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AIRLESS SEMI-SOLID COMPOUNDED DRUG PACKAGING

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Abstract: Airless containers isolate contents from air and contaminants, thereby enhancing product stability and extending shelf life. In this study, packaging for semi-solid compounded drugs was evaluated, focusing on the mechanical properties and the effects of the rheological properties of the vehicles on the dose size and dosing reproducibility. The research included tests on three airless packages (AL 10, AL 30, and AL 100) using seven ointment vehicles. The force required to activate an applicator and extract a single dose depends on the dispenser mechanism, type of vehicle used, and temperature. The hydrogel base (Celugel) exhibited the best pumpability regardless of temperature (5°C or 22°C). In contrast, a harder base like Eucerin required significantly greater force for application, especially when cooled (increase of 20 N). Sterility tests confirmed that the AL 10 package effectively protects ophthalmic drugs from microbial contamination for 28 days of normal use. The applicators reproducibly dispense approximately 0.2 mL (AL 10, AL 30) or 1.0 mL (AL 100). However, using the vehicle directly at storage temperature (5°C) reduces the dose size. Based on the research results, practical guidelines for pharmacists and patients were formulated. The combination of new airless heads with mixing jars allows for direct compounding of the drug within the final container, eliminating the need for repackaging and minimizing product loss. The study concluded that airless packaging represents a significant improvement in the compounding and application of medicinal products, offering a higher standard of hygiene, stability, and dosing precision.

Keywords: airless container, compounded drug, ointment base, topical application.

Pharmaceutical compounding is a crucial part of pharmacy practice in Poland. Compounded drugs are prepared according to a physician's prescription with a personalized composition and dosage. As a result, they supplement the range of drugs produced by the pharmaceutical industry in terms of both dosage form and active substance metering.

The composition of these custom-made medicines can take into account specific therapeutic needs and limitations, such as allergies or hypersensitivity to certain excipients, including preservatives. Depending on the patient's needs or preferences, it is also possible to select an appropriate dosage form and packaging type [1, 2].

Packaging of drugs, including compounded medicines, plays a crucial role in the manufacturing, storage, and distribution of medicinal products. It helps maintain the proper quality and stability of the drug, thereby ensuring its safety for use [3–6].

A good container should be:

– durable and barrier-protective to shield the product from external factors like radiation (light, temperature), moisture/humidity, contamination (including microbiological), and mechanical damage,
– made of inert materials that do not react with the drug formulation or adsorb its components,
– easy to open, which is especially important for use by the elderly or individuals with motor disabilities,
– convenient to use to encourage patient compliance with the recommended dosage regimen,

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– constructed to allow for visual inspection of the content level.

The implementation of the above recommendations requires the development of an appropriate mechanism and proper selection of construction materials. In pharmaceutical packaging, materials that comply with pharmacopoeial monographs or are approved by the authorized marketing-authorization body are used. These may include glass, metals (aluminum, stainless steel), and plastics.

The selection of materials should take into account the following aspects:

– mechanical: related to the function of the mechanism's components (kinematics of motion, friction, elasticity),
– technological: concerning the feasibility of manufacturing/producing the parts and potential sterilization methods (forming methods, joining components, sterilization techniques),
– chemical: chemical resistance and a lack of interaction with the formulation's ingredients (water solubility, absorbency, and resistance to acids, bases, solvents, bases, etc.).

New airless containers designed for semi-solid compounded medications are made of plastics such as polyethylene (PE), polypropylene (PP), and polyacetal (POM), as well as elastomers such as ethylene-vinyl acetate copolymer (EVA), silicone, and stainless steel.

Plastics have a number of advantages that make them a preferred choice in the pharmaceutical industry. First, they are unbreakable, which significantly increases safety during transport and use. Their low mass is a result of the relatively low density of the materials, which translates into lower logistical costs. Plastics are also characterized by high flexibility and ease of molding, allowing for the production of containers of various shapes and sizes to suit specific needs. Additional benefits include ease of manufacturing and the ability to color the material, which allows for both colored and transparent products. They are also corrosion-resistant and have low thermal and electrical conductivity. Their versatility makes them suitable for packaging various types of drugs.

Despite their numerous advantages, plastic containers also have limitations. Compared to glass, they are not as chemically inert, which can affect the stability of the stored product. They are also more permeable to gases and water vapor. Additionally, additives used in the production of plastics may migrate into the medicinal product, or ingredients of the drug may be adsorbed onto the surface of the container, thereby reducing its final efficacy. Plastics are also flammable and, after use, pose an environmental problem due to the difficulties associated with their degradation.

A crucial components of airless packaging are springs, which are made of stainless steel. Typically, grade 1.4310 stainless steel is used, as it is characterized by high corrosion resistance and high mechanical strength.

In addition to selecting materials with appropriate construction and mechanical properties, an effective sterilization method must be chosen for all elements and materials used in airless packaging.

Ethylene oxide (EtO), used for sterilization, has a surface-level effect and does not cause changes in the structure of plastics. However, this method is time-consuming and requires the removal of residual gas. There is also the risk of difficult-to-remove contaminants, such as ethylene glycol in the presence of water or 2-chloroethanol in the presence of chlorine. Common materials compatible with EtO include polypropylene, polyethylene, polycarbonate, polyvinyl chloride, polyethylene terephthalate, polytetrafluoroethylene, rubber, elastomers (silicone, latex), glass, and metals.

In the radiation sterilization method, the entire volume of the product is sterilized in its final (or even bulk) packaging in a short time (a few seconds)

Figure 1. Existing packaging of semi-solid compounded drugs: containers, aluminium tubes, mixing jars with a sliding bottom (piston) and different applicators.

without harmful chemical residues. On the other hand, ionizing radiation can cause the degradation of plastics or the phenomenon of radiation cross-linking of polymers, which may lead to a minor increase in durometer and modulus. This radiation method can be used for polyethylene (LDPE and HDPE), polypropylene (only isotactic), and polystyrene. However, it is not recommended for polyvinyl chloride, polytetrafluoroethylene, or elastomeric materials [7–9].

Traditionally, semi-solid compounded drugs have been packaged in simple plastic containers, aluminum tubes, or polypropylene containers with a sliding base (mixing jars) (Figure 1).

Specifically, the first type of packaging does not provide adequate protection for the contents. To retrieve a dose, it is necessary to open the container and transfer a portion of the product using a finger or spatula, which allows for the entry of air as well as mechanical and microbiological contaminants. In the case of aluminum tubes, the product remains in contact with the external environment through the outlet orifice. The third type of packaging is intended for preparing the formulation using a compounding mixer and serves as the final container for the patient. Dispensing involves advancing the contents by pressure exerted on the movable base and distributing the product using an applicator. None of these mentioned packages have the function of measuring a precise dose of the product.

UnoDose™ packages are also available, which enable the preparation of a formulation using disposable mixing blades with a compounding mixer, as well as ointment application in fixed doses of 0.25 mL. ExactDose™ is an example of a dispensing head that attaches to a mixing jar. It enables the precise dosing of equal aliquots of the formulation, with a volume of 0.5 mL.

