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OPTIMIZATION AND EVALUATION OF MOISTURIZING CREAM CONTAINING DEXPANTHENOL

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Abstract

Background/aim: The main purpose of this work was to prepare and evaluate a moisturizing cream containing dexpanthenol. **Materials and methods**: In this study, several cream formulations were prepared using the oil-in-water (O/W) emulsion technique to investigate the effect of varying concentrations of the independent variable on the physical appearance, pH, electrical conductivity, viscosity and spreadability. Different formulations were prepared with different combinations of Cera alba and Stearic acid with various excipients. The developed formulations were examined with the QbD approach. A process known as "quality by design" uses statistical, analytical, and risk-management techniques in the planning, development, and production of pharmaceuticals to guarantee the predetermined quality of the product.
Results: According to the QbD studies, the Design Space is given for optimum formulae. After establishing the model equations for the main effects and responses, various cream formulations containing stearic acid and cera alba were optimized based on spreadability, viscosity, and electrical conductivity.
Conclusion: In conclusion, the outcomes of different formulations obtained in this research study clearly showed that a moisturizing cream containing a certain ratio of Cera alba and Stearic acid have an up-and-coming potential. Therefore, proportions of Cera alba and Stearic acid are included in the moisturizing cream to win its cosmetic benefits.
Keywords: QbD, dexpanthenol, spreadability, textural

1. Introduction

A critical equilibrium between the water content of the stratum corneum and skin surface lipids maintains the appearance and function of the skin. Because the skin is the body's most superficial layer, it is continually exposed to many environmental stimuli. Endogenous factors, in addition to exposure to exogenous stressors, can upset this balance. Furthermore, the use of soap, detergent, and topical irritants such as hot water and alcohol on a regular basis can eliminate lipids from the skin's surface. Disruption of the skin barrier results in a variety of skin disorders (Draelos, 2012). The most common condition is roughness, scaling, cracks, redness, and loss of water content leading to an uncomfortable feeling of tightness, and sometimes dryness of the skin such as itching and stinging. Treatment with the cream aims to protect the integrity and well-being of the skin by ensuring that the person has a healthy appearance. While a variety of moisturizers are labelled under the natural, safe, organic, and herbal label, the basic qualities of humectant, occlusive, and emollient are shared by all moisturizers. The base of most modern moisturizers is made up of synthetic adhesives, fragrance agents, emulsifiers, pigments, thickeners, and surfactants. Pantothenic acid is essential for normal epithelial function. Dexpanthenol, a stable alcoholic analog of pantothenic acid, is applied topically to increase stratum corneum hydration, minimize trans-epidermal water loss, and maintain skin suppleness and elasticity. Today, dexpanthenol topical formulations suited to individual needs are available. In dermatology and skincare, topical dexpanthenol has become a popular product. Various studies have confirmed dexpanthenol's hydrating and skin barrier-strengthening potential. It prevents skin irritation, stimulates skin regeneration, and promotes wound healing (Baron et al., 2020). The aim of this study was to design, prepare and evaluate a moisturizing cream using dexpanthenol that did not show visible signs of physical instability such as creaming, cracking, phase inversion, and/or cream base flowing from the container. In the study, 11 full factorial designs were applied to examine the effect of varying concentrations of the independent variables Cera alba and stearic acid on the dependent variables spreadability and viscosity. Oil-in-water cream was initially prepared by melting Cera alba at 70-80 °C and adding propylene paraben, stearic acid, liquid paraffin, isopropyl myristate, lanoline, and glyceryl monostearate to the molten mass. Together with glycerine, propylene glycol, borax, methylparaben, and distilled water, the aqueous phase is heated at the same temperature as the oil phase. Both phases were mixed until homogeneous. Physical instability was assessed immediately after production and after 24 hours of storage at room temperature (25°C). All prepared moisturizing cream formulations were evaluated in terms of physicochemical parameters. In addition, the optimized formulation was compared and evaluated in terms of physicochemical parameters such as pH, spreadability, and electrical conductivity (Ebner et al., 2002).

