



“Formulation and evaluation of Topical Analgesic Creams: A Comprehensive Review”

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Abstract

The skin, the body's largest organ, serves as a protective barrier and plays a key role in maintaining homeostasis. Pain, an unpleasant sensory and emotional response, can be managed through various pharmaceutical approaches, including topical formulations. Creams, as semisolid emulsions, offer advantages such as ease of application, improved patient compliance, and targeted drug delivery. This review explores skin structure, pain classification, cream formulations, evaluation parameters, and marketed analgesic creams. Understanding these aspects aids in the development of more effective and stable topical treatments for pain management.

Keyword: Skin structure, Pain management, Creams, Marketed Formulation for Pain relief Cream, essential oil

Introduction

Skin: The Skin is the largest organ of the body, and major portion interface with the environment, the skin composed of specialized epithelia and connective tissue cells have many protective and synthetic Function.^{1,2} The skin contains several layers, in that outer layer is called epidermis; the layer below epidermis is called dermis. The dermis contains a network of blood vessels, hair follicle, sweat gland and sebaceous gland. Beneath the dermis, subcutaneous fatty tissues.³ and bulbs of hairs projects towards the fatty tissue.

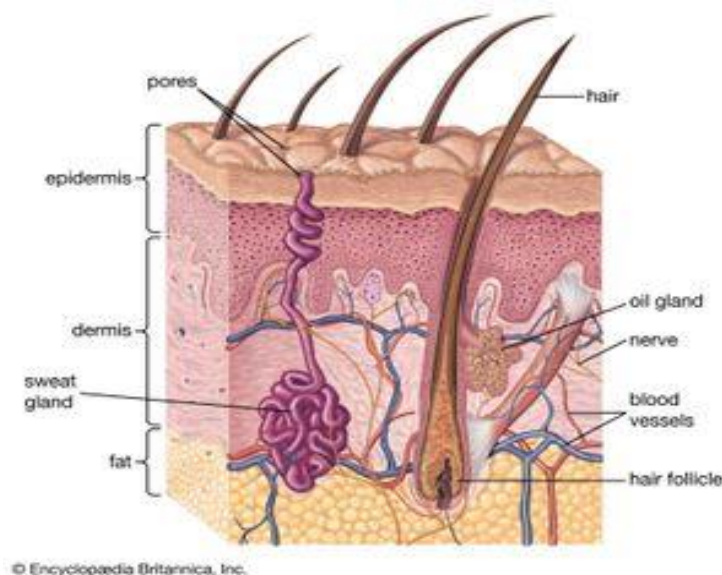


Figure1: Cross Section of Skin

Functions of skin:

- Helps as hindrance for physical, organic and compound operators.
- Avert parching
- Photochemical production of vitamin D
- Assists as tangible organ
- Excretion by means of sweat

Layers of Skin:

1. Epidermis: The epidermis is external layer of the skin, characterized as a delineated squamous epithelium; essentially containing keratinocytes in reformist phases of separation.⁴ Keratinocytes produce the protein keratin and are the significant structure blocks (cells) of the epidermis. As the epidermis is avascular (contains no veins), it is altogether reliant upon the hidden dermis for supplement conveyance and garbage removal through the storm cellular layer. The great capacity of the epidermis is to go about as a physical and natural boundary to the outside climate, forestalling entrance by aggravations and allergens. Simultaneously, it forestalls the deficiency of water and keeps up inward homeostasis.⁵

The layers are:

- Stratum corneum (horny layer)
- Stratum lucidum (found only in thick skin – i.e., the palms, the soles and the digits)
- Stratum granulosum (granular layer)
- Stratum spinosum (prickle cell layer)
- Stratum basale (germinative layer)

2. Dermis: The dermis frames the inward layer of the skin is thicker than the epidermis (1-5mm).⁶ The essential part of the dermis is it's arrangement between the cellar film zone and the subcutaneous layer to maintain and uphold the epidermis.

The fundamental elements of the dermis are:

- Protection
- Cushioning the more profound designs from mechanical injury
- Providing sustenance to the epidermis
- Playing a significant part in injury mending

3. Hypodermis: The hypodermis is the subcutaneous layer lying underneath the dermis; it comprises generally of fat. It offers the primary underlying help for the skin, just as protecting the body from cold and supporting stun retention. It is joined with veins and nerves.

