervals: immediately after preparation and after 1, 2, 3 and 4 weeks of storage. Ointment samples were applied to a slide and spread evenly with a coverslip. All microscopic images were observed with an MT4300H microscope (Meiji Techno Co., Saitama, Japan) at a magnification of 500×. The particle size was measured using Motic Image Plus 2 (Meiji Techno Co., Saitama, Japan) software intended for capturing images from the microscope. Then, 100 particles from different fields of view were measured in each sample. At the end of each week, the ointment samples were examined for any changes in physical state, appearance, and particle size.

The formulations selected for further testing were P-6, P-E-30, E-24, and E-E-36, for which no changes in colour, consistency, odour, or phase separation were observed and the API content was within 90% of the initial value [33].

2.2.4. Viscosity Measurement

Lamy RM 200 Touch rotational rheometer (Lamy Rheology Instruments, Champagne au Mont d'Or, France) equipped with the MK-CP 2445 measurement system and the CP-1 Plus laboratory thermostat was used for viscosity testing. Viscosity measurements were carried out at a temperature of 32.0 ± 0.5 °C with two shear rates of 500 s^{-1} and 900 s^{-1}.

2.2.5. *In Vitro* Release Studies

Dissolution studies of benzocaine from selected ointments (P-6, P-E-30, E-24, E-E-36) were carried out by using a standard paddle Erweka DT 600 Dissolution Apparatus (ERWEKA GmbH, Langen, Germany) with a 500 mL dissolution medium at 32 ± 0.5 °C and 50 rpm for 360 min. As dissolution media, a mixture of phosphate-buffered saline (PBS), pH 7.4 with 96% ethanol, in a ratio of 80:20 v/v was used. The excess ointment was placed in a cavity located at the base of the extraction chamber. The surface of the ointment was smoothed with a spatula, its excess was removed, and then the loaded amount of ointment was precisely determined by weight. A pre-wetted regenerated cellulose membrane Spectra/Por®2 Dialysis Membrane MWCO: 12–14 kDa, imitating the skin barrier (Fisher Scientific, Loughborough, UK) was placed on top of the ointment. At appropriate time intervals, 3 mL aliquots were collected with the replacement of equal volumes of temperature-equilibrated media filtered through a 0.45 µm membrane filter. The amount of released drug was determined using a UV-VIS Cecil CE 3021 spectrophotometer (Cecil Instruments Limited, Cambridge, UK) by monitoring the absorbance at λ max = 289.5 nm. The concentrations of benzocaine in samples were determined according to the standard curves of the drug solution: y = 0.1023x − 0.0075, R = 0.999. The release profiles were made based on obtained results.

In order to evaluate them, the model-independent method of similarity and difference was used [34].

The dissolution profiles of the benzocaine ointment were compared using the coefficient of similarity (f_2):

$$f_2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{J-1}^{n}|R_t - T_t|^2\right]^{-0.5} \times 100\right\}$$

where n is the number of dissolution time points, and R_t, and T_t are the released value of the reference and the test batch at time t, respectively.

Dissolution profiles of test samples were considered similar to those of the reference samples if $f_2 > 50$.

Kinetics Calculations

The release results were fitted with different kinetics models such as zero order (% benzocaine release vs. time), first order (log of % benzocaine remaining vs. time), Higuchi's model (% benzocaine release vs. square root of time) and the Korsmeyer–Peppas model (log of % benzocaine release vs. log time). For each model R^2 values were calculated.

2.2.6. Statistical Analysis

Statistical analyses were performed with the use of Statistica 13.0 software (STATSOFT; Statistica, Tulsa, OK, USA). Data were shown as mean (M) with standard deviation (SD). The ANOVA Kruskal–Wallis test for many independent variables was performed. A statistical significance level—$p \leq 0.05$ was established.

3. Results and Discussion

3.1. Visual Inspection of Formulation Appearance

The prepared ointments were characterised by the colour, smell, and consistency of the base on which they were made. The formulations ranged in colour from snow white (Lekobaza) through a shade of pink (Lekobaza Lux) to beige in comparison to Nourivan™ Antiox. When benzocaine was ground with Lekobaza Lux, a colour change from white to pink was observed, the intensity of which increased slightly with the time of grinding the medicinal substance. Formulations made on Nourivan™ Antiox showed a tighter consistency. In benzocaine formulations made on Nourivan ™ Antiox and Fitalite ™ bases, with different mixing parameters, subtle differences in shades of freshly prepared formulations were observed.