1. MATERIALS AND METHODS

1.1. Chemicals and Equipment

In this experiment, pH/electrical conductivity meter (HannaHI 9812-5), rotational viscometer (VR 3000 MYR), texture analyser (TA.XTplusC, Stable Micro Systems), magnetic stirrer with heating (HeidolpH MR Hei-Standard), and analytical balance (Sartorius Entris) were used. For chemicals, propyl paraben, liquid paraffin, glycerine, propylene glycol, borax, Cera alba, and methyl paraben were purchased from Tekkim Kimya Sanayi TİC.LTD.ŞTİ, Turkiye. Stearic acid and lanolin were purchased from Galenik, Turkiye. Glyceryl monostearate was purchased from Carl Roth GmbH + Co KG, Germany. Isopropyl myristate was purchased from Doğa, Turkiye. Dexpanthenol was gently gifted from BASF, Germany.

1.2. Methods

Moisturizing cream containing dexpanthenol was prepared using the O/W emulsion technique. Physical instability was assessed immediately after manufacture, 24 hours later, and two weeks later at room temperature (25 °C). Formulations showing signs of physical instability were considered inappropriate. To prepare oil-in-water emulsion cream, the raw materials are divided into two phases, A and B phase. In phase A (disperse phase, oil phase): Cera alba, propylene paraben, stearic acid, liquid paraffin, isopropyl myristate, lanoline, and glyceryl monostearate (Maru & Lahoti, 2018). In phase B (continuous phase, aqueous phase): there are glycerine, propylene glycol, borax, methylparaben, and distilled water. The raw materials are weighed by using a spatula, plastic weighing boat, pipette, and graduated cylinder. Phase A and phase B were prepared in two different beakers. First, Cera alba was melted and propylene paraben, stearic acid, liquid paraffin, isopropyl myristate, lanoline, and glyceryl monostearate were added to the melted mass. Then, phase A was mixed mechanically with the help of a glass rod and heated in a water bath until it reached 70-80 °C. The homogeneous phase A was prepared. While preparing phase B, firstly distilled water and borax were added to the beaker, and the mixture was heated in a water bath and stirred until the borax dissolved in distilled water. Then glycerine, propylene glycol, and methylparaben were added. Then it was mixed mechanically until it reached 70-80 °C and homogenized with the help of a glass rod, and phase B was also prepared. After it was determined that both phases were at the same temperature (70-80 °C) with the help of an electronic thermometer, the oil phase (A) was added to the water phase (B) in a controlled manner, and with the help of magnetic stirrer, it was mixed at 500 rpm until it became homogeneous (Naeimifar et al., 2020). After homogenization, the formulation was placed at cold place and allowed to cool. The formulation, which was left to cool, continued to be mixed mechanically with the help of a glass rod at the same time. In formulations, the addition rate, mechanical mixing of the disperse phase, mixing time, and cooling time are important in the formation of the creams. The same procedures were repeated by changing only the percentages of stearic acid and Cera alba in the formulations, and 11 different formulations were prepared. Formulations are prepared with mechanical mixer method. To see the effect of variables on responses, 11 designs were prepared. The levels of the two factors were chosen based on studies done before the experimental design was applied (Maru & Lahoti, 2018). The formulations are as in the Table 1.

Table 1. Formulations ratios

Ingredients in grams	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9	MF10	MF11
Propyl paraben	0,07	0,07	0,07	0,07	0,07	0,07	0,07	0,07	0,07	0,07	0,07
Stearic acid	1	4	1	4	1	4	2,5	2,5	2,5	2,5	2,5
Cera alba	1	1	4	4	2,5	2,5	1	4	2,5	2,5	2,5
Liquid paraffin	8	8	8	8	8	8	8	8	8	8	8
Lanoline	1	1	1	1	1	1	1	1	1	1	1
Glyceryl monostearate	3	3	3	3	3	3	3	3	3	3	3
Isopropyl myristate	2	2	2	2	2	2	2	2	2	2	2
Glycerin	4	4	4	4	4	4	4	4	4	4	4
Propylene glycol	4	4	4	4	4	4	4	4	4	4	4
Borax	0,2	0,2	0,2	0,2	0,2	0,2	0,2	0,2	0,2	0,2	0,2
Methyl paraben	0,03	0,03	0,03	0,03	0,03	0,03	0,03	0,03	0,03	0,03	0,03
Water	75,7	72,7	72,7	69,7	74,2	71,2	74,2	71,2	72,7	72,7	72,7