New airless packaging for semi-solid compounded drugs has recently become available. These are either pre-packaged kits or additional dispensers compatible with mixing jars (Tables 1 and 2). Equipping the mixing jars with airless applicators is beneficial, as it eliminates the step of repackaging the product from a processing container (a mortar or mixing jar) into the final package. An ointment in the form of a gel,

Table 1. „Classic" packaging types for semi-solid compounded medications

Packaging	As proces container	Application	Visual control of the drug amount	Metered dosing
Jar	no	skin and mucous membranes	no	no
Aluminium tube	no	skin and mucous membranes	no	no
Aluminium tube with nasal/ rectal/ vaginal applicator tip	no	nasal/ auricular/ rectal/ vaginal	no	no
Sterile aluminium tube with applicator tip	no	eyes and conjunctival sacs	no	no
Mixing jar with dispensing nozzle	yes	skin and mucous membranes	yes*	no
Mixing jar with short/ long applicator	yes	nasal, auricular/ rectal, vaginal	yes*	no
Sterile mixing jar with applicator	yes	eyes and conjunctival sacs	yes*	no
UnoDose™	yes	skin and mucous membranes	yes	yes
Mixing jar with ExactDose™	yes	skin and mucous membranes	yes*	yes

* the piston's position is visible via the packaging's base

Table 2. Airless packaging types for semi-solid compounded medications

Packaging	As proces container	Application	Visual control of the drug amount	Metered dosing
Mixing jar with airless applicator	yes	skin and mucous membranes	yes*	yes
Sterile airless packaging (5-10 mL)	no	eyes and conjunctival sacs	no	yes
Airless packaging (15-240 mL)	no	skin and mucous membranes	yes	yes

* the piston's position is visible via the packaging's base

emulsion, or suspension is mixed in a container, which, after the head is attached, becomes the final airless package. An additional advantage is the ability to attach to various container sizes (15–240 mL) from different manufacturers.

Airless technology ensures superior chemical and microbiological stability of the drug and enables precise dosing, thereby extending its shelf life. The device's mechanism prevents the ointment within the reservoir from contacting the air, which in turn prevents the ingress of chemical and biological contaminants. This maintains product stability and purity throughout its use. An additional advantage of using this system is the ability to reduce the amount of preservatives in formulations. These containers also provide protection against light and UV radiation, further enhancing the stability of the compounding drug.

Currently, two mechanisms are used to compensate for changes in the volume of the product: a piston system or a bag system. The device consists of a suction-and-discharge mechanism and an ointment reservoir, which can be either a container with a mobile bottom-piston system (Figure 2) or an internal flexible bag-bag system (Figure 3).

Mechanism of Operation of Airless Dispensers

The dispensing of semisolid medications from an airless dispenser is a volumetric process. When pressure is applied to the pump head, a single dose of the preparation is released. When the pressure stops, the elastic component of the pumping mechanism creates a vacuum, drawing a new portion of the product and moving it toward the dispensing orifice.

The decrease in the volume of the product is compensated by either the simultaneous, stepwise movement of a sliding bottom (Figure 2) or the gradual collapse of a flexible inner bag until it is completely empty (Figure 3). Both of these solutions prevent the contents from flowing back and limit the access of bacteria and other contaminants. The currently available compounding packages for ointments are equipped with a piston system.

The pump (a suction-and-discharge device) operates through the proper interplay of its working components: a piston, one-way valves, and elastic elements. The piston, under pressure, generates force, while two one-way valves ensure unidirectional flow of the ointment. A spring accumulates the energy required to draw the product and refill the dosing chamber.

These actuating components can take various forms in different applicators, as shown in our own drawings made based on real objects after disassembly (Figures 4 and 5).

Unidirectional flow from the ointment reservoir to the dispensing outlet is managed by check valves, which can be sliding or hinged flaps, poppets, or elastomeric membranes. The force needed to draw the ointment into the pump chamber accumulates when the pump head is pressed down and then released by metal springs or elastic plastic bellows (Figure 14).

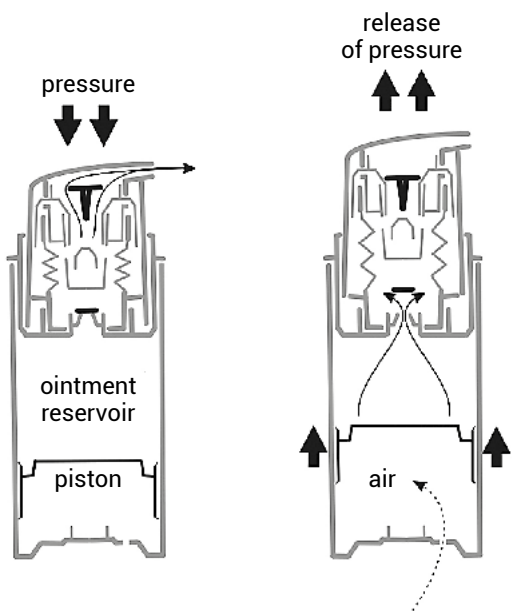


Figure 2. Airless piston system.

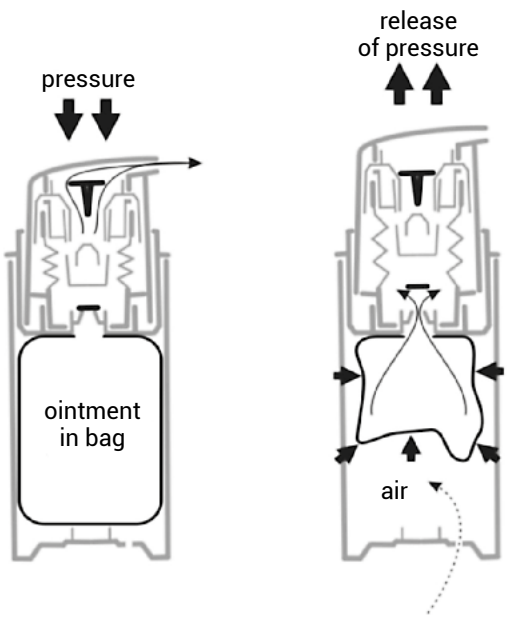


Figure 3. Airless bag system.

