History, Preparation, Characterization and Applications of Moisturizers

Subjects: Materials Science, Characterization & Testing | Others | Others

Contributor: Saeid Mezail Mawazi, Jo Ann, Noordin Othman, Jiyauddin Khan, Sultan Othman Alolayan, Sultan S. Al thagfan, Mohammed Kaleemullah

Moisturizers are one of the most widely used preparations in cosmetics and have been extensively used to soften the skin for consumers. Cosmetically, moisturizers make the skin smooth by the mechanism of increasing the water content in the stratum corneum, hence exerting its most vital action, which is moisturizing action and maintaining a normal skin pH.

Keywords: moisturizers ; cosmetics ; characterization

1. History of Moisturizer

Even though cosmetics have most certainly existed for much longer, the first evidence of cosmetics dates from about 6000 years ago in Ancient Egypt. Aloe, myrrh, and frankincense are common among Egyptians. Ancient Egyptians believed these products, particularly frankincense, had anti-aging properties and used them as anti-wrinkle creams [1]. Jain et al. (2009) also reported that men and women in Egypt used scented oils and ointments to clean and smooth their skin and mask body odor as early as 10,000 BC. Egyptian hygiene and wellbeing were inextricably linked to cosmetics. For protection against the hot sun and dry winds, oils and creams were used [2]. Egyptian customs were exported and utilized by Greeks and Roman [1][3].

Crocodile excrement, white lead and chalk were commonly used by ladies to enhance the appearance of their skin. They also made face masks out of starch and eggs, which were thought to tighten the skin, reduce wrinkles, and keep the face looking youthful [1]. The term “cosmetic” comes from the Greek word “kosmetos,” which means “adornment” or “ornament.” Ointments containing cypress, cedar, and incense resins were applied at night. Lead acetate (white lead) and cinnabar were used to treat the skin (Hg).

After the conquest of Carthage, figs (*Ficus carica L.*) became very common in Rome. In order to formulate facial cream, they were combined with banana (*Musa L.*), oats (*Avena L.*), and rose water. Galen is credited with inventing the *Frigus crepito*, a precursor to the present cold cream. It is used as a skin protector, comprising almond oil, rose water and beeswax [3]. Gels and salves were used to blanch skin in China, especially during the Shang Dynasty (1760BC). New fixings and techniques were developed and presented as skincare moved to Europe and the Middle East.

The first virus cream was made with rose oil and water, with beeswax liquefied into it. Scabs were treated with the mineral alum, and skin inflammation was treated with olive lead [1]. Creams, also known as topical formulations, have been a staple in cosmetics since ancient civilizations. Creams are cosmetic or pharmaceutical products based on the techniques applied. Unmedicated creams are widely used in a number of dermatological conditions. In ancient times, creams were simply made through the combination of two or more ingredients with water as a solvent [4]. Albert Kligman coined the term “cosmeceuticals” (a mixture of “cosmetics” and “pharmaceuticals”) in 1984 to provide an expert description of products with both cosmetic and therapeutic value [5]. Newer approaches for cream formulation are being used as technology advances; hence, the cosmetics industry today is very different from the one described earlier [4][5].

Surprisingly, there is no agreement about what constitutes a moisturizer, despite having a deep history. The word is a neologism invented by Madison Avenue advertisers to promote the simplistic notion that they moisturize the skin [6]. The inclination to add oily materials to the skin is almost instinctive, and it can date back to the dawn of time [6]. Natural substances, such as honey, oils or lipids, and fiber have been used in topical treatments to heal wounds since the ancient Egyptians [7]. Moisturizers were once thought to prevent transepidermal water loss (TEWL) by occlusion, preventing dryness, in addition to skin smoothness and elasticity maintenance [6][8].

The bricks and mortar model suggests that the stratum corneum (SC), while being a dead layer, functions as an active membrane [6]. Corneocytes are the bricks, with their tough cell membranes and keratin microfibrils, while the lipid layers between the cells are the mortar [9]. The loss of the predominant intercellular lipids that play a vital role in regulating skin humidity by forming bilayers, such as ceramides, cholesterol, and fatty acids, results in damage to the structure of the water barrier, resulting in dry skin [6][10]. When the moisture content of the skin falls below 10% and the SC loses its continuity, it is considered dry.