A 28-day observation of possible changes in colour and consistency of the samples, revealed the phase separation of formulations LLX-E-33 and LLX-E-34, obtained by combining benzocaine dissolved in ethanol and emulsifying it into Lekobaza LUX (Figure 2). In these formulations, there was a persistent and distinct emulsion phase separation. Separation of liquid and lumpy substance was observed (Table 4).

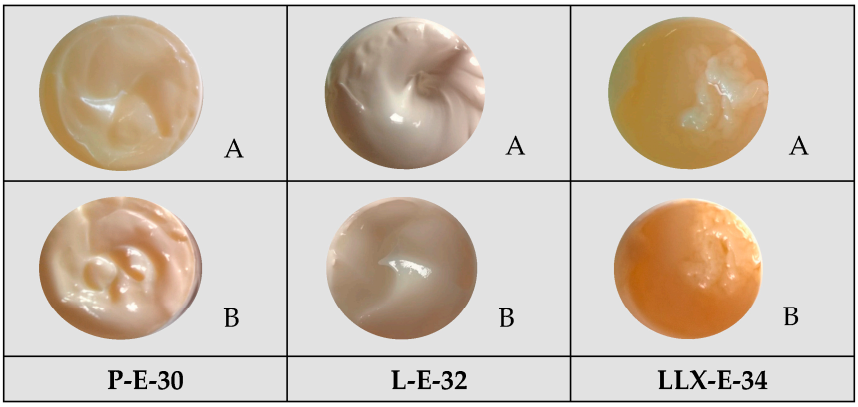

Figure 2. Pictures of selected ointments with benzocaine—after preparing them (**A**) and after 28 days (**B**).

In the other formulations, the visual changes observed during storage were related to subtle differences in the shades of ointment colour depending on the mixing parameters used. Benzocaine ointments mixed more intensively in Unguator® with *Ung*. Eucerini I became more transparent and lost its whitish colour. At the same time, no colour change was observed in ointments made on Lekobaza after 4 weeks of the study.

3.2. Stability Studies of Semi-Solid Formulations

Tables 3 and 4 show the particle size values observed under the microscope immediately after formulation, and then, after 28 days (particle observations had been made at 7-day intervals). The observed changes after the four weeks were shown in the tables: Tables S1–S6.

Among the different bases analysed in our study, Eucerin Ointment I is a popular compounding basis recommended for formulations with benzocaine [27]. For this reason, this base was selected to prepare our exemplary suspension-type ointments, without using the levigation process.

Table 3 shows the particle size distribution of API in suspension-type formulations. Microscopic observations of the E-19 and E-20 formulations showed that prior levigation of benzocaine is necessary before its introduction to the base because the obtained formulations included benzocaine particles that exceeded the allowed size more than 2.5 times. As shown in Table 3, the size of API particles in the formulations of Eucerin Ointment I, after levigation, decreased significantly ($p \leq 0.05$). In addition, no particles with a diameter of >90 µm were found.

Table 3. Change in benzocaine particle size in suspension-type ointments depending on the used base and storage time.