1.3. Evaluation of formulations

The formulations were characterized by spreadability and electrical conductivity, and pH. Since phase separation was observed 24 hours after preparation in the MF3 formulation, it was not evaluated.

1.3.1. pH and electrical conductivity measurement

1 g was taken from the creams with the help of spatula diluted to 10% with distilled water. Cream pH and electrical conductivity were measured at 25 °C using a pH meter. The measurements were repeated 3 times for each formulation and the average was taken (Varma et al., 2014; Yapar et al., 2013; Ashara et al., 2014; Yilmaz et al., 2019).

1.3.2. Viscosity

The viscosities of the obtained formulations were measured at a constant rotation speed of 2-100 rpm and at 25°C using the number 4 spindle (L4) and Brookfield viscometer (Yorgancioglu & Bayramoglu, 2013). Viscosity values were found in mPa.s. Samples in 100 mL beakers were to let equilibrate for 1 minute before measuring the dial reading using a L4 spindle at 2, 4, 6, 12, 20, 30, 50, 60, 100 rpm (Sabri et al., 2016; Shelke & Kulkarni, 2019).

1.3.3. Spreadability

Spreadability measurements were made with TA.XT plus-C brand TTC Spreadability hardware HDP/SR. It consists of a 90° cone probe and precisely matched hard plastic cone-shaped product holders. First, we calibrated the device. With the help of a cream spatula, the cone-shaped product was filled in the holder so that there were no air bubbles, and then the surface was smoothed. During testing, the product was forced to flow outwards at 45 degrees from the cone probe and product holder between the cone surfaces, the ease of operation indicates the degree of spreadability. During the measurement spreadability is equivalent to the area under the curve. Measurements were repeated 3 times for each sample (Sainy et al., 2021; Glibowski et al., 2008; Calixto et al., 2018).

1.3.4. QbD studies

After generating model equations for main effects and responses, various cream formulations containing stearic acid and Cera alba were optimized based on spreadability, viscosity, and electrical conductivity. Optimal values for responses were obtained by QbD based on desirability criteria, previous studies, background knowledge, and experimental trials (Aksu et al., 2013).

Table 2. Design space formulations

Ingredients in grams	Optimum* formulation	Low edge	High edge	Low	High
Propyl paraben	0,07	0,07	0,07	0,07	0,07
Stearic acid	2,6	2	3,2	1,16	4
Cera alba	1,8	1,2	2,6	0,23	3,3
Liquid paraffin	8	8	8	8	8
Lanoline	1	1	1	1	1
Glyceryl monostearate	3	3	3	3	3
Isopropyl myristate	2	2	2	2	2
Glycerin	4	4	4	4	4
Propylene glycol	4	4	4	4	4
Borax	0,2	0,2	0,2	0,2	0,2

Methyl paraben	0,03	0,03	0,03	0,03	0,03
Water	75,7	72,7	72,7	69,7	74,2

*Optimum formula has 5 g of dexpanthenol

To optimize the experiment statistically, different batches are created using Central Composite Face design and the optimal batch was selected. The independents (Stearic acid, Cera alba) and dependents (viscosity, spreadability, electrical conductivity) were entered into the MODDE® (MODDE Pro 12.1) software program (Yilmaz et al., 2019). In this way, the Design Space and optimum formulation are given. Five different cream formulations were prepared in the range that might be good according to Design Space, to prove that creams made with values in this range will give desirable results (Kalayi et al., 2022). From previous studies, dexpanthenol has almost no effect on dependent values. For this reason, dexpanthenol is added only to the optimum formulation. QbD included formulations are prepared according to the same method as mentioned above and the quantities are given as in the Table 2.