2. Methods of Preparation

Moisturizers can be categorized into oil in water (*o*/*w*) moisturizers and water in oil (*w*/*o*) moisturizers based on the nature of the dispersed phase [11]. Compared to ointments, water in oil (*w*/*o*) is less greasy and has better spreadability, while oil in water (*o*/*w*) readily rubs into the skin and is easily removed by water (**Table 1**) [12].

Table 1. Different dispensing formulations of moisturizers.

Class	Ointments	Lotions	Gel	Creams	References
Phase	**Oil in water (*o*/*w*) or water in oil (*w*/*o*)**	**Oil in water**	**hydrophilic or hydrophobic**	**Oil in water (*o*/*w*) or water in oil (*w*/*o*)**	[12][13]
Composition	***o*/*w* formulation consists of liquid and solid polyethylene glycol mixtures *w*/*o* formulation consists of water-insoluble hydrocarbons (hard, soft, liquid paraffin), vegetable oil, animal fats, waxes, polyalkylsiloxanes and synthetic glycerides**	**Water, propylene glycol and mineral oil**	**Hydrophilic gel (hydrogel): Water, glycerol/propylene glycol gelled with suitable agents, such as tragacanth, starch, cellulose derivatives, magnesium aluminium silicates and carboxyvinyl polymers Hydrophobic gel (oleogel): Liquid paraffin with polyethylene or fatty oils gelled with aluminium, colloidal silica or zinc soaps**	***o*/*w* formulation consists of emulsifying agents, such as sodium or triethanolamine soaps, polysorbates and sulfated fatty alcohols combined, if necessary, with *w*/*o* emulsifying agents *w*/*o* formulation consists of an emulsifier, such as wool fat, monoglycerides and sorbitan esters**	[6][14]
Preparation	**Mostly 20% water and 80% oil and hence insufficient water for separation into the second phase at room temperature**	**For better spreadability, oil in water is prepared with emulsifiers. Typically comprises of aqueous vehicle, >50% water and volatiles**	**Contains liquid phase within a three-dimensional polymeric matrix that is cross-linked physically or chemically using appropriate gelling agents**	**Preparation of *o*/*w* creams at elevated temperatures and subsequently cooled down to room temperature to allow the internal phase to solidify oil (50%) and water (50%)**	[6][14][15]
Usage	**Beneficial when a high degree of occlusion is needed. In intertriginous and moisture-bearing regions, this product should not be used**	**After-shave lotions, moisturizers for the face (daytime), body and hairy parts**	**Since it is easily absorbed and noncomedogenic, it can be used in intertriginous areas and has a high acceptability on the face**	**When occlusion is not needed. Moisturizers that can be used at night. Hands, non-hairy bits, and face (at night)**	[6][14]
Features	**Greasy, glossy look when applied. Develops a protective layer on the skin, which is particularly useful when the humidity is low (60%)**	**Nongreasy, thinner which easily cover larger area**	**Easily absorbed, smooth finishing, noncomedogenic and non-oily**	**Viscous, opaque, non-greasy to mildly greasy**	[6][14][15]

2.1. Preparation of Oil in Water (o/w) Moisturizer

The emulsifier and oil-soluble components are combined in a beaker and melted at 75 °C in a water bath. Water, water-soluble materials and preservatives are melted at 75 °C in another beaker. The oil phase is placed in a mortar and pestle after heating, and the water phase is gradually added and triturated until a clicking sound is heard. Finally, perfuming

agents and/or preservatives are added as the temperature cools down. The amount of water in this preparation will be greater than the amount of oil [16].

2.2. Preparation of Water in Oil (w/o) Moisturizer

The emulsifier and oil soluble components are melted together at 75 °C in one beaker. Water and water-soluble materials are taken to another beaker and melted at 75 °C. The water phase is placed in a mortar and pestle after melting, and the oil phase is gradually added and triturated until a clicking sound can be heard. The perfuming agent is added after the cream has cooled to the desired temperature. This preparation would have a lower amount of water phase and a higher amount of oil phase [16].

Depending on the dispensing medium, moisturizers come in a variety of formulations. A cosmetic emulsion is the most common delivery method. The emulsification method incorporates several steps that contain the active ingredients (**Table 1**) [6].