Formulation Code	Time (Days)	Percentage of Individual Benzocaine Particles in the Sample (%)				$p \leq$
		<30 μm	31–60 μm	61–90 μm	>91 μm	
P-1	after preparation	72.50 ± 0.67	16.83 ± 0.83	9.00 ± 0.67	1.67 ± 0.78	
	28	58.83 ± 0.56 *	25.00 ± 0.67 *	7.83 ± 0.56 *	8.33 ± 0.44 *	0.01
P-2	after preparation	78.33 ± 0.67	19.67 ± 0.78	2.00 ± 0.67	0.17 ± 0.28	
	28	62.33 ± 0.78 *	23.67 ± 1.11 *	9.33 ± 1.00 *	4.67 ± 1.33 *	0.01
P-3	after preparation	82.17 ± 1.22	16.17 ± 0.61	1.67 ± 0.78	0.00 ± 0.00	
	28	69.83 ± 2.22 *	24.67 ± 1.00 *	5.50 ± 1.50 *	0.00 ± 0.00	0.01
P-4	after preparation	9.83 ± 1.22	6.00 ± 1.00	2.00 ± 1.00	0.00 ± 0.00	
	28	75.33 ± 1.00 *	20.00 ± 0.67 *	4.50 ± 1.50 *	0.00 ± 0.00	0.01
P-5	after preparation	95.67 ± 0.78	4.33 ± 0.78	0.00 ± 0.00	0.00 ± 0.00	
	28	89.83 ± 1.56 *	10.17 ± 1.56 *	0.00 ± 0.00	0.00 ± 0.00	0.01
P-6	after preparation	96.00 ± 1.33	4.00 ± 1.33	0.00 ± 0.00	0.00 ± 0.00	
	28	91.83 ± 1.83 *	6.33 ± 1.67 *	1.83 ± 0.89	0.00 ± 0.00	0.01
P-7	after preparation	88.00 ± 1.33	10.00 ± 1.67	2.00 ± 1.00	0.00 ± 0.00	
	28	72.50 ± 2.33 *	24.67 ± 1.67 *	4.17 ± 0.89	0.00 ± 0.00	0.01
P-8	after preparation	88.17 ± 1.50	11.83 ± 1.50	0.00 ± 0.00	0.00 ± 0.00	
	28	75.83 ± 2.17 *	18.17 ± 1.56 *	2.00 ± 1.00 *	4.00 ± 1.00	0.01
L-9	after preparation	87.33 ± 1.33	10.83 ± 1.17	1.83 ± 0.56	0.00 ± 0.00	
	28	63.67 ± 2.44 *	26.00 ± 2.00 *	8.33 ± 1.78 *	2.00 ± 1.00	0.01
L-10	after preparation	88.00 ± 1.00	12.00 ± 1.00	0.00 ± 0.00	0.00 ± 0.00	
	28	68.50 ± 2.17 *	25.17 ± 1.50 *	4.17 ± 1.22	2.00 ± 1.00	0.01
L-11	after preparation	94.00 ± 1.00	6.00 ± 1.00	0.00 ± 0.00	0.00 ± 0.00	
	28	75.67 ± 1.33 *	20.17 ± 0.89 *	4.17 ± 0.56	0.00 ± 0.00	0.01
L-12	after preparation	96.17 ± 0.89	4.00 ± 1.00	0.00 ± 0.00	0.00 ± 0.00	
	28	85.00 ± 3.00 *	10.67 ± 1.67 *	2.33 ± 0.78	2.00 ± 1.00	0.01
L-13	after preparation	88.80 ± 1.44	11.50 ± 1.50	0.00 ± 0.00	0.00 ± 0.00	
	28	64.00 ± 2.00 *	31.83 ± 1.56 *	4.17 ± 1.56	0.00 ± 0.00	0.01
LLux-14	after preparation	89.60 ± 1.92	8.50 ± 1.50	1.83 ± 1.17	0.00 ± 0.00	
	28	80.00 ± 2.00 *	18.00 ± 3.00 *	2.00 ± 1.00 *	0.00 ± 0.00	0.01
LLux-15	after preparation	94.17 ± 0.89	5.83 ± 0.89	0.00 ± 0.00	0.00 ± 0.00	
	28	85.83 ± 0.61 *	8.50 ± 1.50 *	5.67 ± 1.00	0.00 ± 0.00	0.01
LLux-16	after preparation	95.17 ± 1.22	5.83 ± 1.17	0.00 ± 0.00	0.00 ± 0.00	
	28	87.67 ± 1.44 *	8.50 ± 1.50 *	3.83 ± 0.89	0.00 ± 0.00	0.01
LLux-17	after preparation	96.33 ± 1.33	3.67 ± 1.33	0.00 ± 0.00	0.00 ± 0.00	
	28	92.23 ± 1.33 *	7.67 ± 1.33 *	0.00 ± 0.00	0.00 ± 0.00	0.01
LLux-18	after preparation	92.17 ± 1.17	7.83 ± 1.17	0.00 ± 0.00	0.00 ± 0.00	
	28	92.17 ± 1.83	7.83 ± 1.83	0.00 ± 0.00	0.00 ± 0.00	
E-19	after preparation	47.67 ± 1.11	17.83 ± 1.56	10.67 ± 2.00	23.83 ± 2.22	
	28	38.17 ± 1.17 *	30.17 ± 0.89 *	15.50 ± 1.50 *	16.00 ± 0.67 *	0.01
E-20	after preparation	49.00 ± 2.33	26.00 ± 1.00	10.17 ± 0.89	14.17 ± 1.17	
	28	44.00 ± 2.67 *	23.83 ± 1.17	20.17 ± 1.17 *	12.00 ± 1.00 *	0.01
E-21	after preparation	85.83 ± 0.83	14.17 ± 0.83	0.00 ± 0.00	0.00 ± 0.00	
	28	73.67 ± 0.78 *	18.17 ± 0.89 *	8.17 ± 0.56	0.00 ± 0.00	0.01
E-22	after preparation	89.67 ± 1.11	8.17 ± 0.56	2.17 ± 0.56	0.00 ± 0.00	
	28	77.67 ± 1.44 *	14.17 ± 0.89 *	8.17 ± 0.89 *	0.00 ± 0.00	0.01
E-23	after preparation	93.83 ± 0.56	6.17 ± 0.56	0.00 ± 0.00	0.00 ± 0.00	
	28	87.67 ± 0.79 *	6.17 ± 0.89	6.17 ± 0.89	0.00 ± 0.00	0.01