1.3.5. Characterization of QbD Formulations

The 5 Design space formulations were evaluated in terms of pH, viscosity, spreadability, and electrical conductivity with the same methods as mentioned above.

2. Results

Eleven different batch formulations are prepared and the pH, spreadability, viscosity, and electrical conductivity measurement results are given as below.

2.1. pH and electrical conductivity

The pH of the formulations varied between 6.2 and 7.1. This pH is typical for creams containing borax, and according to ISI standards, this pH is acceptable (Maru & Lahoti, 2018). These ratios are at a level that can be buffered by the skin. The average of the 3 measurements of the creams is shown in the Table 3 below.

Table 3. pH and electrical conductivity results

Formulation Code	MF1	MF2	MF4	MF5	MF6	MF7	MF8	MF9	MF10	MF11
pH	6,8	7,1	6,4	6,9	6,6	6,3	6,6	6,5	6,3	6,6
Electrical Conductivity (µS/cm)	110	70	83,3	123,3	76,7	83,3	90	80	90	86,7

2.2. Viscosity

Viscosities of all formulations were measured and noted. Viscosity changes of cream formulations between 2-200 rpm are shown in Figure 1 and Figure 2.

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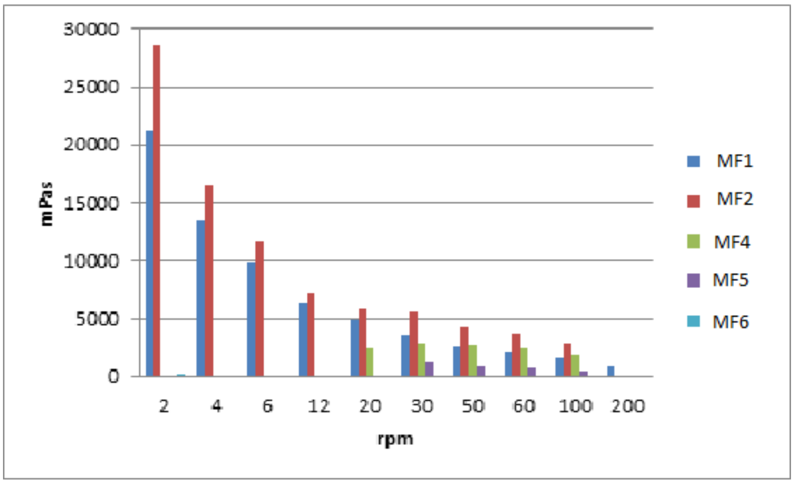

Figure 1. Viscosity comparison of MF1-MF6

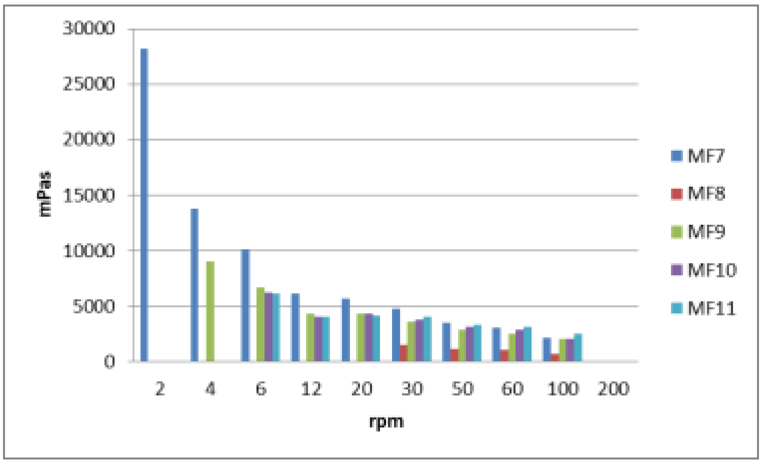

Figure 2. Viscosity comparison of MF7-MF11

2.3. Spreadability

The spreadability test was performed in triplicate for each formulation. The results are given in the Table 4.