3. Characterization

3.1. Determination of pH

At room temperature, the pH of the cream can be determined using a standard digital pH meter by diluting an appropriate quantity of the formulation with a suitable solvent in a beaker [16]. However, it is advisable to calibrate the pH meter before use with a standard buffer solution at pH 4 and pH 7 [17][18]. Meanwhile, according to Maha et al. (2018), the pH of a topical preparation should be between 4.5 to 6.5, which corresponds to the pH of the skin. The pH should not be too acidic, as this can irritate the skin, nor should it be too alkaline [19].

3.2. Organoleptic Properties/Physical Appearance

Involves grading of its texture and color [16]. To be more precise, the clarity, smell, texture, and foreign particles present were evaluated. The grittiness and stickiness were determined by rubbing them between two fingers [20]. Esoje et al. (2016) suggested that this test was to be conducted randomly, at different temperatures and storage duration to observe for any changes [21].

3.3. Centrifugation Test

It is conducted to assess the chemical and physical stability of the formulation under the influence of centrifugal force [22] [23]. Five to ten grams of sample were centrifuged at 3000 rpm for 30 min at room temperature. The formulation was examined for phase separation after the centrifugation process, which is an indicator of formulation instability [22][23][24]. Meanwhile, Fernandes et al. (2018) evaluated both organoleptic (look, color, feel, thickness) and physical (phase separation and creaming) properties. Phase separation is denoted by the presence of caking, coalescence, and flocculation [25].

3.4. Mechanical Vibration Test

This test assesses the formulation's stability when subjected to mechanical vibration, which can result in phase separation and indicate instability. Five grams of sample were vibrated for 10 s on a vortex shaker (Haidalph) [24].

3.5. Spreadability

Spreadability is a term used to describe the area a topical application spreads after being applied to the skin of the affected areas, with shorter intervals indicating better spreadability [26]. Between two glass slides, the formula was applied and pressed to achieve a uniform film thickness. Following that, a weight of 10 g was added to the pan, and the top plate was pulled using a string attached to a hook. The time it takes for the upper glass slide to travel 10 cm over the lower plate is recorded, and the spreadability (S) is calculated using the formula [27].

$$\text{Spreadability} = \frac{Weight\ tied\ to\ upper\ slide\ \times\ glass\ slide\ length}{Time\ taken\ to\ separate\ slides} \quad (1)$$

3.6. Saponification Value

The saponification value is a measure of saturation, with higher values indicating shorter chain fatty acids in the glycerol bond [28]. Meanwhile, Saraf et al. (2011) stated that the saponification value is a measurement of the amount of free fatty acid esters in a sample which affects the formulation's stability, pH, and cleaning properties. The formulation's saponification value should be appropriate; if the fat content is too high, it can contain too much fatty acid, which is susceptible to hydrolysis and may lead to rancidification and microbial growth [29]. Two grams of substance were refluxed for 30 min with 25 mL of 0.5 N alcoholic KOH; then, 1 mL of phenolphthalein was applied and titrated with 0.5 N HCl right away, marking the result as 'a'. The procedure was repeated, this time omitting the material to be tested, marking the result as 'b' in the reading [16].

$$\text{Saponification value} = \frac{(b-a) \times 28.05}{weight\ of\ subtance\ (gram)} \quad (2)$$

3.7. Density

This is the proportion of a substance's mass to the volume it takes up. This parameter is an indication of air incorporation or the loss of volatile ingredients in liquids or semi-solids. A graduated cylinder and a balance were used to determine the (apparent) density of the formulations. The test was performed in triplicate with 10 mL of each formulation, and an average was determined. The apparent density is correlated with the recipient's capacity [24].

3.8. Light Test

The formulations were placed in clear plastic containers and exposed to intense light for 15 days using a daylight bulb with a photoperiodicity system consisting of 16 h of light and 8 h of dark. The samples were analyzed for any changes in physical properties, such as clarity, appearance, or color, as well as liquefaction, at the end of the exposure period. Any visible phase separation or color change is an indication of product instability [24].

3.9. Acid Value

The acid value is a measurement of the amount of free acid in fats or oils that causes rancidity upon exposure to heat or light [30]; 10 g of substance was dissolved in a precisely weighted 50 mL mixture of equal parts alcohol and solvent ether. The flask was attached to a reflux condenser and slowly heated until the sample was fully dissolved; 1 mL of phenolphthalein was added and titrated with 0.1 N NaOH until the appearance of a slightly pink color after 30 s of shaking [16].

$$\text{Acid value} = \frac{no.\ of\ mL\ of\ 0.1\ \text{N KOH solution} \times 5.61}{weight\ of\ subtance\ (gram)} \quad (3)$$

3.10. Viscosity

The viscosity is used to evaluate the formulation's stability with regard to consistency and as a result, to predict how the substance will behave over time [24]. The Brookfield Viscometer can be used to calculate the viscosity of formulated creams [16]. Viscosity values are calculated by multiplying the dial reading with correction factors in the Brookfield viscometer. Increased viscosity during storage indicates kinetically unstable emulsions, in which free-moving droplets collide and appear to coalesce [19].