Table 3. *Cont.*

Formulation Code	Time (Days)	Percentage of Individual Benzocaine Particles in the Sample (%)				$p \leq$
		<30 μm	31–60 μm	61–90 μm	>91 μm	
E-24	after preparation	97.83 ± 0.89	2.17 ± 0.89	0.00 ± 0.00	0.00 ± 0.00	
	28	90.67 ± 0.67 *	9.33 ± 0.67 *	0.00 ± 0.00	0.00 ± 0.00	0.01
N-25	after preparation	73.33 ± 1.89	22.17 ± 1.17	2.17 ± 0.89	2.00 ± 0.67	
	28	59.33 ± 2.22 *	20.33 ± 1.33	14.17 ± 1.22 *	6.17 ± 0.89 *	0.01
N-26	after preparation	79.33 ± 2.89	18.33 ± 2.11	2.33 ± 0.78	0.00 ± 0.00	
	28	65.50 ± 0.83 *	16.17 ± 0.89 *	16.17 ± 0.56 *	2.17 ± 0.89	0.01
F-27	after preparation	75.67 ± 1.78	18.17 ± 1.17	6.17 ± 0.89	0.00 ± 0.00	
	28	35.83 ± 1.17 *	45.83 ± 0.89 *	14.17 ± 1.22 *	4.17 ± 1.22	0.01
F-28	after preparation	75.67 ± 1.44	22.17 ± 0.89	2.17 ± 0.89	0.00 ± 0.00	
	28	62.00 ± 1.33 *	18.17 ± 0.89 *	17.83 ± 0.56 *	2.00 ± 1.00	0.01

* Statistically significant ($p \leq 0.01$) compared to the sample immediately after preparation; n = 6; M—mean; SD—standard deviation.

Table 4. Change in benzocaine particle size in emulsion ointments depending on the used base and storage time.

Formulation Code	Time (Days)	Percentage of Individual Benzocaine Particles in the Sample (%)			
		<30 μm	31–60 μm	61–90 μm	>91 μm
P-E-29	after preparation	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	28	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
P-E-30	after preparation	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	28	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
L-E-31	after preparation	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	28	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
L-E-32	after preparation	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	28	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
LLX-E-33	after preparation	ps *	ps	ps	ps
	28	ps	ps	ps	ps
LLX-E-34	after preparation	ps	ps	ps	ps
	28	ps	ps	ps	ps
E-E-35	after preparation	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	28	76.17 ± 0.89	17.83 ± 1.22	4.00 ± 1.00	2.00 ± 0.33
E-E-36	after preparation	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	28	68.83 ± 0.89	20.00 ± 1.00	4.33 ± 0.78	7.83 ± 0.89
N-E-37	after preparation	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	28	94.17 ± 0.56	5.83 ± 0.56	0.00 ± 0.00	0.00 ± 0.00
N-E-38	after preparation	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	28	90.00 ± 1.00	10.00 ± 1.00	0.00 ± 0.00	0.00 ± 0.00
F-E-39	after preparation	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	28	88.55 ± 1.50	9.67 ± 1.67	1.83 ± 0.56	0.00 ± 0.00
F-E-40	after preparation	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	28	86.00 ± 1.00	10.00 ± 1.33	4.00 ± 0.33	0.00 ± 0.00

* Phase separation; n = 6; M—mean; SD—standard deviation.