Pain

Pain is defined as an unpleasant sensory and emotional phenomenon related to actual or potential cell/tissue damage.⁷ This phenomenon common to various biological responses such as as stubbing a toe, burning/heating etc.

Symptoms of pain:

- Nausea
- Dizziness
- Drowsiness
- Depression
- mood swings
- irritability

Causes of pain:

- Restlessness
- Grimacing
- Resistance to care
- Not eating
- Sleeping problems
- Increased wandering

Types of Pain

Pain can be classified into two types

1. Acute pain
2. Chronic pain
3. Neuropathic Pain
4. Nociceptive Pain

Essential Oils

Essential oils (EO) are complex mixtures of volatile organic compounds produced as secondary metabolites in plants; they are constituted by hydrocarbons (terpenes and sesquiterpenes) and oxygenated compounds (alcohols, esters, ethers, aldehydes, ketones, lactones, phenols and phenol ethers).⁸

Table 1. List essential oils used as analgesic activity

S. no	Botanical Name (Family)	Chemical constituents	Experimental Model	Activity	Reference
1	<i>Eucalyptus citriodora</i> Myrtaceae	Monoterpenoid Citronellal	Hot plate test Acetic acid-induced writhing test	Analgesic Anti- inflammatory	9
2	<i>Eucalyptus globulus</i> Myrtaceae	Eucalyptol (1,8-cineole)	Hot plate test Acetic acid-induced writhing test	Analgesic Anti- inflammatory	9
3	<i>Eucalyptus tereticornis</i> Myrtaceae	eucalyptol (1,8-cineole)	Hot plate test Acetic acid-induced writhing test	Analgesic Anti- inflammatory	9
4	<i>Senecio rufinervis</i> Asteraceae	Germacrene D β -pinene β -caryophyllene	Acetic acid writhing test Hot-plate test	Analgesic	10
5	<i>Lippia gracilis</i> Verbenaceae	flavonoids triterpenoids carbohydrate	Acetic acid-induced abdominal writhes test	Analgesic Anti- inflammatory	13
6	<i>Pelargonium inquinans</i> Geraniaceae	Camphor α -caryophyllene β -caryophyllene linalool α -terpineol	Acetic acid-induced writhing test Hot plate test	Analgesic Anti- inflammatory	14
7	<i>Piper aleyreanum</i> Piperaceae	Caryophyllene oxide b-pinene camphene	Formalin-induced Test	Analgesic Anti- inflammatory	15
8	<i>Ocimum gratissimum</i> Lamiaceae	humulene epoxide germacrene D β - caryophyllene	Hot plate test Formalin test	Analgesic	16
9	<i>Sphaeranthus indicus</i> Asteraceae	eugenol, myrcene tran- caryophyllene	Hot plate test	Analgesic	17
10	<i>Citrus aurantium</i> Rutaceae	Citral myrcene geraniol caryophyllene linalool	Acetic acid-induced writhing test Hot plate models	Analgesic Anti- inflammatory	18

11	<i>Bunium persicum</i> Apiaceae	gamma-terpinene cuminal p-cymene	Acetic acid-induced writhing test Formalin test	Analgesic Anti- inflammatory	23
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Creams: Creams are semisolid topical formulations designed for application to the skin and mucous membranes, including rectal and vaginal use. They are widely utilized in both pharmaceutical and cosmetic applications, with unmedicated creams playing a significant role in managing various dermatological conditions. Pharmaceutical creams are emulsions, classified as either water-in-oil (e.g., Cold Cream) or oil-in-water (e.g., Fluocinolone Acetonide Cream), containing active pharmaceutical ingredients dissolved or dispersed in a suitable base. The Fingertip Unit (FTU) concept serves as a guideline for determining the appropriate quantity required for application to different body areas.⁸

Types of Creams

They are divided into two types:

1. Oil-in-Water (O/W) creams : which are composed of small droplets of oil dispersed in a continuous phase, and an emulsion in which the oil is dispersed as droplets throughout the aqueous phase is termed an oil-in-water (O/W) emulsion.