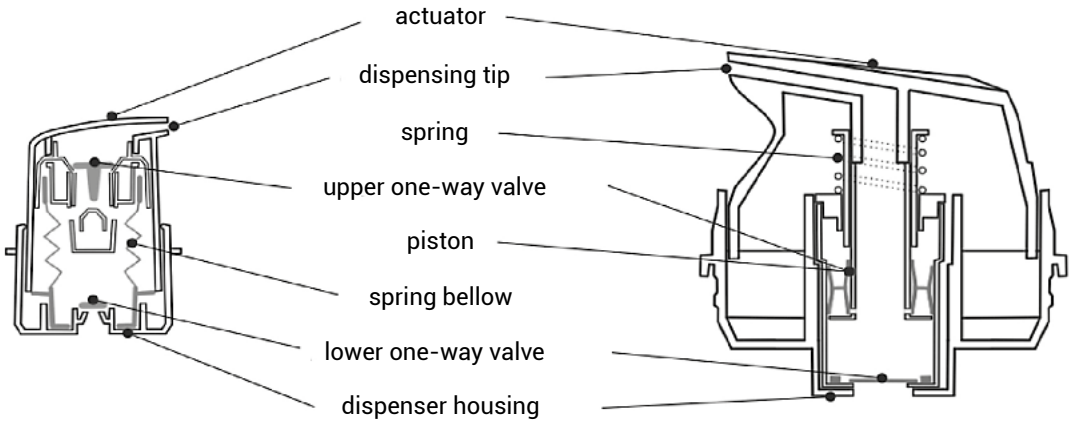


Figure 4. Different airless dispensing system designs - AL1 0 (left) vs AL 100 (right).

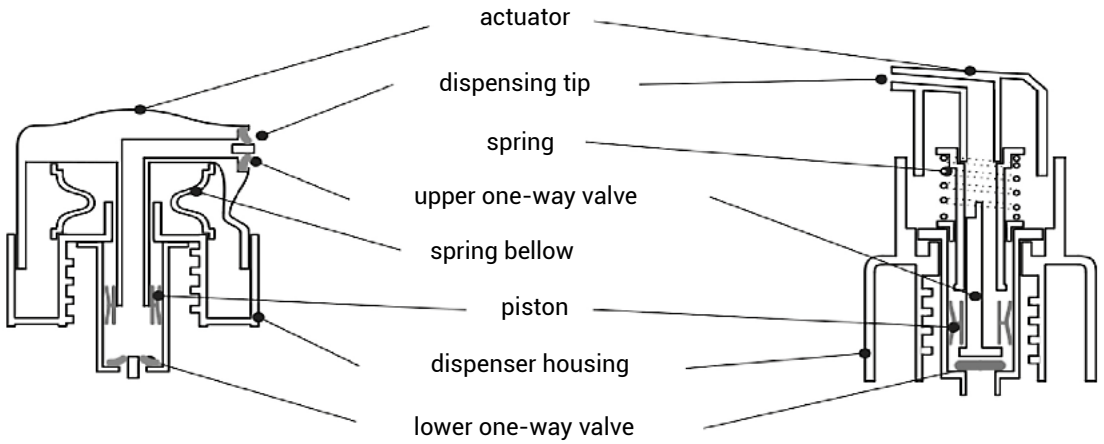


Figure 5. Different airless dispensing system designs – AL 30 I (left) vs AL 30 II (right).

Depending on the design, the precisely defined volume of the dosing chamber can include either the internal space of the pump cylinder or the space inside the polymer bellows, which also functions as an elastic element. Dosing devices also differ in how well they protect the portion of the product in the device's dispensing channel. In some cases, this part of the preparation has a small contact surface with the external environment (Figures 4 and 5), while in others, it is protected by a flexible barrier that opens only during application (Figure 5).

For a pharmacist, it is crucial to fill airless containers in a specific manner: the suction port must be directly submerged in the drug formulation, which should be free of air bubbles. Therefore, it is recommended to fill the containers from the bottom and to repeatedly tap the container to remove any trapped air.

This procedure is not necessary when using mixing jars with airless pump heads. In this case, both the weighing and preparation of the formulation occur within a single mixing jar, which then serves as the final compounded medication packaging. Before attaching the dosing head, it is only necessary to remove the excess air above the preparation by moving the sliding bottom.

The aim of this study was to evaluate the functionality of new airless packaging used for preparing semisolid compounded medications.

The following were evaluated (Table 4):

- a 10 mL airless container for semisolid ophthalmic preparations,
- two prototype dosing heads with a container for a 30 mL mixing jar,
- a 100 mL airless container.

To achieve this objective, the rheological properties of the vehicles were analyzed using the back extrusion method, and the packages were subjected to the following tests:

- force required for applicator activation,
- uniformity of the dispensed dose mass depending on the type of substrate and storage temperature,

– sterility test (for AL 10) of ophthalmic ointments during simulated use and storage at 5°C for a period of four weeks,
– actual capacity and residual volume after emptying the package.

EXPERIMENTAL

Materials

All vehicles and packaging used are listed in Tables 3 and 4.

METHODS

General Note

Most semisolid, compounded topical formulations are systems of the W/O, O/W emulsion or hydrogel type. According to the national monograph titled "Medicines Prepared in the Pharmacy" published in the Polish Pharmacopoeia XIII, the shelf life of a compounded preparation should not exceed the duration of therapy. Non-preserved drugs with water in conventional packaging must be stored at

Table 3. Vehicles used

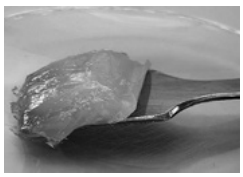
Vehicle	appearance
Celugel (C) Composition: hydroxyethylcellulose, glycerol, potassium sorbate, sorbic acid, purified water *Actifarm*	
Oleogel (O) Composition: liquid paraffin, high-pressure polyethylene *Actifarm*	
Eucerin (E) (Ung. Eucerini II) Composition: white petrolatum, cetyl alcohol, cholesterol *Fagron*	
Lekobaza (L) Composition: white petrolatum, medium-chain triglycerides of saturated fatty acids (Miglyol 812), propylene glycol, glycerol, glyceryl monostearate, cetostearyl alcohol, polysorbate 40, water *Actifarm*	
Lekobaza Lux (LL) Composition: triglyceryl isostearate, isopropyl palmitate, hydrophobic gel base, potassium sorbate, citric acid anhydrous, magnesium sulfate heptahydrate, glycerol, water *Pharma Cosmetic, Fagron*	
Zinc Oxide Paste (PZ) Composition: zinc oxide, wheat starch, white petrolatum *Coel*	
Absorption base for eye ointment (Uo) Composition: white petrolatum 10%, liquid paraffin 80%, lanolin 10% *made in-house*	

Table 4. Packages tested

Applicator/container/jar/ volume	Abbreviation	Appearance		Dimensions of container internal diameter/depth [mm]
		general	head	
Sterile airless packaging for ointments Amapack 10 mL	AL 10			19/51
Mixing jar 30 mL + dosing airless head prototype Eprus	AL 30 I			35/46,5
Mixing jar 30 mL + dosing airless head prototype Eprus	AL 30 II			35/46,5
Airless packaging for ointments (dosage 1 mL) Actifarm 100 mL	AL 100			44/80

a temperature of 2°C to 8°C to extend their shelf life up to 14 days. Therefore, in line with these recommendations, studies on rheological properties and applicator functionality were conducted at two temperatures: 5°C (refrigerator storage temperature) and 22°C (room temperature/application temperature).

Back Extrusion Study

The purpose of this study was to evaluate the rheological properties of selected vehicles using the back extrusion method. This was used to determine the extent to which the physical characteristics of the bases—such as hardness, consistency, cohesion, and viscosity—might affect the precision and comfort of dispensing the product from airless packaging.

