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Design and Preparing a Topical Semi-solid Formulation of a Combination of *Plantago ovata* seeds and Rosehip oil to Provide an Analgesic and Anti-inflammatory Medicine

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Abstract

Considering the importance of pain, this study aims to present a standard topical formulation for pain control. In the texts of traditional Persian pharmaceutical books, many verbs, and citrus fruits are mentioned as pain relievers. In this study, the *Plantago ovata* Forsk. plant was selected from the book of *Makhzen al-Adviyah*, and related aqueous and acidic extractions were yielded in rose oil. After microscopic characterization and determining the identification number of the plant and FTIR test, *Plantago ovata* Forsk seed extract was prepared with different acidic and aqueous types, and the mucilage was prepared after evaluating several cream formulations, finally, the proportion of 70% oil and 30% stearic acid contained 65% extract. It was chosen as the appropriate formulation, which was more suitable for appearance characteristics (uniform texture and proper spreading without feeling rough on the skin). The final semi-solid formulation was examined in terms of the uniformity and integrity of the cream and the examination of rubability and cream consistency tests, the examination of spreadability, pH measurement, and the examination of viscosity and rheology properties, and the results showed that this formulation in terms of pharmaceutics tests and the total saccharide content was in the acceptable range. After passing the clinical trials, the mentioned product can be effective as a product derived from herbal compounds for pain control.

Keywords: Analgesic, Medicinal plants, Pain, Topical.

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1. Introduction

According to the description of IASP (International Association for the Study of Pain), pain can be an unpleasant and disturbing sensation due to direct or potential tissue damage (1, 2). Pain is a complex feeling and the reason for this is the difference in the origin of pain between people (various injuries and diseases) and the resistance and experience of each person to pain can be different even if the damage is the same (3, 4). Pain is divided into two types, acute and chronic. Acute pain is a biological goal and its cause can be diag-

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nosed and controlled. But chronic pain has no biological purpose and its end time is not very recognizable (5, 6).

Pain neurons are scattered all over the body, and after contact with the stimulus, they transmit electrical impulses to the spinal cord and brain. One of the parts of the body where pain neurons are present to a considerable extent is the joint. Joint pain can have different causes, such as autoimmune diseases (rheumatoid arthritis and lupus), bursitis, viral infection, fracture, and the formation of crystals in the joint, such as gout (7). Among joint diseases, gout is caused by increased uric acid. It causes inflammation, swelling, and redness in the joints, especially the toe joint (8).

Today, various solutions are used to control pain, such as non-steroidal painkillers, acetaminophen, muscle relaxants, anticonvulsants and antidepressants, opioids, creams, ointments, and multiple gels for massage and with cooling properties or creating Heat to reduce inflammation and loosen muscle stiffness (9, 10).

In addition to the many different solutions and lines of treatment in today's knowledge, complementary medicine or alternative medicine under the title CAM (Complementary and Alternative Medicine) has also offered a variety of treatment processes in this field. CAM can include treatment methods whose effects and results in many cases have not yet been proven in modern medicine and with modern evaluation indicators in the form of clinical trials and treatment reviews (11, 12). A variety of complementary medicine methods in the field of pain control include acupuncture, chiropractic (a model of manipulation of the spine and vertebrae), massage, hypnosis, electrical nerve stimulation, aromatherapy (a treatment that reduces pain by applying volatile oils to the skin or smelling them), oral diets to reduce inflammation and other similar cases (13-15).

Traditional or complementary medicine (countries with modern medical services often use the term complementary medicine instead of Traditional Medicine) is a set of skills, knowledge, and indigenous cultures of each culture in health maintenance. Traditional Persian Medicine is one of the oldest medicines in the world and differs in different geographical areas regarding therapeutic materials and treatment methods. This medicine has a holistic view and maintaining health is a priority over treatment (16-18).