2. Water-in-Oil (W/O) creams: which are composed of small droplets of water dispersed in a continuous oily phase. When water is the dispersed phase and an oil the dispersion medium, the emulsion is of the water-in-oil (W/O) type.⁹

Classification of Creams¹⁰

All the skin creams can be classified on different basis:

1. According to function, e.g. cleansing, foundation, massage, etc.
2. According to characteristics properties, e.g. cold creams, vanishing creams, etc.
3. According to the nature or type of emulsion.

Types of creams according to function, characteristic properties and type of emulsion:

1. Make-up cream (o/w emulsion):

- Vanishing creams.
- Foundation creams.

2. Cleansing cream, Cleansing milk, Cleansing lotion (w/o emulsion)

3. Winter cream (w/o emulsion):

- Cold cream or moisturizing creams

4. All-purpose cream and general creams

5. Night cream and massage creams

6. Skin protective cream

7. Hand and body creams

Advantage of cream

- Convenience and easy to apply
- Smoother consistency
- Exhibit better contact with the skin
- Avoid first pass metabolism
- Easily washable

Disadvantage of cream

- Water content makes them prone to microbial contamination
- Some ingredients can cause sensitivity or irritation

Method of preparation

1. Preparation of o/w emulsion cream

The oil soluble components and the emulsifier are taken in one beaker and melted in a water bath at 75°C.



Other beaker water, preservatives and water-soluble components are taken and melted at 75°C.



After heating water phase are taken in mortar and pestle and slowly oil phase was added and triturated till clicking sound was heard.



Finally, when the temperature cools down, perfuming agents and/or preservatives are added. In this preparation, water content will be more than the oil.