3.11. Homogeneity

Shows the distribution of materials in the formula [19]. Touch and visual appearance were used to check for homogeneity [16]. The homogeneity of cream can be assessed by smearing 50 mg of preparations onto a clean object-glass, showing a homogeneous arrangement with no clear grain observation [19]. Homogeneity and texture were conducted simultaneously by Chen et al. (2016) by pressing a small amount of the formulation between the thumb and index finger to assess the presence of coarse particles. The immediate skin feel was also assessed, which includes stiffness, grittiness, and greasiness [31].

3.12. Dye Test

To determine the type of emulsion [17]. A drop of cream was placed on a slide after the cream was mixed with scarlet dye. Then, the slide was covered with a coverslip and examined under a microscope; *o*/*w* creams have dispersed globules that appear red and the ground is colorless and vice versa for *w*/*o* creams [16].

3.13. After Feeling Test

After application of a fixed amount of cream, the slipperiness, emollience and residue left were assessed [16].

3.14. Type of Smear

The smear pattern developed on the skin after the cream application was assessed [16].

3.15. Irritancy Study

This test determines the characteristics of produced formulations in terms of skin irritation [32]. On the left-hand dorsal surface, draw a 1 sq.cm section. The cream was applied to the designated location, and the duration was recorded. Erythema, irritation and edema were assessed and recorded at regular intervals for up to 24 h [16]. Another type of skin irritation test was conducted using albino rabbits. During the test time, these animals were held in separate cages and given fresh food and water; 24 h before the test, the fur on the neck and thighs was shaved to reveal a sufficiently wide test area. Surgical spirit was used to disinfect the test site briefly. The test area was then covered with cream. For 24 h, 48 h, and 72 h after application, the test site was monitored for erythema and edema [26]. Irritancy studies should be performed on animals prior to human studies. Once the prepared formulation demonstrated high compliance in animal tests, then it could be applied to healthy human volunteers to determine its safety for topical use [33]. Both animal and human studies are preferably conducted in skin irritancy tests as some substances are harmful to rabbits but not to humans, and vice versa [33][34].

3.16. Spectrophotometric Test

It is another form of stability testing involving the dilution of formulations in ultra-pure water at a ratio of 1/100 (*m*/*v*); then they are analyzed using spectrophotometry in the UV-VIS region (210 nm to 600 nm), with the spectrum compared to the control formulation's reference spectrum. Formulation instability is described as variations in intensity or absorption bands' wavelength. This indicates that some changes have occurred in the color intensity or even modification of the coloring content [24].

3.17. Microbial Stability

The microbial contamination test was used to assess the formulations' microbial stability. After preparing the bacteria and yeast culture medium, it was autoclaved for 20 min at 125 °C, and then 20 mL of the culture medium was poured into a sterile Petri dish. The Petri dishes were then inoculated with 0.2 g of each formulation in the center of each plate, and incubated for 3 days at 37 °C or 25 °C, depending on the inoculated microorganisms. Plates were removed after the incubation period and tested for microbial growth, which indicates contamination [24].

3.18. In Vitro Occlusivity Test

The occlusion factor was used to assess the formulations' occlusivity. When the occlusion factor is zero ("0"), there is no occlusion effect when compared to the reference; "100" is the highest occlusion factor, indicating complete surface coverage by the topical formulation [35][36]. Creams with a higher occlusion effect result in more moist skin that is more pliable and maintains its moisturizing effect [36]. Each beaker with a height of 4.6 cm and a diameter of 3.2 cm was filled with 10 g of distilled water. Then, the open end was covered with Whatman filter paper (0.45 pore size) on which 200 mg of the sample was uniformly distributed. After that, the beakers were set at 37 ± 2 °C/607 ± 5% RH for 48 h. The in vitro occlusivity of all formulations, prototype formulations, and the negative control in which the filter paper was left uncovered were investigated to determine the water flux. The occlusion factor F was determined as follows [37]:

$$\mathrm{F} = \frac{A - B}{A} \times 100 \quad (4)$$

where *A* = Water flux via uncovered filter (percent water loss) and *B* = Water flux via filter when covered by test preparation (percent water loss).