In the texts of Traditional Persian Medicine, there are many therapeutic solutions for the phenomenon of pain, especially in joints and typically gout. From all types of traditional formulations, medicinal oils, either in combination or individually, play a role in the treatment and healing of various diseases. In the area of citrus fruits and herbs present in the texts of Traditional Persian Medicine, a variety of control and treatment solutions have been mentioned in the form of topical formulations. One of those formulations includes *Plantago ovata* (Bazreqatuna) along with or extracted with vinegar-based on rose oil, which in the form of a topical formula, according to the extensive report mentioned in the text of the book *Makhzan al-Advieh*, can have analgesic and anti-inflammatory effects in joint pain and gout, and it also has properties to reduce swelling and local inflammation (19-21).

Plantago ovata Forssk. is an annual plant with a short hairy stem of 10 to 45 cm height. Due to the stem's shortness, this plant's leaves are linear or stringy and the flowers appear terminal and circular and white. The seeds of this plant are membranous hairless and oval in shape (22-24). This plant, known as Bazreqatuna in Traditional Persian Medicine, has analgesic and anti-inflammatory effects according to what has been documented. The mechanism of its anti-inflammatory effect is through the reduction of some pro-inflammatory mediators such as NO, leukotriene B4, and TNF-α (25-27).

The second component of the studied formulation or the base used is rose oil. Rose oil from soaking Rose petals with the scien-

tific name *Rosa damascena* Mill. is prepared in base oil (sesame or olive) for several days under sunlight or mild heat (28, 29). Rose oil has anti-inflammatory properties due to the presence of fatty acids present in it and the presence of flavonoids in rose petals, it has analgesic effects (30, 31).

2. Materials and Methods

2.1. Plant Used

The seeds of the plant *Plantago ovata* forssk. and *Rosa damascena* Mill. flowers were purchased from the herbal market in Shiraz and identified by the botanist of the Phytopharmaceuticals Department at the School of Pharmacy, Shiraz University.

2.2. Microscopic Characterization

For this purpose, the *Plantago ovata* Forssk. seed was poured into the test tube and 5% hydrated chloral solution was added to it. The sample was heated for further analysis. The solution along with the boiled tissue of the plant was studied via microscopic characterization.

At first, the plant sample was powdered and the powder was passed through a 70-mesh sieve. Then 5 grams of the sample was weighed and transferred to a test tube and 5% hydrated chloral was added. The test tube was boiled and then centrifuged. Then the upper layer was discarded and 50 ml of distilled water was added to the remaining materials and centrifuged. Subsequently, the supernatant layer was separated and thrown away, and then the bottom layer, which was the plant fragments, was transferred to the watch glass. A few drops of phloroglucinol-hydrochloric acid solution were added to the plant pieces. Then a slide was prepared from the small segments and the slide was observed under a microscope and different parts were recorded with a photographic camera. The mentioned plant was then entered into the extraction phase to enter the considered formulation.

Since the text of *Makhzan Al-advieh* was used for the preparation of the product and the type of extract was not explicitly mentioned, for this purpose, both aqueous and acidic extracts were yielded, and later, based on the evaluations, aqueous extracts were used in semi-solid formulations.

2.3. Preparation of sesame oil

Sesame oil was purchased ready and prepared for the separation of impurities by centrifuging.

2.4. Preparation of Rose (Rosa damascena Mill.) Extract in Sesame Oil

The purchased flower was added in a ratio of 1/10 to sesame oil in an oven at 50 °C for 24 hours and repeated 3 times, and at each stage, about 15% of sesame oil remained in the tissue of the rose petals. Then the oil was separated with a net cloth and centrifuged. The pure oil was kept for formulation.

2.5. Preparation of primary extract from Plantago ovata forssk. seed

2.5.1. Aqueous extraction

2.5.1.1. The first method

Twenty grams of Plantago ovata forssk. seeds were added to 500 ml of distilled water in a sonicator for 30 min. Then a cloudy gelatinous composition was obtained. The gelatinous part was separated. The composition was very cloudy and inseparable and could not be dried.