The study showed that the process of levigation and then mixing in a recipe mixer during the preparation of dispersible ointments significantly affects the change in the size of benzocaine particles in ointment formulations. In formulations in which an active substance was ground with base for a minimum of 5 min, a narrowing of the API size

distribution (over 82%) towards particle diameters below 60 µm and the absence of particles was observed.

Our study has revealed that the disintegration of benzocaine with a basis of 1.5 min is not sufficient to meet the pharmacopoeia requirements, with regard to the particle's size. For this reason, during our study, such a short levigation process of the active substance was terminated.

There was a significant ($p \leq 0.01$) change in the percentage of API particles within the proposed size ranges in the formulations obtained immediately after preparation and after 4 weeks of storage. In formulations based on: Pentravan®, Lekobaza LUX and Eucerin Ointment I, with the use of 5 min or 10 min grounding of benzocaine with the base, as well as in the case of the L-11 formulation, no particles with a diameter above 90 µm were found throughout the study.

The most optimal time of grinding of the active substance appears to be 10 min, which allows for obtaining relatively homogenous particles, with the smallest sizes. Prolongation of the levigation time, by a subsequent 5 min did not have any beneficial effect on the particle's size.

Table 4 demonstrates the particle size distribution of API in emulsion-type formulations. The emulsion-type ointments, prepared on Lekobaza LUX, were the only ones to delaminate, making their observation under the microscope impossible. In the ointments, prepared on Pentravan® and Lekobaza, no precipitation of benzocaine crystals was noted throughout the study period. In formulations made on Eucerin Ointment I (E-E-35, E-E-36), the precipitation of crystals was visible after only one week, and from the 4th week, their size exceeded 90 µm. In the bases: Nourivan™ Antiox and Fitalite™ crystal precipitation also occurred after one week, but even after 4 weeks of storage, the particle size in these formulations did not exceed the required.

3.3. Viscosity Assay

The viscosity of the formulations was determined 24 h after preparation and after 28 days of storage at 20–22 °C. It was found that its value varies depending on the ointment base used, the method of introducing the active substance into the base, as well as the set shear rate (Table 5). As the shear rate increased, the viscosity of the tested formulations decreased.

Table 5. Viscosity parameters for four benzocaine semi-solid ointments.

Formulation Code	Shear Rate (mPa·s)	
	500 s^{-1}	**900 s^{-1}**
P-6	1289.03 ± 31.54	868.76 ± 16.60
P-E-30	1009.14 ± 34.06	547.29 ± 17.40
E-24	1511.49 ± 98.94	1157.05 ± 13.83
E-E-36	1294.89 ± 64.88	946.36 ± 35.50

Formulations prepared on a lipophilic absorption base (Eucerin Ointment I) were characterised by higher viscosity compared to formulations on a hydrophilic base (Pentravan®), on average 1.25 times ($p < 0.05$) for suspension-type ointments and on average 1.5 times ($p < 0.01$) for emulsion-type ointments. Higher viscosity values had formulations to which benzocaine was introduced in solid form, after levigation (suspension systems), while emulsion systems showed lower viscosity. All prepared formulations showed thixotropy, which is a desirable phenomenon in the case of semi-solid forms and allows an easy and pleasant application to the skin. The thixotropy present in Pentravan® was also confirmed in a study by Boisgard *et al*. [35]. No significant changes in the viscosity of the tested formulations were observed after 28 days of storage at 20–22 °C, confirming their rheological stability.

3.4. In Vitro Assay Release

The release profiles of benzocaine from selected ointments into the buffer solution are presented in Figure 3. In the *in vitro* drug release study from semi-solid ointments, it was shown that most of the drug substance—26.26%, was released from the E-E-36 formulation. Subsequently, from the remaining formulations, 20.73% of the benzocaine was released from the P-6 formulation, 17.54% from P-E-30 and the least, 10.70% from E-24.