3.19. Accelerated Stability Study

According to ICH guidelines, all formulations were subjected to accelerated stability testing for a duration of 2 weeks at a temperature of 25 ± 2 °C and 40 ° ± 2 °C, with two relative humidity conditions, specifically 60 ± 5% RH and 75 ± 5% RH. The cosmetic formulations were examined for organoleptic characteristics (texture, smell, color, phase separation and consistency) and their pH value was determined after 8 days. At the end of the storage period, the process was repeated [16][24].

3.20. Preference Test

Color, scent and skin sensation were the criteria of preference tests focused on sensory assessment. A numerical scale was used to determine the degree of preference as based on the **Table 2** [27]:

Table 2. Different dispensing formulations of moisturizers.

5	**like extremely**
4	**like**
3	**neutral**
2	**dislike**
1	**dislike extremely**

4. Uses and Applications

Moisturizers are beneficial for a variety of purposes. There is evidence of biological effects that support the use of moisturizers in medicine [38]. Many moisturizers block cyclooxygenase activity, which inhibits the development of proinflammatory proteinoids, and thus have a calming effect on inflamed skin, leading to their anti-inflammatory action. Mineral oil-based moisturizers have a low-level antimitotic effect on the epidermis, making them effective in inflammatory dermatoses, such as psoriasis, which have increased epidermal mitotic activity. Emollients reduce itching by inhibiting the development of cytokines. In addition, the cooling effect of water evaporating from the skin surface after using water-based moisturizers contributes to the antipruritic effect. Sunscreens with varying sun protection factors are also used in moisturizers, offering extra sun protection (photoprotective action). Moisturizers also have antimicrobial and wound-healing properties [6].

Skin hydration, friction, scaling, and mechanical properties are all affected by moisturizers. A series of changes occur after a single application of a moisturizer, all of which reflects the moisturizer’s composition. Initial changes tend to be related to the moisturizer’s water content, which includes increased evaporation from the skin surface, decreased temperature, and skin softening. Changes occur with repeated applications over time, which are assumed to be caused by the moisturizer’s lipid phase, involving a reduction in scaling, increased hydration and discrete color changes. Specific additives, such as urea, alpha-hydroxy acids, or glycerol, may help to reinforce some of these improvements [38].

Moisturizers are often prescribed as preventative measures and adjunct therapy for a variety of dermatological conditions. Moisturizers seem to be able to reverse some of the barrier defects seen in conditions, such as atopic dermatitis, allowing for improved disease control. Moisturizers have been studied for their adjuvant properties. The use of a moisturizer as an alternative to active corticosteroid treatment of the skin has been shown to minimize the quantity of corticosteroids required, without compromising treatment efficacy. It is postulated that the moisturizer’s lipid content may play a role, but the mechanism underlying this remains unclear [38].

There is also a possibility that applying a moisturizer meets an atavistic psychological desire for physical contact, which is reinforced by the moisturizer’s immediate physical impact. Using a moisturizer necessitates extensive touching, either by oneself or by another person, resulting in enhanced sensory perception. It is also likely that additional psychological factors may be overlooked when moisturizers are used, such as stress coping and a sense of security, thus reinforcing the use of moisturizers [38].

Moisturizers are often advertised and, as a result, are able to generate significant revenue for all advertising companies. While emolliency is an essential feature of moisturization, advertisement has almost fully replaced the conventional definition of creams or emollients. Marketing concepts promote that skin that is dry and dull is unattractive, while young and attractive skin is supple and moist. Moisture is needed for dry skin, which obviously can be compensated by the

usage of moisturizers. Although there is no sufficient evidence of a sex disparity in dryness parameters, the strong focus on this chain of reasoning has persuaded a large number of women that their skin is dry, further promoting the expanded use of moisturizers [38].