2.5.1.2. The second method

Twenty grams of *Plantago ovata* forssk. seeds were added to 500 ml of distilled water in a sonicator for 30 min. A cloudy gelatinous mixture was obtained. Then, additional water was added to the obtained gelatin and was heated to make it possible to pass through a strainer or a net.

2.5.1.3. The third method

Twenty grams of *Plantago ovata* forssk. seeds were added to 500 ml of distilled water in a sonicator for 30 min. Then a cloudy gelatinous mixture was obtained. A Buchner

funnel was used to separate the seeds. However, the mixture was not able to pass.

2.5.1.4. The fourth method

After crushing the seeds with a grinder, it was passed through a 30-mesh sieve and the coarser particles and the remaining shell were used for the extraction process. Then, 20 grams of coarse seeds and the husk were passed through a sieve and added to 500 ml of distilled water in a sonicator for 24 hours. Then the final product was filtered through a net. The final mucilage was used to continue the process.

2.6. Method of acid extraction of Plantago ovata forssk seeds

Traditional grape vinegar with measured pH was employed. Twenty grams of *Plantago ovata* forssk. seeds were added to 500 ml of the vinegar placed in a sonicator for 30 min and kept in a beaker covered with aluminum foil for 24 hours. The final product was filtered through a net. The final mucilage was used to continue the process.

2.7. Drying mucilage for use in formulation

2.7.1. The first method

The final aqueous and acidic mucilage obtained from the previous steps was dried by indirect heat and the resulting aqueous phase was evaporated. Due to the change in color and texture, this method was not used to yield the dry mucilage.

2.7.2. The second method

The final aqueous and acidic mucilage obtained from the previous steps was placed on the tray. However, this method was not also efficient.

2.7.3. The third method

The final aqueous and acidic mucilage obtained from the previous steps was placed on a tray covered with parchment paper. Due to penetration into the texture of the parchment paper and the inappropriateness of the final product, this method was not continued.

2.7.4. The Fourth method

The final aqueous and acidic mucilage obtained from the previous steps was placed on a tray covered with a cooking liner. It was kept for two days, and then a very fragile and thin layer was obtained by bending the cooking liner. It could be easily separated.

2.8. Preparation of semisolid formulation with aqueous extract

The oil in water emulsion, vanishing cream was selected as the base formulation for delivery of aqueous extract and oil. Different percentages of aqueous extract and oil were used in the cream base presented in Table 1. The best formulation was selected based on organoleptic properties such as appearance, homogeneity, consistency, and spreadability. In this formulation, the stearic acid reagent was replaced with a different percentage of a similar constituent. The dried mucilage was added in the aqueous phase with different percentages. Finally, the formula with more favorable characteristics was selected as the appropriate formulation.

At first, different percentages of dry mucilage (0.5, 0.7, 1%) were used in the aqueous phase, while the stearic acid was 100% in the oil phase. Based on the physical characteristics of formulations, 0.7% of extracts have the best performance. By the next step, the effect of different percentages of oil instead of stearic acid was evaluated in the formulation, and the formulation with 65% oil and 35% stearic acid was selected as the better formulation based on its physical characteristics such as spreadability and homogeneity.

2.9. Preparation of semisolid formulation with acidic extract

The formulation with acidic extract was prepared with a similar method as mentioned in the previous section. The performances of acidic extracts were not suitable in this formulation, further study was continued

Table 1. Different formulation was prepared based on different compositions of oil and extract