Seven different ointment bases were tested (Table 3): Eucerin, an ophthalmic absorption base, Lekobaza, Lekobaza Lux, Celugel, Oleogel, and zinc oxide paste. These vehicles were chosen for their varied properties and intended uses [10–17]. Each base was tested in triplicate at 22°C and 5°C. A Shimadzu EZ SX (Japan) universal

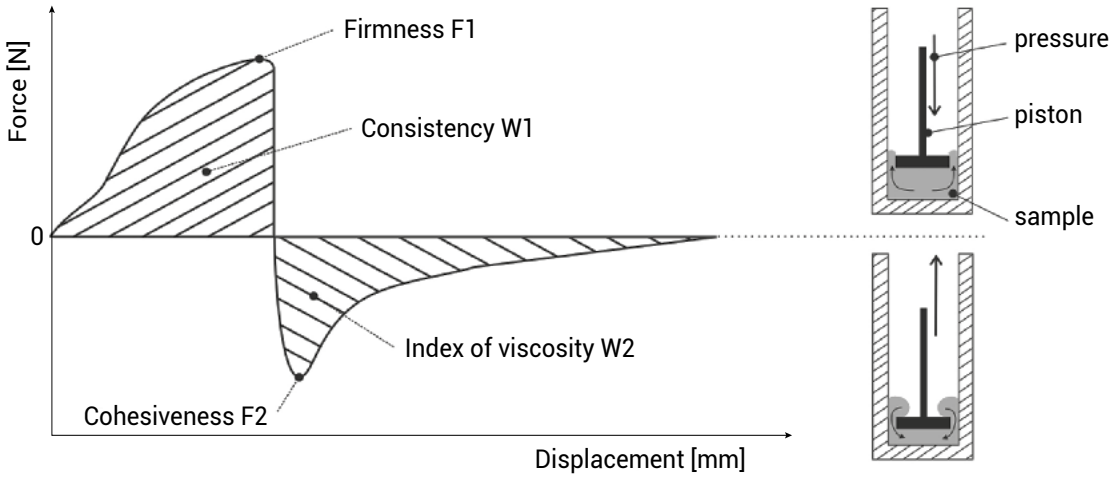


Figure 6. Textural properties of ointment vehicle using the back extrusion method.

testing machine equipped with a 500 N load cell was used. The measurements were conducted using a cylindrical measurement vessel with a diameter of 32.5 mm and a circular probe (piston) with a diameter of 27.5 mm and a thickness of 8 mm (Figure 6). The mass of each sample was 10 g. The measurement involved immersing the piston at a speed of 50 mm/min to a depth of 6 mm and then withdrawing it by 12 mm.

During the study, the force required to immerse the piston into a substrate sample and the force during its retraction were recorded (Figure 6). The following parameters were read from the force-displacement graph:

Immersion Parameters

– maximum immersion force: This is the greatest resistance the vehicle exerts as it is displaced by the disk. It is a measure of the firmness of the base.
– area under the immersion curve: This represents the area beneath the force-displacement curve during the immersion of the piston. It characterizes the consistency of the base.

Retraction Parameters

– maximum retraction force: This is the greatest force acting in the opposite direction as the piston is withdrawn from the sample. Its value is proportional to the cohesiveness of the base.
– area above the retraction curve: This serves as an indicator of adhesiveness or tackiness, which refers to the substrate's adhesion to the surface of the piston (and, in practice, to skin or packaging).

The collected data are presented graphically as force-displacement curves and in a table.

Sterility Test

The ophthalmic ointments—0.5% atropine sulfate ointment and 2% hydrocortisone ointment—were prepared under aseptic conditions in AL 10 packaging. The sterility test (FP XIII, monograph 2.6.1) was carried out under aseptic conditions using the direct inoculation method [10]. The preparations were stored in a refrigerator between successive inoculations. The test was performed daily for 28 days for each preparation, in a manner imitating the daily use of the preparation by the patient.

Before inoculation, the preparations were taken out of the refrigerator and the ointment bottles were left at room temperature for 60 minutes. Then, one portion of approximately 0.2 g of the tested preparation was diluted in a 1 : 10 ratio in an emulsifier solution (Polysorbate 80, PolAura Poland) in a sterile diluent of neutral casein peptone solution (1 g/L, Merck Germany), and then transferred to 900 μL of a culture medium that did not contain an emulsifier, which constituted no more than 10% of its volume. The study used the culture media required by the Polish Pharmacopoeia XIII: liquid thioglycollate medium (THIO-ST, bioMériuex, Poland) for the growth of anaerobic bacteria and casein-soybean digest broth (TSB-ST, bioMériuex, Poland) for the growth of aerobic bacteria and fungi. The cultures were incubated in an incubator for 14 days, with the liquid thioglycollate medium at 35°C, and the casein-soybean digest broth at 25°C. The sterility and fertility of the media were also checked each time. The following test strains of microorganisms, appropriate for use in the fertility test and method suitability test, were used: *Pseudomonas*

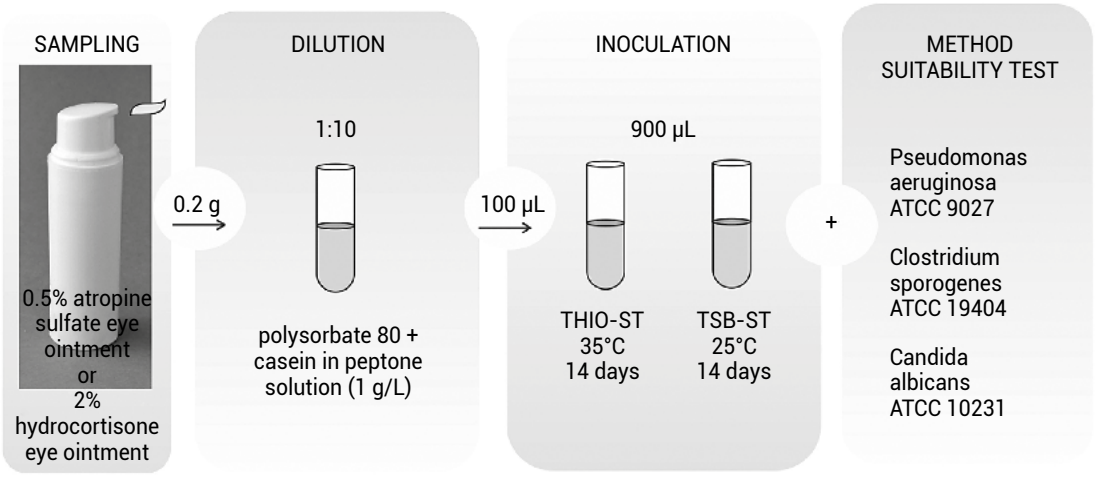


Figure 7. Study design of sterility test.

aeruginosa ATCC 9027, *Clostridium sporogenes* ATCC 19404, and *Candida albicans* ATCC 10231. The appearance of the incubated cultures was checked macroscopically daily. The preparation was considered sterile if microbial growth was not observed after the recommended incubation period.