References

1. Cheong, W.K. Gentle Cleansing and Moisturizing for Patients with Atopic Dermatitis and Sensitive Skin. Am. J. Clin. Dermatol. 2009, 10, 13–17.
2. Ak, M. Cosmetics in use: A pharmacological review. J. Dermatol. Cosmetol. 2019, 3, 50–67.
3. Chaudhri, S.K.; Jain, N.K. History of cosmetics. Asian J. Pharm. 2009, 3, 164–167.
4. González-Minero, F.J.; Bravo-Díaz, L. The Use of Plants in Skin-Care Products, Cosmetics and Fragrances: Past and Present. Cosmetics 2018, 5, 50.
5. Mohiuddin, A.K. Skin Care Creams: Formulation and Use. Am. J. Dermatol. Res. Rev. 2019, 2, 1–45.
6. Sethi, A.; Kaur, T.; Malhotra, S.; Gambhir, M. Moisturizers: The slippery road. Indian J. Dermatol. 2016, 61, 279–287.
7. Amberg, N.; Fogarassy, C. Green Consumer Behavior in the Cosmetics Market. Resources 2019, 8, 137.
8. Hartmann, A. Back to the roots-die Anfänge der Dermatologie in der altägyptischen Medizin. JDDG 2016, 14, 389–396.
9. Hamishehkar, H.; Same, S.; Adibkia, K.; Zarza, K.; Shokri, J.; Taghaee, M.; Kouhsoltani, M. A comparative histological study on the skin occlusion performance of a cream made of solid lipid nanoparticles and Vaseline. Res. Pharm. Sci. 2015, 10, 378–387.
10. Wickett, R.R.; Visscher, M.O. Structure and function of the epidermal barrier. Am. J. Infect. Control 2006, 34, S98–S110.
11. Sarkar, R.; Sinha, S. The Sensitive Skin: Treatment Modalities and Cosmeceuticals, 1st ed.; Jaypee Brothers Medical Pub: New Delhi, India, 2019.
12. Ghadially, R.; Halkier-Sorensen, L.; Elias, P.M. Effects of petrolatum on stratum corneum structure and function. J. Am. Acad. Dermatol. 1992, 26, 387–396.
13. Simões, A.; Veiga, F.; Vitorino, C.; Figueiras, A. A Tutorial for Developing a Topical Cream Formulation Based on the Quality by Design Approach. J. Pharm. Sci. 2018, 107, 2653–2662.
14. Loden, M. The clinical benefit of moisturizers. J. Eur. Acad. Dermatol. Venereol. 2005, 19, 672–688.
15. Garg, T.; Rath, G.; Goyal, A.K. Comprehensive review on additives of topical dosage forms for drug delivery. Drug Deliv. 2014, 22, 969–987.
16. Gilbert, L.; Picard, C.; Savary, G.; Grisel, M. Impact of Polymers on Texture Properties of Cosmetic Emulsions: A Methodological Approach. J. Sens. Stud. 2012, 27, 392–402.
17. Annunziata, M.C.; Cacciapuoti, S.; Cosentino, C.; Fabbrocini, G. Urea-containing topical formulations. Int. J. Clin. Pract. 2020, 74, 1–4.
18. Buhse, L.; Kolinski, R.; Westenberger, B.; Wokovich, A.; Spencer, J.; Chen, C.W.; Turujman, S.; Gautam-Basak, M.; Kang, G.J.; Kibbe, A.; et al. Topical drug classification. Int. J. Pharm. 2005, 295, 101–112.
19. Muthukumarasamy, R.; Ilyana, A.; Fithriyaani, N.A.; Najihah, N.A.; Asyiqin, N.; Sekar, M. Formulation and evaluation of natural antioxidant cream comprising methanolic peel extract of Dimocarpus longan. Int. J. Pharm. Clin. Res. 2016, 8, 1305–1309.
20. Apriani, E.F.; Rosana, Y.; Iskandarsyah, I. Formulation, characterization, and in vitro testing of azelaic acid ethosome-based cream against Propionibacterium acnes for the treatment of acne. J. Adv. Pharm. Technol. Res. 2019, 10, 75–80.
21. Maha, H.L.; Sinaga, K.R.; Masfria, M. Formulation and evaluation of miconazole nitrate nanoemulsion and cream. Asian J. Pharm. Clin. Res. 2018, 11, 319–321.
22. Mawazi, S.M.; Al-Mahmood, S.M.A.; Chatterjee, B.; Hadi, H.A.; Doolaanea, A.A. Carbamazepine Gel Formulation as a Sustained Release Epilepsy Medication for Pediatric Use. Pharmaceutics 2019, 11, 488.
23. Esoje, E.; Muazu, J.; Madu, S.J. Formulation and in-vitro assessment of cream prepared from Allium cepa L., bulb. Asian J. Pharm. Sci. Technol. 2016, 6, 1–5.
24. Tan, A.S.B.; Tüysüz, M.; Ötük, G. Investigation of preservative efficacy and microbiological content of some cosmetics found on the market. Pak. J. Pharm. Sci. 2013, 26, 153–157.