Formulation	Base content	% of oil phase	% of extract
F1	Stearic acid (2 g), borax (0.15 g), water (7.3 cc), potassium (0.05 g), ethanol 90% (0.5 cc)	100% stearic acid	- (0%)
F2	Stearic acid (2 g), borax (0.15 g), water (7.3 cc), potassium (0.05 g), ethanol 90% (0.5 cc)	100% stearic acid	0.5%
F3	Stearic acid (2 g), borax (0.15 g), water (7.3 cc), potassium (0.05 g), ethanol 90% (0.5 cc)	100% stearic acid	0.7%
F4	Stearic acid (2 g), borax (0.15 g), water (7.3 cc), potassium (0.05 g), ethanol 90% (0.5 cc)	100% stearic acid	1%
F5	Stearic acid (1g), Borax (0.15g), Water (7.3cc), Potassium (0.05g), 90% ethanol (0.5cc), Oil (1g)	50% stearic acid 50% oil	0.7%
F6	Stearic acid (0.8 g), Borax (0.15 g), water (7.3 cc), potash (0.05 g), ethanol 90% (0.5 cc), oil (1.2 g)	40% stearic acid 60% oil	0.7%
F7	Stearic acid (0.6 g), borax (0.15 g), water (7.3 cc), potash (0.05 g), ethanol 90% (0.5 cc), oil (1.4 g)	30% stearic acid 70% oil	0.7%
F8	Stearic acid (0.7g), borax (0.15g), water (7.3cc), potash (0.05g), ethanol 90% (0.5cc), oil (1.3g)	35% stearic acid 65% oil	0.7%

on the aqueous extracts.

2.10. Physicochemical characterization of the final formulation

2.10.1. Color and smell test

The stability in color and smell of the final product was evaluated because of probable oxidation of aromatic substances, microbial growth, incompatibilities between active ingredients and other substances in the formulation (32-34). The color and smell of the best formulation remained unchanged during the first, second, and third days of the study, the first, second, and third weeks, and the first, second, and third months after the cream was prepared.

2.10.2. Evaluation of the pH and conductivity

As one of the parameters for determining the stability of formulation, the pH and conductivity of formulation were evaluated using the pH meter and conductometer. To measure the pH, one part of the prepared formulation was diluted and mixed with 9 parts of deionized water (32, 34). The pH of the samples was measured on the first, and third days, the first week, the second week, the first month, and the second month with three replicates.

For determining the electrical conductivity of formulation, one part of the product is mixed with 9 parts of deionized water and after mixing with the shaker, its electrical current conductivity was measured by the glass electrodes of the device (35).

2.10.3. Evaluation of rheological properties

A cone/plate rheometer was used to evaluate the rheological properties of the final formulation.

2.10.4. Physical stability of the formulation

The physical stability of the formulation was investigated in both the room and the refrigerator. The physical characteristics of the formulation such as color, smell, homogeneity and spreadability were evaluated at different time points (0, 1, 3 days, 1, 2, 3 weeks, 1, 2, 3 months).

2.10.5. Centrifuge stability test

In this test, the stability of the emulsion was evaluated by a centrifuge at different speeds (between 2000 and 15000 rpm). To perform the test, 2 g of the samples were transferred to a glass test tube and centrifuged at

a uniform speed, during this test, the possible phase separation was investigated at different time points (5 to 30 minutes) (35).

2.10.6. Spreadability test

To check the spreadability of the semi-solid formulation, 0.5 g of the final formulation was put under pressure by plates weighing 42 g, 200 g, and 500 g for three minutes, and then the area covered by the semi-solid formulation. By comparing the results obtained with the criteria reported in the references the spreadability of the formulation can be evaluated.

2.10.7. Homogeneity test

To perform this test, 0.5 g of the final semi-solid formulation was added to a tube and pressed to the end. The sample should be continuously removed from the tube by creating a slight pressure in a homogeneous strip without phase separation or bubbling.

2.10.8. Microbial stability

Before starting, all the necessary tools and containers were autoclaved. The sample of the final semi-solid formulation was evaluated for microbial evaluation in the microbial control laboratory to check for the presence of microorganisms (total count of fungi and bacteria). These tests include determining the total number of microbes, which in the formulation should not be more than 100 non-pathogenic masses per gram. Determining the total number of molds and yeasts in this formulation should not be more than 100 mass per gram. It was also checked for the absence of two microorganisms *Staphylococcus aureus* and *Pseudomonas aeruginosa* in formulation.