Measurement of Force Required to Activate Applicator and Dispense Substrate

The force required to activate the applicator and dispense a single dose was measured. For this purpose, a Shimadzu EZ SX texture analyzer equipped with a measuring cell with a range of up to 500 N was used. The test was performed on packages filled with the vehicle at temperatures of 22°C and 5°C, as well as on empty packages for comparison.

The collected data were processed using Trapezium X and Microsoft Excel software (Shimadzu, Japan and Microsoft, USA, respectively). The results are presented graphically in plots showing the relationship between the compression force and displacement.

Measurement of Single Dose Mass

The study involved weighing single doses of the substrate stored at either room temperature (22°C) or in a refrigerator (5°C) (Polar TS 135, Poland). An electronic scale was used for the mass measurements. Consecutive doses were manually dispensed by pressing the applicator with fingers. The study included 60 measurements for the AL 100, AL 30 I, and AL 30 II packages, and 20 measurements for the AL 10 package. The mean values of the single-dose masses and their standard deviations were calculated. The results are summarized in Table 4 and presented graphically in Figure 9.

Verification of Residual Drug/ Vehicle Quantity

The mass of the substrate required for complete filling of the tared package was weighed. The packages were emptied by dispensing the product until empty. The emptied containers were then weighed again, and the difference between the mass of the empty package and the mass after it was emptied was calculated. The results are summarized in Table 8. The percentage of the remaining ointment base was calculated, which allowed for an assessment of the possibility of complete product removal.

Statistical Analysis

The results achieved in the study (firmness, consistency, cohesion, viscosity index, and single dose masses) are presented as mean values with relative standard deviation. Data were analyzed by Kruskal-Wallis H test with Post-Hoc Dunn's test (https://www.statskingdom.com/kruskal-wallis-calculator.html). Differences were considered significant if the p-value was < 0.05.

RESULTS AND DISCUSSION

Back Extrusion Method for Evaluating Rheological Properties of Substrates

The results of the back extrusion test showed a significant effect of temperature on the rheological properties of the individual ointment bases (Table 5, Figure 8).

Table 5. Textural properties of vehicles at temperature 22°C i 5°C (n=3)

Vehicle	Firmness F1 [N] ± SD		Consistency W1 [N x mm] ± SD		Cohesiveness F2 [N] ± SD		Index of viscosity W2 [N x mm] ± SD	
	22°C	5°C	22°C	5°C	22°C	5°C	22°C	5°C
E	2.74 ± 0.42	29.6 ± 8.27	0.01 ± 0.001	0.04 ± 0.01	2.56 ± 0.48	20.37 ± 4.94	0.01 ± 0.002	0.08 ± 0.02
Uo	5.74 ± 0.76	47.59 ±3.67	0.02 ± 0.003	0.07 ± 0.02	5.82 ± 0.73	28.78 ± 2.17	0.02 ± 0.004	0.13 ± 0.04
O	3.10 ± 0.15	4.46 ± 0.06	0.01 ± 0.001	0.01 ± 0.0008	2.53 ± 0.22	3.71 ± 0.07	0.01 ± 0.001	0.02 ± 0.0004
C	1.12 ± 0.0002	1.77 ± 0.13	0.004 ± 0.0002	0.007 ± 0.0003	0.88 ± 0.008	1.56 ± 0.11	0.005 ± 0.0002	0.008 ± 0.0005
LL	2.46 ± 0.04	3.42 ± 0.05	0.008 ± 0.0003	0.01 ± 0.0004	2.20 ± 0.06	3.09 ± 0.08	0.009 ± 0.0003	0.01 ± 0.00006
L	4.35 ± 0.29	10.82 ± 0.81	0.01 ± 0.001	0.02 ± 0.004	3.32 ± 0.14	7.95 ± 1.03	0.02 ± 0.001	0.03 ± 0.008
PZ	40.5 ± 3.62	111.12 ± 10.95	0.08 ± 0.007	0.18 ± 0.09	29.49 ± 2.58	50.43 ± 8.89	0.13 ± 0.03	0.30 ± 0.13

At room temperature, the hydrophilic gel vehicle Celugel exhibited the lowest values for firmness (1.12 N) and cohesiveness (0.88 N), which facilitates pumping in airless dispensing systems. The remaining vehicles showed greater resistance to dispenser mechanisms, as their firmness was in the range of 2.46–5.74 N and their cohesiveness was 2.20–5.82 N.

Storing the vehicles in a refrigerator and lowering their temperature to 5°C resulted in an increase in firmness, cohesiveness, and adhesiveness, which translated to greater resistance and more difficult dispensing.

The most significant differences between 22°C and 5°C were observed for the absorbent vehicle for eye ointments and for Eucerin (Table 5). The firmness of the eye ointment vehicle increased 8-fold, while its cohesiveness rose five-fold. Such large changes can lead to a decline in application comfort and precision. Similarly, Eucerin showed a strong temperature dependence, with its firmness increasing by nearly 11-fold and its cohesiveness by approximately eight-fold at the lower temperature. The Oleogel and Lekobaza Lux vehicles showed an increase in firmness and adhesiveness at 5°C, but these changes were considerably smaller. The lowest parameter values and smallest differences between them were observed for Celugel.

Zinc oxide paste showed an exceptionally high hardness of 40.5 N at just 22°C, which was comparable to that of cooled Eucerin and Uo (29.6 N and 47.6 N, respectively). A similar relationship was observed for cohesiveness: zinc oxide paste (22°C) was 29.5 N, while Eucerin and Uo (5°C) were 20.37 N and 28.78 N. Additionally, the zinc oxide

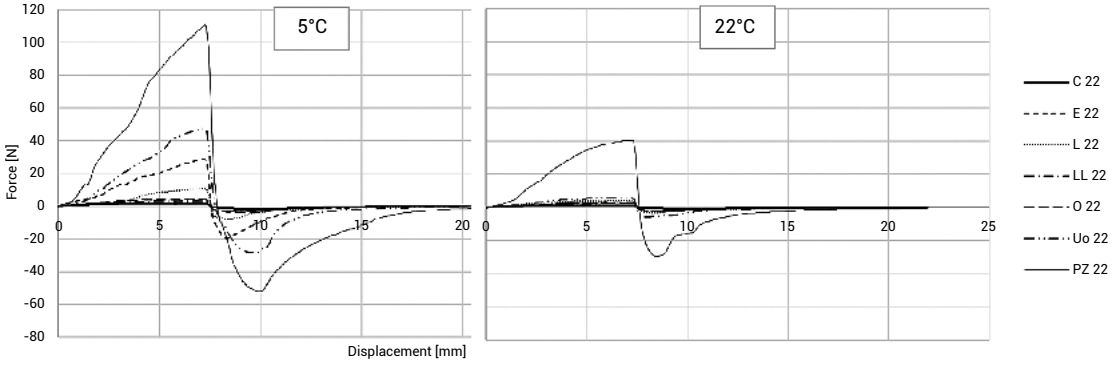


Figure 8. Rheological properties of various substrates - back extrusion method at 5° and 22°C.