Table 4. Results of spreadability

Formulation Code	MF1	MF2	MF4	MF5	MF6	MF7	MF8	MF9	MF10	MF11
Spreadability (g.s)	58,3925	140,9615	62,647	19,7975	62,835	89,789	21,91	71,9005	47,8965	72,0835

2.4. QbD study results

According to the QbD studies, the Design Space is given for optimum formulae. After establishing the model equations for the main effects and responses, various cream formulations containing stearic acid and Cera alba were optimized based on spreadability, viscosity, and electrical conductivity. The Design Space is as in the Figure 3. The effect and coefficients of different variables are given in the Figure 4.

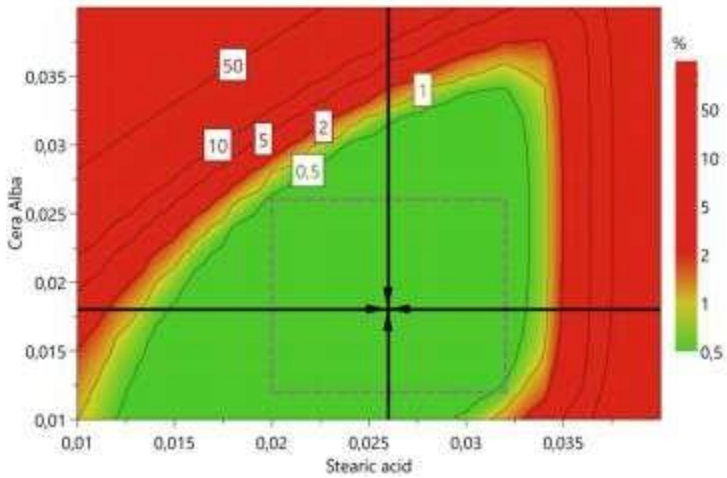

Figure 3. Design space

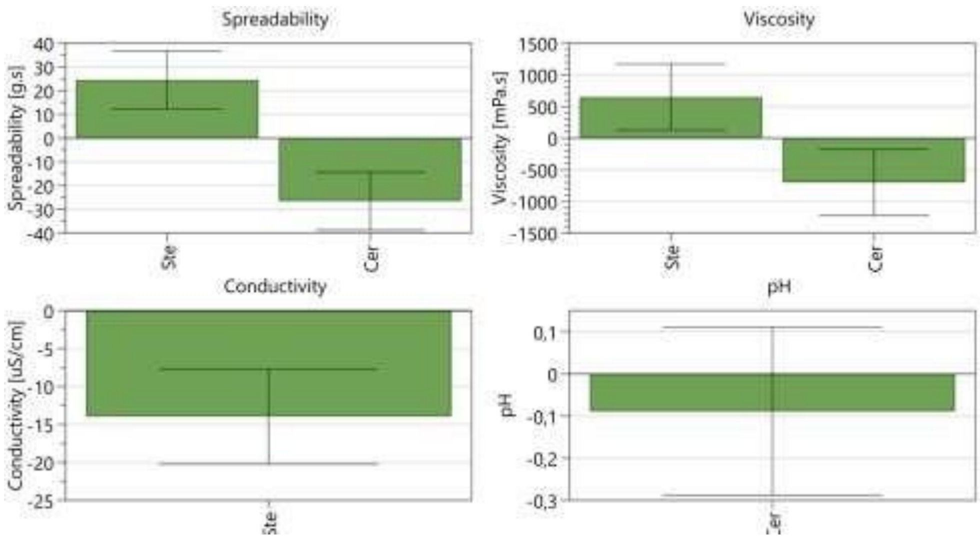

Figure 4. Coefficients

2.5. Characterization of QbD formulations

2.5.1. pH and conductivity of QbD formulations

The pH and conductivity values of the creams were found, the results as in the Table 5.