3. Results and Discussion

According to previous studies and research, *Plantago ovata* Forssk. seed was selected as an effective agent in controlling chronic pain. After purchasing, identifying, and obtaining an identification number, seeds were extracted

3.1. Microscopic characterization

The size, shape, and relative position of different cells and tissues as well as the chemical nature of cell walls, shape, and na-

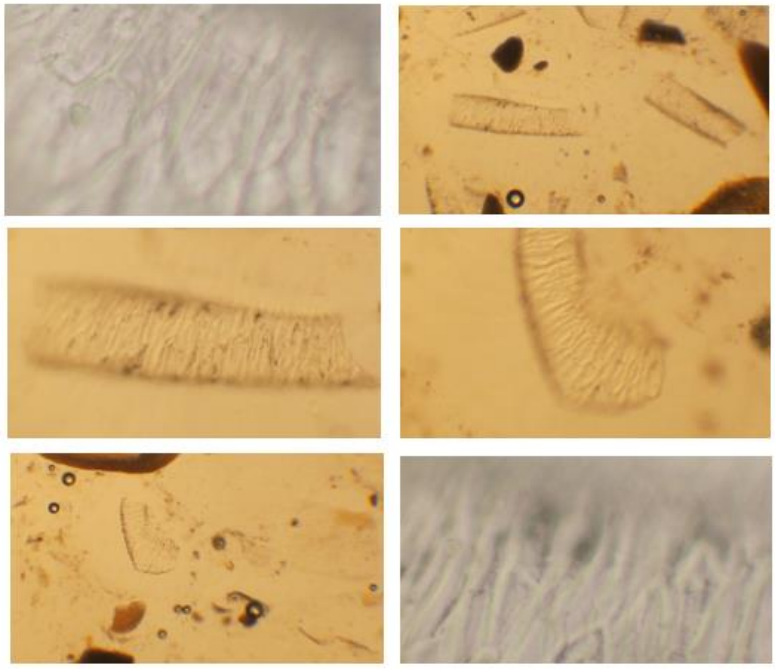

Figure 1. Micrograph of a piece of mucilaginous epidermis of seed coat in different surface views.

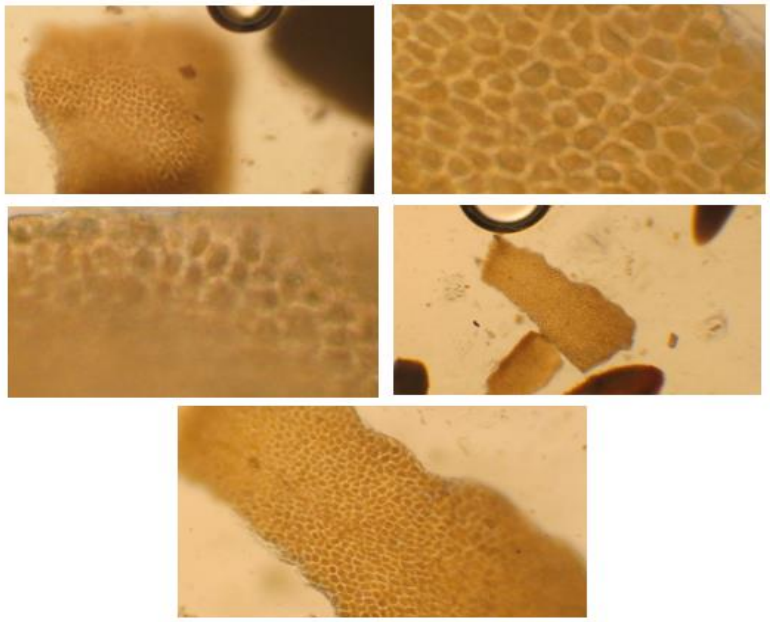

Figure 2. A piece of seed endosperm in different surface views.

ture of cell contents are considered in the microscopic analysis of drugs (36).