Table 6. Average single dose mass (grams) (n=60, for AL 10 n=20)

Vehicle	AL 10	AL 30 I	AL 30 II	AL 100
Uo	0.193 ± 0.125	-	-	-
C	0.221 ± 0.009	0.223 ± 0.028	0.262 ± 0.003	0.998 ± 0.014
O	0.148 ± 0.012	0.078 ± 0.008	0.217 ± 0.002	0.759 ± 0.085
E	0.164 ± 0.020	0.041 ± 0.009	0.214 ± 0.002	0.772 ± 0.086
LL	-	0.057 ± 0.009	0.239 ± 0.004	0.863 ± 0.038
L	-	0.032 ± 0.005	0.232 ± 0.002	0.787 ± 0.060
PZ	dosing is not possible*			

*a single application is possible at 22°C. However, a subsequent application requires waiting from several to a few dozen minutes, as the refilling of the mechanism's chamber proceeds very slowly. Subsequent doses are not full.

paste exhibited the highest consistency and viscosity values, regardless of temperature. This characteristic makes it unsuitable for dispensing with the tested applicators.

Figure 8 presents the force-displacement graphs obtained from the back extrusion test for the different types of vehicles at 22°C and 5°C. At 22°C, all samples showed significantly lower maximum force values, both during piston immersion and retraction from the bases, compared to the results obtained at 5°C. This indicates an increase in the hardness and stiffness of the cooled substrates. The highest force values at both tested temperatures were observed for the zinc paste, while the lowest were observed for Celugel.

An increase in rheological parameters at lower temperatures leads to a more difficult application of ointments, especially for rigid substrates such as Eucerin or ophthalmic ointment bases. This can create challenges for patients in their daily use. If the ointment must be stored at a reduced temperature, the pharmacist could suggest to the doctor the choice of vehicles such as Oleogel, Celugel, or Lekobaza Lux, because they are less susceptible to changes in rheological properties under the influence of temperature. For the remaining vehicles, it is recommended to leave the ointment at room temperature for several dozen minutes before application.

Sterility Test

Macroscopic readings were taken in accordance with pharmacopoeial recommendations 14 days after inoculation. Microbial growth was observed as turbidity of the media, whereas clear, transparent media indicated the sterility of the culture. The cultures were compared to a sterility control, that is, media without the addition of the preparation that were subjected to incubation. Based on the macroscopic readings of the incubated cultures over a 28-day period, no microbial growth was observed. The tested atropine and hydrocortisone eye ointments met the sterility testing requirements.

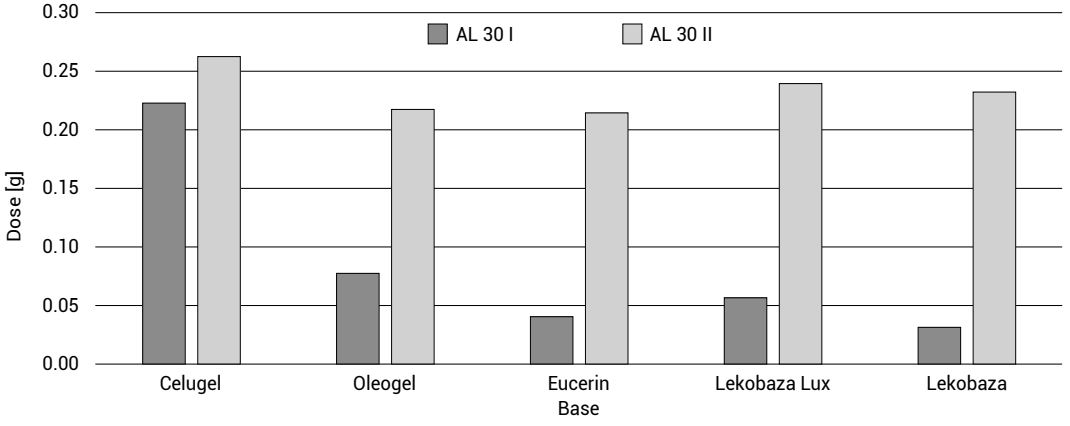


Figure 9. Dose released depending on the vehicle for AL 30 I and AL 30 II.

Table 7. Single dose mass at 22°C and 5°C (n=60, for AL 10 n=20)

Packaging	Vehicle	Dose weight [g] ± SD		Difference [%]
		22°C	5°C	
AL 10	E	0.164 ± 0.020	0.104 ± 0.045	36.59
	C	0.221 ± 0.009	0.220 ± 0.012	0.45
	O	0.173 ± 0.012	0.148 ± 0.009	14.45
	Uo	0.193 ± 0.125	0.047 ± 0.017	75.65
AL 30 I	E	0.051 ± 0.009	0.035 ± 0.027	31.37
	C	0,223 ± 0.028	0.220 ± 0.017	1.34
	LL	0.057 ± 0.009	0.024 ± 0.008	57.89
	O	0.078 ± 0.008	0.022 ± 0.007	71.79
AL 30 II	E	0.214 ± 0.002	0.180 ± 0.021	15.89
	C	0.262 ± 0.003	0.253 ± 0.013	3.43
	LL	0.239± 0.004	0.237 ± 0.003	0.84
	O	0.217 ± 0.002	0.208 ± 0.003	4.15
AL 100	E	0.772 ± 0.086	0.487 ± 0.066	36.92
	C	0.998 ± 0.014	0.987 ± 0.009	1.10
	LL	0.863 ± 0.038	0.862 ± 0.025	0.12
	O	0.759 ± 0.085	0.699 ± 0.024	7.91

Single Dose Mass

The repeatability of individual dose masses of a product impacts treatment efficacy. Each type of packaging or dispensing head has a defined dispensing volume. According to distributor specifications, the declared volumes for individual applicators are: AL 10, AL 30 I, and AL 30 II – 0.2 mL; AL 100–1.0 mL. In other markets, the AL 100 packaging is available with four dosage options: 0.25, 0.5, 1, and 1.5 mL. Table 6 presents the average mass of a single dose of the product dispensed from airless packaging, depending on the type of substrate used.

The largest single dose masses were obtained from the AL 100 packaging, which is equipped with a dispenser for 1.0 mL of the product. The highest values were observed for Celugel (the substrate with the highest density, approx. 1 g/mL), averaging 0.998 g.

The influence of the substrate type is clearly visible. Substrates with a higher density, such as Celugel, were dispensed in larger quantities, whereas formulations with a lower density, such as Lekobaza, Lekobaza Lux, Oleogel, and Eucerin, were dispensed in smaller quantities.

In smaller-capacity packages (AL 30 and AL 10), the volume of a single dose was significantly less—about 0.2 mL. For the AL 30 II dispenser, the dosage ranged from 0.21 to 0.26 g, while for AL 10, the dose mass ranged from 0.22 g for Celugel to approximately 0.15 g for Oleogel. The AL 30 I applicator was sensitive to the type of substrate, with average dose quantities ranging from 0.22 g for Celugel to as little as 0.03 g for Lekobaza (Table 6, Figure 9). These differences may have been caused by the dispenser's construction.