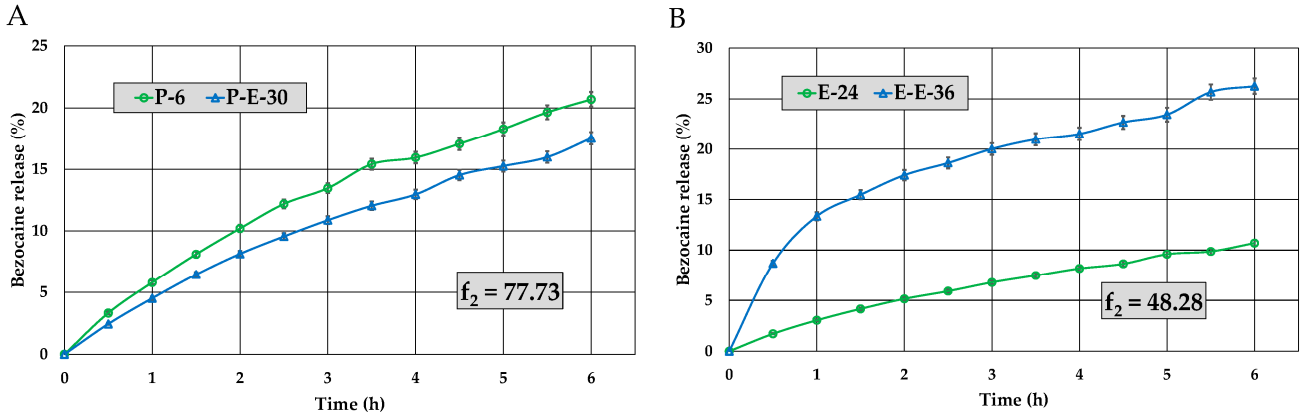

Figure 3. *In vitro* drug release profiles of four benzocaine semi-solid ointments: (**A**) formulations P-6, P-E-30, (**B**) formulations E-24, E-E-36. Mean ± SD, n = 6.

It was shown that P-E-30 was characterized by a significantly slower release of the drug compared to P-6 (Table 6). It is probably related to the change in the specific surface of the drug and its "packaging" into liposomes present in Pentravan® [36]. This can be attributed to the interactions and chemical bonds between the benzocaine, the ethanol (co-solvent) and components of Pentravan®, which contains a 20–30% Pluronic F127 solution as the aqueous phase and a mixture of lecithin and isopropyl myristate as the oil phase. The similarity coefficient value f_2 obtained from comparing the release profiles of P-6 with P-E-30 was calculated to be 77.73.

Table 6. Q factor, regression coefficient R^2 and fitting of mathematical models to the data of benzocaine release from selected ointments.

Formulation Code	Cumulative Release Benzocaine, Q (%)	Kinetics Release Models			
		Zero Order R^2	First Order R^2	Higuchi R^2	k_H (μg/cm^2 h$^{1/2}$)
P-6	20.73 ± 0.51	0.9734	0.8468	0.9978	226.91
P-E-30	17.54 ± 0.84 [a]	0.9832	0.8526	0.9979	244.07 [a]
E-24	10.70 ± 0.45	0.9835	0.8629	0.9981	153.37
E-E-36	26.26 ± 1.04 [b]	0.9388	0.8363	0.9830	471.16 [b]

k_H—average release rate, R^2—regression coefficient, Statistically significant difference: [a] $p \leq 0.01$ with respect to P-6, E-E-36, [b] $p \leq 0.01$ with respect to P-6, E-E-30; n = 6; M—mean; SD—standard deviation.

The authors suppose that dissolving benzocaine in ethanol and introducing it into the base could have changed its release from the transdermal base containing Lipoil. Perhaps the lack of co-solvent addition, combined with the medium lipophilic nature of the benzocaine particle, allowed the drug to be preserved in a nonionized form, in which the drugs have a higher penetrating ability than in the ionized form. Polonini *et al.* indicated that the lipophilic nature of the introduced particle has a greater possibility of being released from the hydrophilic base [37]. In addition, the pH of the formulation also influences the permeability, because depending on its value, weak acids and bases can be ionized, which is not always the desired effect, because neutral substances penetrate

more easily. Therefore, in this case, further research is needed and is planned for the near future. The use of the preparation on the patient's skin is also important because the skin is rich in enzymes that can affect the metabolism of the drug itself. In addition, it should be remembered that the active substance used in the experiment may create pharmaceutical incompatibility with cationic compounds.

In contrast, ointment E-24 exhibited a significantly lower release rate among all the tested formulations. The release process from benzocaine from this formulation was approximately three times slower compared to the E-E-36 formulation. A comparison of profiles E-24 and E-E-36 confirmed the discrepancy between the formulations. The use of ethanol as a co-solvent for benzocaine led to different release profiles ($f_2 < 50$).