The organ used by the psyllium plant is the seed, whose various components have been detailed. Figure 1 shows the micrograph results of a piece of mucilaginous epidermis of seed coat in different surface views. Also, the micrograph results of a piece of seed endosperm in different surface views can be seen in Figure 2.

3.2. Extraction and Yield

After extracting and drying according to the methods, the cream was prepared with different percentages, and the most suitable semi-solid formulation with 35-65% oil to stearic acid was selected. In this test, the initial weight of the seeds used was 20 g, the amount of water added to the seeds was half a liter, and according to the calculations, the percentage of dry mucilage powder extraction from Plantago was calculated as 13±1.2 percent.

3.3. Physicochemical characterization of the final formulation

After preparing the appropriate formulation of the cream, pharmaceutics tests that could be performed in the laboratory were performed on the final sample. The tests performed included color and odor tests, pH, electric current conductivity, centrifugation, homogenous pressure or outflow, expandability and spreadability, rheology, microbial test, and stability .The mentioned formulation was suitable in terms of the pharmaceutics tests and it was successful. The F8 was considered as the most suitable formulation.

Table 2. The pH of the best formulation.

Day	pH
first day	8.58±0.03
third day	8.45±0.03
first week	8.39±0.04
Second week	8.3±0.068
first month	8.22±0.04
second month	8.22±0.11

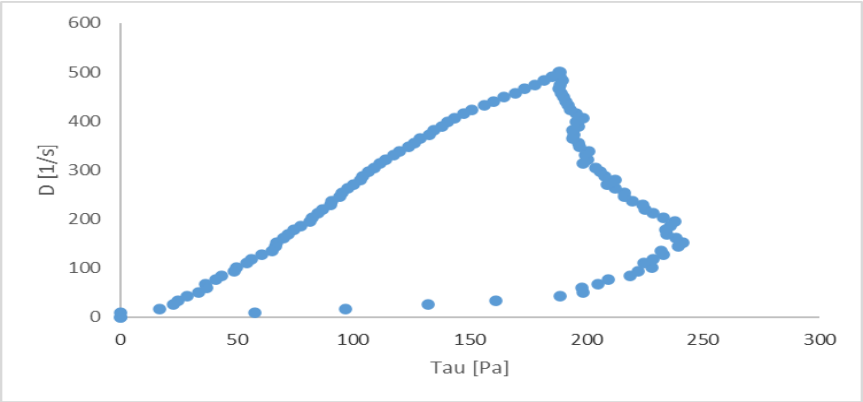

Figure 3. The rheology of the best formulation.

3.4. Color and smell

The color and smell of the formulation were examined on Day 1, Day 3, Week 1, Week 2, Month 1, and Month 2. At the end of the determined times, no change in the color and smell of the examined sample was observed.

3.5. Evaluation of the pH and conductivity

The pH of human skin is usually from 4.5-6.0 and pH 5.5 is considered as the average skin pH (37, 38). The pH of the final semi-solid formulation was measured at different times (Day 1, Day 3, Week 1, Week 2, Month 1, and Month 2). The results show that the pH did not change during those times. pH was measured and reported at different times on the first day, the third day, the first week, the second week, the first and second months. The pH obtained in the final formulation is about 8.5, which is an acceptable pH for the skin as a vanishing cream. The conductivity was measured using a dual-purpose pH meter on days 1, 30, and 60, with three replicas, and the obtained value was 85.7±2.13 µs/cm^2 for two months. The results show that the product is stable in terms of electrical conductivity.

3.5.1. Evaluation of rheological properties

The rheology of the sample was measured using a cone 25 cm, on days 1, 30, and 60, with three repetitions. The results were shown in figure 3. The hysteresis loop was presented in this formulation and the pseudoplastic behavior was determined by the results of this study. The final formulation has the thixotropic effect.