Based on the hard consistency of the zinc oxide paste, none of the tested applicators were suitable for its dispensing. Attempts at application resulted in the blockage of flow or the ointment was not drawn from the reservoir.

Effect of Storage Temperature on Single Dose Mass

The storage temperature of the vehicles affected the size of a single dose (Table 7). The smallest differences, regardless of the packaging type, were observed for the hydrophilic gel base Celugel, at 0.45% for the sterile ophthalmic ointment package

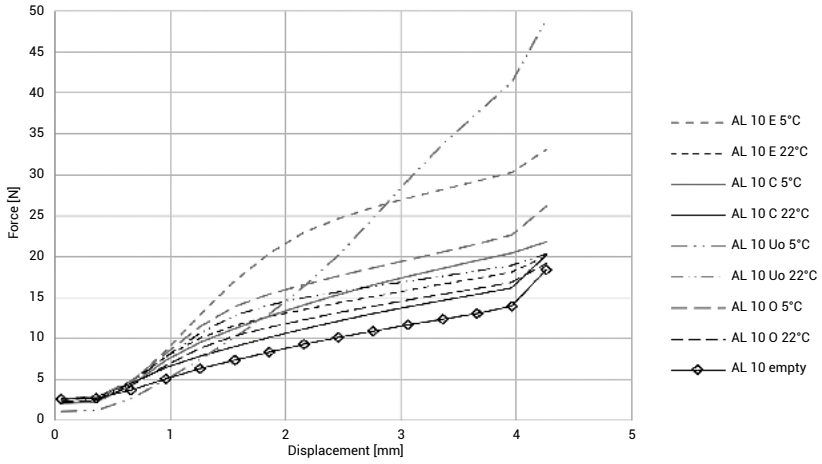


Figure 10.
Profiles of the force required to activate the applicator and extrude the vehicle for AL 10.

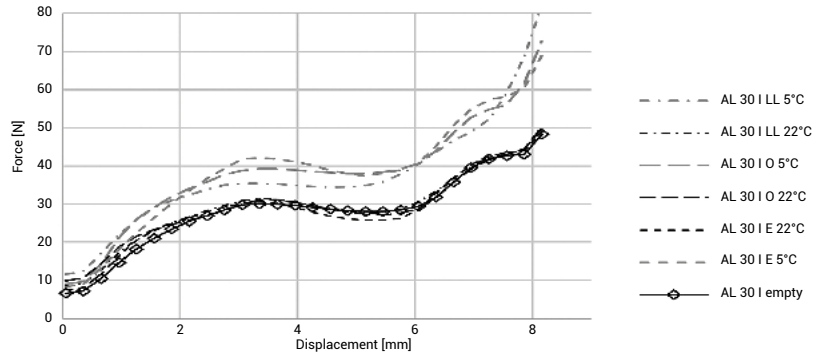


Figure 11.
Profiles of the force required to activate the applicator and extrude the vehicle for AL 30 I.

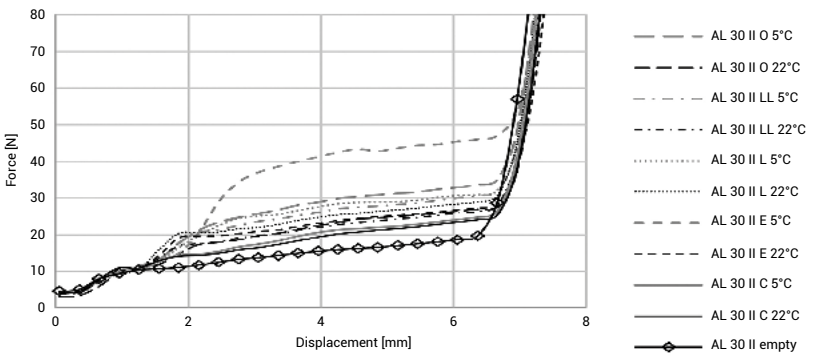


Figure 12.
Profiles of the force required to activate the applicator and extrude the vehicle for AL 30 II.

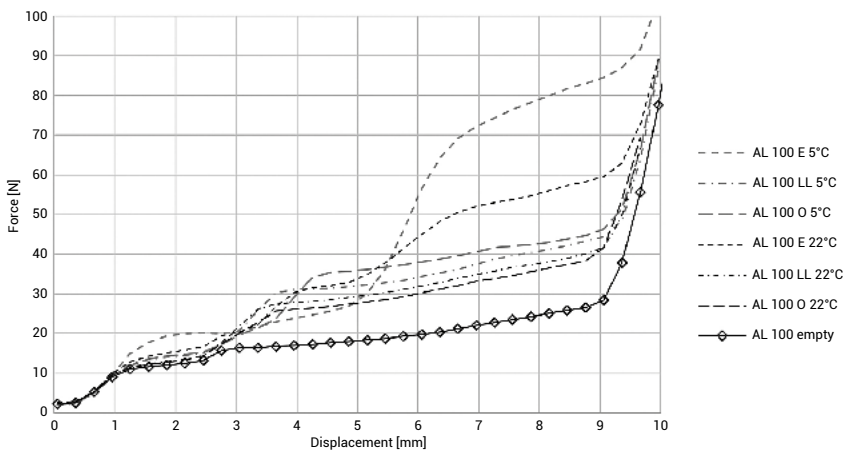


Figure 13.
Profiles of the force required to activate the applicator and extrude the vehicle for AL 100.

Figure 14. Spring elements of the applicators: from the left—AL 10, AL 30 I, AL 30 II, AL 100.

(AL 10), 1.34% and 3.43% (AL 30 I and II), and 1.1% for the 100 mL airless package (AL 100).

A comparison of the doses of vehicles stored under different conditions and applied from various applicators revealed that substrates were dispensed in smaller quantities at 5°C. This was caused by a deterioration in their rheological properties, which resulted in reduced pumpability. For Eucerin, the difference between doses at 22°C and 5°C exceeded 30% for all packages except for AL 30 II, where the difference was about half as much (15.89%).

Smaller differences were observed for Oleogel (4.15–14.45%), and even smaller ones for Lekobaza

Table 8. Summary of packaging weight, contents and residue (n=6)

Packaging	**Vehicle**	**Packaging**			**Residual** (difference before-after)	
		Empty before use [g]	**Filled with vehicle [g]**	**Empty after use [g]**	**[g]**	**[%]**
AL 10	C	11.69	22.55	12.63	0.94	8.66
	O	11.67	22.58	12.68	1.01	9.26
	E	11.67	21.96	12.68	1.01	9.82
	Uo	11.66	22.04	12.61	0.95	9.15
AL 30 I	C	24.96	71.40	27.83	2.87	6.18
	O	24.97	63.40	27.87	2.90	7.55
	LL	24.98	67.56	28.61	3.63	8.53
	E	24.88	63.23	27.67	2.79	7.28
	L	25.14	65.58	27.40	2.26	5.59
AL 30 II	C	23.58	69.03	27.00	3.42	7.52
	O	23.50	63.52	26.69	3.19	7.97
	LL	23.65	64.84	27.14	3.49	8.47
	E	23.52	63.32	26.42	2.90	7.29
	L	23.45	65.60	26.65	3.20	7.59
AL 100	C	60.51	166.45	63.38	2.87	2.71
	O	60.13	155.78	62.99	2.86	2.99
	LL	59.92	162.95	62.91	2.99	2.90
	E	60.32	151.30	62.87	2.55	2.80
	L	60.08	158.89	62.91	2.83	2.86

Lux (0.12–0.84%). The AL 30 I package dispensed the correct dose at different temperatures only for the hydrogel vehicle. Doses for bases with higher hardness (including cooled ones) were many times smaller than the declared amount.