Various mathematical models were used to investigate the kinetic model best fitted to the release data obtained (Table 6). From the value of the regression coefficient, the best-fit kinetic model was selected. It was shown that the *in vitro* release of benzocaine from selected formulations had the highest R^2 values for Higuchi's model. The adjustment of the benzocaine release profiles from selected formulations to the Higuchi model is at the level of 0.9830 to 0.9981.

The release profile of the tested formulations was determined again after 28 days of storage at 20 °C–22 °C. There were no significant changes in the amount of the drug substance released to the acceptor medium. The kinetics of the release process also remained unchanged.

Benzocaine, alongside lignocaine, is a frequently used local anaesthetic [23,38–41]. Its topical application is associated with a low risk of methaemoglobinaemia, compared to other routes of administration [42]. The medium lipophilic nature of benzocaine requires the use of a suitable base, excipients, or absorption promoters. This paper analyzes the possibility of introducing a drug substance into the base by dissolving it in a co-solvent readily emulsifiable into the medium and preparing the drug as a suspension in the base.

In this case, it is very important to use a base with emulsifying properties for drugs introduced at low concentrations. However, it should be noted that ethanol is an absorption promoter and therefore its use at higher concentrations is not recommended. In the absence of a suitable compatible solvent, it remains in pharmaceutical practice to disperse the drug as a suspension. This activity should be preceded by the process of levigation with a liquid miscible with the base or with the base itself. The literature provides different information with regard to the role of levigation in process of obtaining compounded prescription drug substances. For instance, in a study conducted by Maciejewska *et al*., manual setting of the Unguator® 2100 parameters allowed to obtain suspension-type ointments, with particle size in a range of 5–80 µm, fulfilling in this way the pharmacopoeia requirements [1]. However, in a different study, Winnicka and Telejko [43] have shown that salicylic acid, as another compounding substance, available in a form of relatively large crystals, before introduction to a base, should be levigated with liquid paraffin for at least 20 min. It has also been indicated that an active substance should not be disintegrated with ethanol, since this leads to the precipitation of crystals of salicylic acid, with particle size even up to 800 µm. This result indicates another error that can occur in pharmaceutical compounding, during the preparation of suspension-type ointments.

In studies conducted by Ufnal *et al*. [44], it was determined that a grinding time of ketoprofen (1 min or 5 min) does not have an influence on the size of crystals in the preparation. However, it was found that the independent variables, which could have an effect on a drug substances cation quality, include the time of mixing the ointment in a homogenizer, and the type of package in which a drug substance has been stored (*e.g.*, tube/box). In other studies, Nagelreiter *et al*. [45] have indicated that the mixing of fludrocortisone acetate with propylenic glycol, as a levigating substance, before its introduction to a base, has a beneficial influence on size, and equal dispersion of medication crystals in the ointment. Therefore, the selection of the levigating liquid and time of conducting levigation is determined by the physicochemical characteristics of the active substance, as well as the used equipment.

API particle size is a critical parameter for many drug formulations. Pater *et al*. observed that the API particle size in ointment formulations affects its homogeneity. In addition, the viscous nature of the base may hinder the reduction of API particle size [46–48]. The action of a high shear force during the milling or mixing process allows a significant reduction in API particle size compared to that of the original drug substance [47–49]. The use of a recipe mixer for the formulation of ophthalmic ointments resulted in a reduction of API particles from 19 µm to 4 µm [50].

Using ethanol, as a volatile solvent, is related to a risk of its evaporation that in consequence may lead to the precipitation of crystals of the active substance. In our study, this phenomenon was observed in emulsion-type ointments, prepared on: Eucerin Ointment I, Nourivan™ Antiox, and Fitalite™. Crystals of benzocaine were observed only after a week of storing such a formulation, and the precipitation of crystals has been increasing with time. Moreover, precipitation of the crystals (*e.g.*, higher amounts and larger sizes) occurred in the ointments that were more intensely homogenized in Unguator® (4 min, 1630 rpm) compared to the ones that were mixed, using lower working parameters of the mixer (2 min, 1260 rpm). Most probably, a reason for this is the stronger warming of a sample, connected with accelerated evaporation of the alcohol. In emulsion-type ointments, prepared on Pentravan® and Lekobaza, during a period of 4 weeks, there was no precipitation of active substance that could be caused by the properties of these bases. In the case of Pentravan® which contains liposomes, benzocaine could be packaged into nanocarriers. In Lekobaza—a composition and/or structure having limited ethanol evaporation. However, it should be pointed out that in the creams prepared on Lekobaza, despite a lack of benzocaine crystals (from the 3rd week), the microscopic appearances of the bases have changed, indicating a necessity to discard these formulations.