The fact that the cream is thixotropic makes it come out of the tube with less pressure and spreads easily on the skin. The shearing force, causes a decrease in the viscosity of the semi-solid formulation and an increase in its spreadability, which leads to greater patient cooperation and satisfaction (39).

3.6. Centrifuge Stability Test

Centrifugation accelerates instability and simulates aging, and it is possible to predict the stability of semi-solid formulations in the long term based on its results (40). The semi-solid formulation was centrifuged at 3.5, 5, 7.5, and 12,000 rpm in 5, 10, and 20-minute intervals and examined, which was 3500 rpm in 5 and 10-minute intervals. During 5 minutes, the speed of 5,000 rpm was not two-

Table 3. Centrifuge test results in two states of biphasic and non-biphasic.

Time pace	5 minutes	10 minutes	15 minutes
3500 RPM	Not two phases	Not two phases	Not two phases
5000 RPM	Not two phases	Two phases	Two phases
7500 RPM	Two phases	Two phases	Two phases
12000 RPM	Two phases	Two phases	Two phases

Table 4. The results of the spreadability test.

Diameter	Weight
2.7±0.1	48.4 g
4.05±0.5	284.4 g
4.7±0.1	548.4 g

phased, and at other times and speeds, the centrifuge became two-phased. It seems that the product's stability is suitable with the results obtained at room temperature and refrigerator temperature, but the high and long-term spin of the centrifuge makes the product susceptible to two phases (Table 3).

3.7. Spreadability Test

In the final formulation, it is expected that the sample should be removed from the tube by applying less pressure and spread easily on the skin surface. Ideally, the surface covered by the plate should be according to Table 5; that the result of this test was acceptable.

Similar studies conducted with similar formulations show that when a person uses a certain dose of the product, it spreads easily on the skin and has an even distribution on the skin surface.

3.8. Homogeneity Exit Test

The semi-solid formulation exited out of the tube homogeneously and without bubbles from the tube. Pressure test or homogenous withdrawal, where the semi-solid formulation in the tube was completely homogeneous and uniform, and by applying slight pressure, it was taken out of the tube.

3.9. Physical stability

In the stability control test, the semi-solid formulation was kept for 4 weeks at room temperature and 4 °C, and no significant changes were made in terms of appearance and stability in the sample. So, it can be generally concluded that the semi-solid formulation has acceptable stability.

3.10. Microbial test

No specific bacteria, mold, or yeast were observed in the formulation.

Table 5. The covering surface of the sample on the screen is in the desired state .

Incoming force	The area of the created circle
42 g	300-600 mm square
200+42 g	700-1400 square mm
500+42 g	1000-2000 square mm

Regarding the dermatological products, the count of microbial colonies should be according to the guidelines, the sample of the final semi-solid formulation had the following conditions. As can be seen from the results, the present product has suitable conditions in terms of stability against the growth of bacteria and fungi.

4. Conclusion

Considering the importance of studying and presenting new drugs, especially with natural origin, this study has designed and prepared a topical semi-solid formulation containing seed essence to introduce an effective skin product for chronic pain. Accordingly, the mucilage extracted from seeds after crushing was introduced in a semi-solid formulation. The most suitable semi-solid formulation of the cream was obtained with an extract of 0.7 % (dry mucilage) and an oil/ stearic acid ratio of 65/35 (F8). The formulation of the cream designed by passing the required pharmaceutics evaluations showed that it can be a suitable option for topical use or Plantago seed oil. This product, after re-preparation and obtaining a clinical trial license, can be presented as a natural product based on the documentation in traditional pharmaceutical sources in patients suffering from such pains, until after evaluation and achieving the effects. A favorable treatment for production should be offered to the pharmaceutical market.

Authors Contributions

AMZ: laboratory work; AA: writing the manuscript; MMZ: designing and editing the manuscript; HA:designing and editing the manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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