Table 5. pH and conductivity values of design space formulations

Design space formulations	Optimum	Low edge	High edge	Low	High
Conductivity (µS/cm)	250	197	237	247	127
pH	6,9	6,9	7	7,3	6,8

2.5.2. Viscosity of QbD Formulations

The viscosity of the creams was found; the results are as in the Table 6.

Table 6. Viscosity values of design space formulations

Design space formulations	Optimum	Low edge	High edge	Low	High
Viscosity (mPa.s)	3530	3540	3030	3210	3280

2.5.3. Spreadability of QbD Formulations

The spreadability values of the creams were found, the results are as in the Table 7. The Figure 5 shows the spreadability of design space formulations as a function of force-time.

Table 7. Spreadability values of design space formulations.

Design space formulations	Optimum	Low edge	High edge	Low	High
Spreadability (g.s)	95,68	96,41	93,97	95,29	91,29

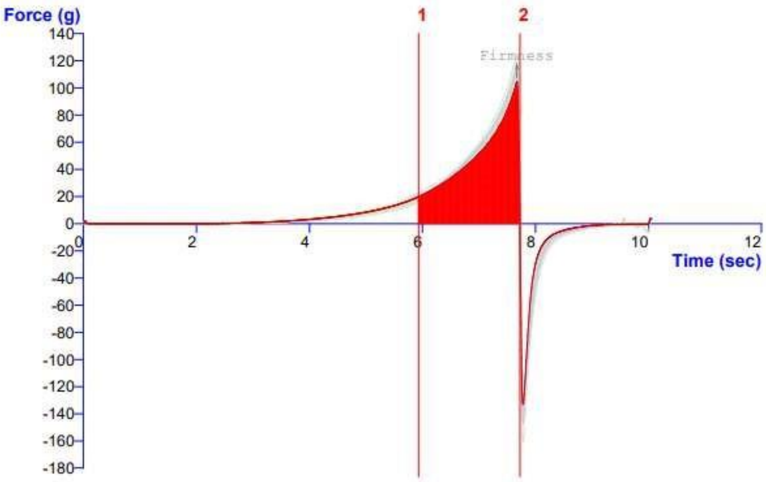

Figure 5. Spreadability of QbD formulations

3. Discussion

Prepared moisturizing cream formulations were subjected to various evaluation parameters and the results were within the rage. Central Composite Face design is suggested as the first line by the MODDE software. 11 batches were produced by the Design Space as a function of stearic acid and Cera alba in differing ratios (Bülbül et al., 2022). The green area in the Design Space is the area that gives desirable outcomes and with lower probability failure. Stearic acid and Cera alba are risk factors, their varying proportions have greatly altered the results as shown in figure 4 above. Increasing amount of stearic acid raises the spreadability and conductivity result values. Increasing amount of Cera alba lowers pH and spreadability result values. High, low, high edge, and low edge formulations from the Design Space are prepared and evaluated and the results exhibited value within the expected range.

The pH values of all formulations were in the range tolerable by the skin (Yavankar et al., 2007). The conductivity approach takes use of the fact that water has a greater conductivity than oil, and that the O/W emulsion has a higher conductivity than the W/O emulsion (Yorgancioglu et al., 2013). Since the conductivity of drinking water ranges from 50 to 1500 (µS/cm), so the emulsion type is O/W (Popek, 2018). In general, it is seen that viscosity is higher in all formulations where the amount of stearic acid is higher than the amount of Cera alba. The viscosity and spreadability are lower in formulations where the amount of Cera alba is higher than the amount of stearic acid. The formulation with the most stearic acid and the least amount of Cera alba gave the highest results in terms of viscosity and spreadability.

The MF2 formulation has greater spreadability compared to other formulations, and it has the highest viscosity according to our comparisons at 50 rpm. The high spreadability makes the active ingredient dexpanthenol easier to be absorbed (Glibowski et al., 2008; Calixto et al., 2018). The appearance, homogeneity, phase separation, colour, odour, and texture of the creams are organoleptically evaluated. Among all formulations, MF1, MF2, MF4, MF5, MF7, MF8, MF9, MF10, and MF11 showed good stability at 25°C for 4 weeks. Optimal values for responses were obtained by QbD based on desirability criteria and the optimal batch was selected. With QbD, the optimized formulation was chosen based on spreadability, electrical conductivity, and viscosity. The responses of the optimum formulation and the other 4 formulations were found within the range in the Design Space and yielded the expected results.