In the available literature, no particular reasons were mentioned for the phase separation of emulsion-type ointments, prepared on Lekobaza LUX. However, characteristics of this basis, and in particular, the presence of emulgators could contribute to the observed discrepancy. Pentravan® is a new compounding base that requires careful observation in the process of preparing various formulations. Its characteristics (emulsion o/w) [4] and the presence of liposomes cause doubt about whether or not the preparations manufactured on such a base can be safely homogenized in a mechanical mixer, without a negative impact on the medication's therapeutic effects. Although studies conducted by Gilewicz *et al*. [51] were relevant to a method of obtaining emulsion, they revealed that the parameters of mixing have an influence on the rheologic properties of the obtained products (since emulsions during the mixing process are exposed on high shearing forces, which can negatively influence their internal structure). Based on the results of our study, we concluded that the parameters of mixing should be individually selected for a given type of emulsion, in order to provide an appropriate grinding, which in turn, translates to stability and quality of the preparation.

The study of the release of benzocaine from selected bases can facilitate the selection of the appropriate medium depending on the skin condition. Absorbent lipophilic bases are indicated for use on dry skin after alleviating inflammation. A contraindication for this type of base is exudative states. However, skin with excessive secretion of sweat or sebaceous glands better tolerates water-washable creams of an o/w emulsion nature. Diseased skin shows increased sensitivity to irritants or allergizing factors. Therefore, the preparation of formulations for the individual needs of the patient, depending on the skin condition, requires both sensory testing and release and retention rates. In this case, the studies carried out on new bases used in formulation practice may contribute to changes in the prescribed formulations.

4. Conclusions

The use of the levigation process in the preparation of suspension ointments affects the grinding of benzocaine in ointment formulations, and the particle size depends on its duration. The minimum grinding time of benzocaine with the base, needed to meet

the requirements of the pharmacopoeia, was set at 10 min. Suspension-type ointments are characterised by greater stability compared to emulsion-type ointments. Homogenization of the emulsion-type ointment, with lower operating parameters of the recipe mixer, contributes to slower precipitation of benzocaine crystals. In the study, an intense colour change was observed for some bases, which may suggest incompatibility in the pharmaceutical phase. *In vitro* tests on the release of API from semi-solid ointments showed that the largest amount—26.26%—was released from the emulsion ointment on the base with w/o absorption properties (E-E-36) and also—20.73%—from the P-6, prepared on a multiphase base with o/w emulsion properties. The best physicochemical parameters after the stability studies were characterised by the formulations prepared on the basis of Pentravan®.

The pharmaceutical market offers a relatively large number of bases for the formulation of dermatological drugs. It seems therefore possible to choose a base that corresponds to the skin condition at different stages of the disease taking into account the site of application. However, the prudent use of all available bases is required, taking into account the therapeutic benefits, using the optimal vehicle base, ointment type and active substance content adapted to the patient's needs. Such activities, however, require the co-operation of the pharmacist and physician to select the type of ointment used, appropriate to the disease process. It is important to make the pharmacist and doctor aware that indiscriminate substitution of the base, without analysing the effects, can lead to obtaining a preparation with low therapeutic effectiveness, and even causing skin irritation.

These results might be helpful for considerations of benzocaine formulations, depending on various clinical contexts. Future studies in this area would be merited.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app13042052/s1, Table S1: Change in particle size of benzocaine in ointment prepared on Pentravan®base, depending on storage time 8. It is recommended that the data from Tables 3 and 4 be represented graphically.; Table S2: Change in particle size of benzocaine in ointment prepared on Lekobaza base, depending on storage time.; Table S3: Change in particle size of benzocaine in ointment prepared on Lekobaza LUX base, depending on storage time.; Table S4: Change in particle size of benzocaine in ointment prepared on Euceryna base, depending on storage time; Table S5: Change in particle size of benzocaine in ointment prepared on Nourivan™ Antiox or Fitalite™ base, depending on storage time.; Table S6: Change in benzocaine particle size in emulsion ointments depending on the used base and storage time.

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