Measurement of Force Required To Activate Applicator and Dispense Ointment Base

A study of the rheological properties of vehicles stored at 5°C and 22°C using the back extrusion method revealed diverse force-displacement curves, indicating to a greater or lesser extent the influence of storage temperature and packaging type (Figures 10–13).

Based on the analysis of the force-displacement curves, a linear increase in force was observed during the application for dispensers AL 10 (1.5–4 mm), AL 30 II (2–6 mm), and AL 100 (6.5–9 mm). The instantaneous force value was composed of two components: the force required to overcome the resistance of the spring, which increased linearly with compression, and the force needed to extrude the vehicle, which was constant at a given temperature.

Generally, the force-displacement curve for a specific ointment base can be described as the curve for an empty package "offset" by the force required for the extrusion of that base. An exception to this rule was the curves for substrates with a hard structure (Figure 10: AL 10 Uo 5°C; Figure 13: AL 100 E 5°C, AL 100 E 22°C). In these cases, the force value required for extruding the ointment was delayed, presumably by the time needed to achieve the necessary pressure within the system.

The AL 30 I dispenser exhibited different, nonlinear properties, likely related to the distinct characteristics of its flexible element, which is polymeric bellows (Figure 14). In the first phase of dispensing, the force required for the initial flexion of the bellows increased to a maximum, and in the second phase of extrusion (as the bellows flex further), it decreased slightly.

Due to the lowest force values and minimal differences between the curves at 5°C and 22°C, Celugel was included for only selected applicators (Figures 10 and 12).

Verification of Residual Drug Quantity

The residual amount of the formulation primarily depended on the type of packaging and the density of the vehicle (Table 8). The lowest residual amount of the product, approximately 1 g, was found in the AL 10 packaging. However, due to its small capacity of 10 mL, this constituted approximately 10% of the total substrate mass. For the other packages, the residue was approximately 3 g, which accounts for approximately 7% – 8% for AL 30 and just under 3% for AL 100.

The residual amount of the product in the packaging consisted of the portion that was not dispensed from the applicator head, including what remained in the outlet channel, pumping device, suction tube, and various recesses within the container. Often, the bottom of the container is specifically designed to minimize the amount of product left between it and the bottom of the dispenser head (Figure 15).

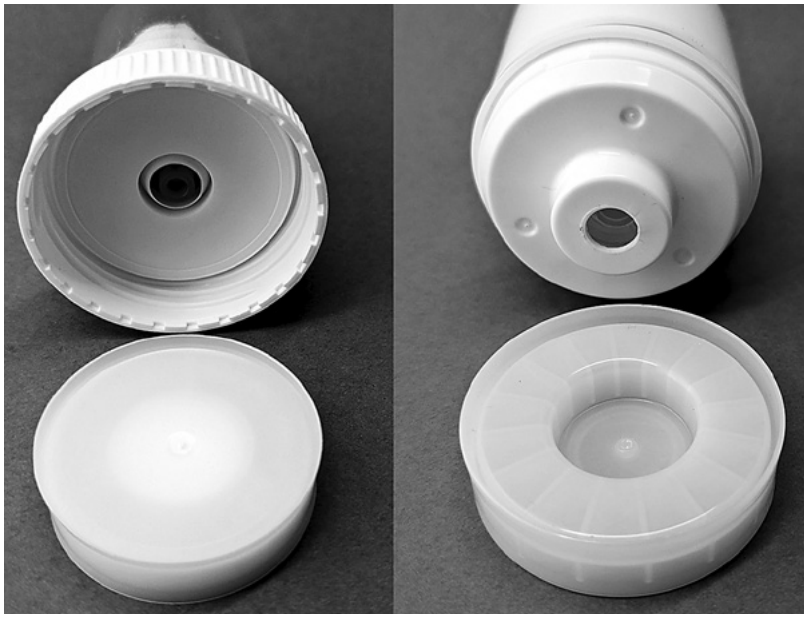


Figure 15.
Container bottom shape: AL 30 I and II (left), AL 100 (right).

CONCLUSION

The use of novel packaging with a dosing device opens up new possibilities for the preparation and administration of semisolid compounded ointments. This positively affects both the quality of the prepared medication and the patient's comfort during use.

These innovative solutions enable precise and repeatable dosing, reduce the risk of contamination, and allow for better utilization of the entire product content. They also support the work of the pharmacist by streamlining the compounding process, minimizing the waste of pharmaceutical raw materials, and improving dosage control.

While these solutions have primarily been used in the pharmaceutical and cosmetic industries, research findings indicate that they can be successfully used to prepare both compounded and pharmacy-prepared medications.

The results obtained from this study allowed for the formulation of findings and practical recommendations for both pharmacists and patients.

Findings:

1. The force required to activate a dispenser and extract a single dose depends on the type of vehicle used.
2. The rheological properties of the substrate, such as viscosity, cohesiveness, or hardness, are dependent on storage temperature and influence the dispensing process (e.g., increased force, smaller dose mass).
3. Substrates with a hard consistency (e.g., zinc oxide paste) may prevent correct dosing.
4. The sterile airless type containers with a movable piston and an applicator (AL 10), maintain the sterility of the tested eye ointments, even when used daily for a period of 28 days after the first opening.

Practical Recommendations for the Pharmacist:

1. For the preparation of semisolid formulations, substrates should be brought to room temperature.
2. In the case of containers with a small diameter and high depth (AL 10), particularly careful filling is necessary to avoid trapping air bubbles.
3. Pharmacists should provide patients with detailed instructions about the correct use of a mixing jar with a movable bottom and how to use the compounded drug applicators.

Practical Recommendations for the Patient:

1. Follow storage instructions carefully.
2. Before use, the medication stored in the refrigerator should be removed and left at room temperature to allow the temperatures to equalize.
3. Dispensing tips should be kept clean by removing any excess product.

Conflict of Interest

The authors declare no conflicts of interest.

Author's Contribution

Research concept and design: K.N., A.M.;
Collection and/or assembly of data: N.D., I.S.-K., K.N.;
Data analysis and interpretation: K.N., A.M., I.S.-K.;
Writing the article: K.N., A.M., I.S.-K.;
Critical revision of the article: K.N., A.M., I.S.-K.;
Final approval of the article: A.M., K.N.

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