4. Conclusion

Human skin consists of three main layers: epidermis, dermis, and subcutaneous. The epidermis, which gives the skin its textural properties and moisture from these three layers, is important both cosmetically and dermatologically. The appearance and function of the skin are maintained by an important balance between the water content of the stratum corneum and skin surface lipids. The skin represents the most superficial layer of the body and is therefore constantly exposed to different environmental stimuli. In addition to being exposed to external factors, internal factors can also disrupt this balance. In addition, frequent use of soap, detergent, and topical irritants such as alcohol and hot water can remove lipids from the skin's surface. Disruption of the skin barrier leads to various skin problems. The most common condition is roughness, scaling, cracks, redness, and loss of water content, leading to an uncomfortable feeling of tightness and sometimes skin dryness such as itching and stinging. Treatment with the cream aims to preserve the integrity and well-being of the skin by ensuring that the person has a healthy appearance. While the number of moisturizers is listed under the label natural, safe, organic, and herbal, the basic properties of humectant, occlusive and emollient are the same in all moisturizers. Most existing moisturizers use synthetic adhesives, emulsifiers, perfumery agents, pigments, surfactants, and thickeners to create the base. Pantothenic acid is essential for normal epithelial function. Topical use of dexpanthenol, the stable alcoholic analog of pantothenic acid, improves stratum corneum hydration, reduces trans-epidermal water loss, and maintains skin softness and elasticity. Various topical preparations of dexpanthenol are now tailored to individual requirements. Topical dexpanthenol has emerged as a frequently used formulation in the field of dermatology and skincare. Various studies have confirmed the moisturizing and skin barrier-strengthening potential of dexpanthenol. It prevents skin irritation, stimulates skin regeneration, and promotes wound healing. Studies show that moisturizing creams containing dexpanthenol can be formulated with the help of borax and ionic emulsifiers. It was found that the thermophysical behaviour of the creams depended on the ratio of Cera alba and stearic acid relative to the emulsifiers. In the study, 11 batches from Central Composite Face design were applied to examine the effect of varying concentrations of the independent variable's stearic acid and Cera alba on the dependent variables which are viscosity, conductivity, pH, and spreadability. Physical instability was evaluated immediately after manufacture and after 24 hours of storage at room temperature (25 °C). All prepared moisturizing cream formulations were evaluated in terms of physicochemical parameters. The pH of all formulations was in the range that the skin could tolerate. The high spreadability facilitates the absorption of our active ingredient, dexpanthenol. Afterward, the developed formulations were examined with the QbD approach. The goals of implementing pharmaceutical QbD are to reduce product variability and defects, thereby improving product development and manufacturing efficiencies and post-approval change management. It is achieved by designing a robust formulation and manufacturing process and establishing clinically relevant specifications. The optimized formulation was compared and evaluated in terms of physicochemical parameters such as pH, spreadability, and electrical conductivity. Viscosity, spreadability, pH, and electrical conductivity tests of the optimum formulation and 4 other formulations were within the range in the design field gave the expected results. The results obtained in this research study clearly demonstrated the promising potential of a moisturizing cream containing a certain proportion of stearic acid and Cera alba and as emulsifiers and dexpanthenol as API in the moisturizing cream to achieve cosmetic benefits. Furthermore, studies can be conducted in the future regarding the stability. The study concludes that we are blessed with many the magic natural ingredients, it depends on our scientific discovery of them to treat skin-related issues. Formulators must play an active role in replacing stearic acid from dermato-cosmetics so that consumers can make the most of our traditional heritage. It is anticipated that this study will ignite further research and belief in the use of natural active ingredients in cosmetics.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR STATEMENT

No ethical approval was needed in this research.

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