25. Deuschle, V.C.K.N.; Deuschle, R.A.N.; Bortoluzzi, M.R.; Athayde, M.L. Physical chemistry evaluation of stability, spreadability, in vitro antioxidant, and photo-protective capacities of topical formulations containing Calendula officinalis L. leaf extract. Braz. J. Pharm. Sci. 2015, 51, 63–75.
26. Navarro-Pérez, Y.M.; Cedeño-Linares, E.; Norman-Montenegro, O.; Ruz-Sanjuan, V.; Mondeja-Rivera, Y.; Hernández-Monzón, A.M.; González-Bedia, M.M. Prediction of the physical stability and quality of o/w cosmetic emulsions using full factorial design . J. Pharm. Pharmacogn. Res. 2021, 9, 98–112.
27. Fernandes, L.D.S.; Amorim, Y.M.; da Silva, E.L.; Silva, S.C.; Santos, A.J.A.; Peixoto, F.N.; Pires, L.M.N.; Sakamoto, R.Y.; Pinto, F.D.C.H.; Scarpa, M.V.C.; et al. Formulation, stability study and preclinical evaluation of a vaginal cream containing curcumin in a rat model of vulvovaginal candidiasis. Mycoses 2018, 61, 723–730.
28. Ugandar, R.; Deivi, K. Formulation and evaluation of natural palm oil based vanishing cream. Int. J. Pharm. Sci. Res. 2013, 4, 3375–3380.
29. Saptarini, N.M.; Hadisoebroto, G. Formulation and evaluation of lotion and cream of nanosized chitosan-mangosteen (Garcinia mangostana L.) pericarp extract. Rasayan J. Chem. 2020, 13, 789–795.
30. Nurah, T.O.; Wmadb, F.; Ranil, C.; Isona, G.; Vijay, J. Effect of extraction techniques on the quality of coconut oil. Afr. J. Food Sci. 2017, 11, 58–66.
31. Jeswani, G.; Saraf, S. Development of novel herbal cosmetic cream with Curcuma longa extract loaded transfersomes for antiwrinkle effect. Afr. J. Pharm. Pharmacol. 2011, 5, 1054–1062.
32. Ahmed, S.; Hoque, M.M.; Zzaman, W.; Thakur, M.U.; Hossain, M.M. Study on physicochemical and anti-oxidant properties of coconut cream extracted from two BARI varieties. Int. Food Res. J. 2019, 26, 153–160.
33. Chen, M.X.; Alexander, K.S.; Baki, G. Formulation and Evaluation of Antibacterial Creams and Gels Containing Metal Ions for Topical Application. J. Pharm. 2016, 2016, 5754349.
34. El-Gied, A.A.A.; Abdelkareem, A.M.; Hamedelniel, E.I. Investigation of cream and ointment on antimicrobial activity of Mangifera indica extract. J. Adv. Pharm. Technol. Res. 2015, 6, 53–57.
35. More, B.H.; Sakharwade, S.N.; Tembhurne, S.V.; Sakarkar, D.M. Evaluation for Skin irritancy testing of developed formulations containing extract of Butea monosperma for its topical application. Int. J. Toxicol. Appl. Pharmacol. 2013, 3, 10–13.
36. Bracken, M.B. Why animal studies are often poor predictors of human reactions to exposure. J. R. Soc. Med. 2009, 102, 120–122.
37. Shetty, P.K.; Venuvanka, V.; Jagani, H.V.; Chethan, G.H.; Ligade, V.S.; Musmade, P.B.; Nayak, U.Y.; Reddy, M.S.; Kalthur, G.; Udupa, N.; et al. Development and evaluation of sunscreen creams containing morin-encapsulated nanoparticles for enhanced UV radiation protection and antioxidant activity. Int. J. Nanomed. 2015, 10, 6477–6491.
38. Lundov, M.D.; Moesby, L.; Zachariae, C.; Johansen, J.D. Contamination versus preservation of cosmetics: A review on legislation, usage, infections, and contact allergy. Contact Dermat. 2009, 60, 70–78.