Figure 2: Flowchart of Preparation of o/w emulsion cream

2. Preparation of w/o emulsion creams

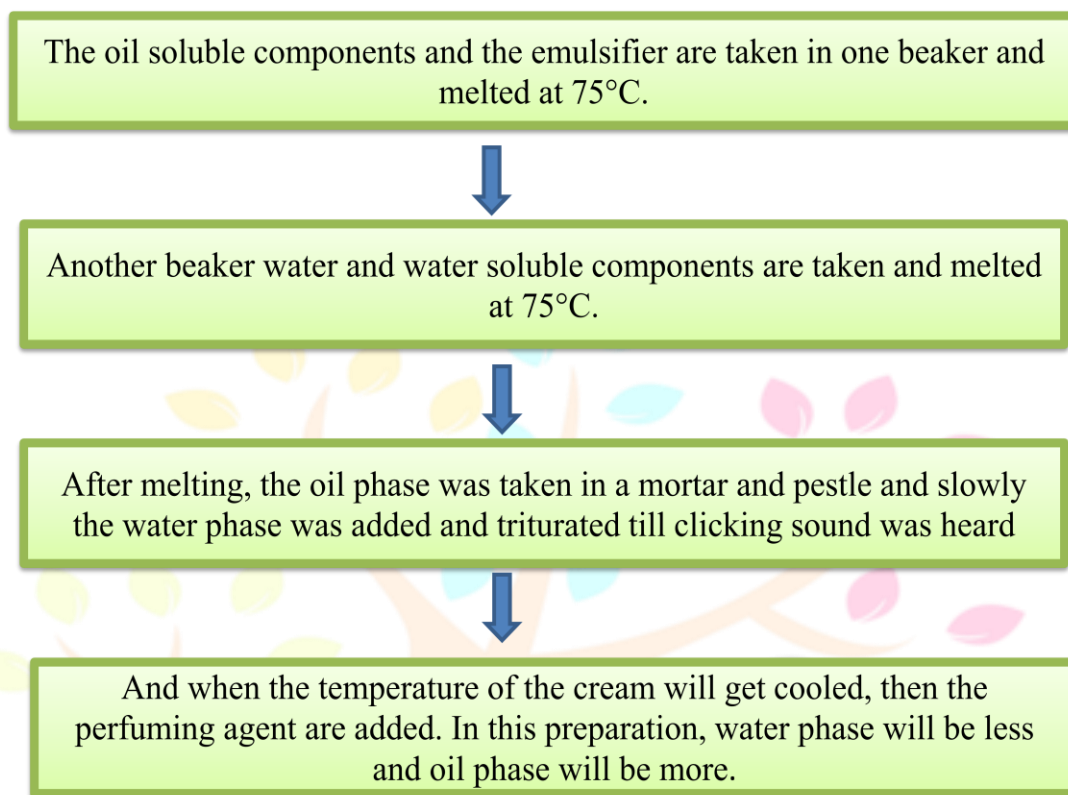


Figure 3: Flowchart of Preparation of w/o emulsion cream

Application of Cream

- Skin softening
- Smoothing
- Moisturizing
- Anti-allergic
- Antiseptic

Table 2: Marketed Formulation for Pain relief Cream

S.no	Brand name	Active ingredient	Inactive ingredient
1	Aspercreme	Lidocaine HCL	Water, alcohol denat (10%), cetearylalcohol, ceteth-20phosphate, dimethicone, caprylmethicone, dicetylphosphate, glycerylstearate, methylparaben, disodium EDTA, Aloe barbadensis leaf juice, panthenol, tocopherylacetate, magnesium ascorbyl phosphate, aminomethylpropanol, C30-45alkylcetearyl dimethicone crosspolymer, acrylates/C10-30 alkyl acrylate cross polymer, ethylhexylglycerin, Citric acid
2	Bengay	Camphor -4% Menthol-10% methyl Salicylate-30%	Carbomer, Stearic acid, Potassium hydroxide, polysorbate 80, lanolin, purified water, edetate disodium glyceryl stearate se
3	Capsaicin	Capsaicin- 0.1%	Aloe barbadensis leaf juice, Ethylparaben glycerin, glyceryl monostearate mineral oil, petrolatum, purified water, sodium lauryl sulfate, stearyl alcohol
4	Icyhot	Menthol – 10% Methyl salicylate -30%	Carbomer, cetearylalcohol, cetyl esters, Oleth-3 Phosphate Polysorbate 60, Stearic acid triethanolamine, water
5	Salonpas	Lidocaine HCl 4% (Topical anesthetic) Benzyl Alcohol 10% (Topical anesthetic)	Aloe barbadensis leaf juice, Aminomethyl propanol, Butylene glycol, Carbomer copolymer, Cetearyl alcohol, Ceteth phosphate, Dicetyl phosphate, Dimethicone, Glyceryl monostearate, Hydroxyl acrylate/sodium acryloyldimethyl taurate copolymer Polysorbate, SD alcohol 40-B Squalane, Steareth, Water
6	Tylenol	Lidocaine-4%	Carbomer copolymer Cetearyl olivate, Cetylalcohol, Fragrance, Glycerin, Isopropyl Palmitate, Phenoxyethanol, Sodium polyacrylate, Sorbitane olivate, Vanillyl butyl ether water
7.	Rugby	Menthol – 1.0% Methyl Salicylate – 15.0%	Carbomer, Cetearyl Alcohol, Dimethicone, Glycerin, Methylparaben, Polysorbate 60, Propylparaben, Sodium Hydroxide, Sodium Lauryl Silfate, Water.

8.	Topricin	Aesculus hippocastanum 6X Arnica montana 3X Belladonna 6X Crotalus horridus 12X - Echinacea 3X Graphites 3X Heloderma 12XL achesis mutus 12X Naja tripudians 12X Rhus toxicodendron 8X Ruta graveolens 3X	Captex 300 (from coconut fatty acids), Carbopol® Ultrez 10 (from Sucrose), Cetyl Alcohol (from coconut oil), Glycerine (vegetable-based), Hydrokote(palm kernel oil with lecithin), Isopropyl Myristate emollient (from palm seeds), Lipomulse (from coconut fatty acids), Purified water, Sodium Hydroxide, Spectrastat G2 (derived from coconut), Steareth-21 (from stearic acid cocoa butter).
9.	Walgreens	Lidocaine HCL – 4%	Benzyl alcohol, Carbomer, Glycerin, hydrogenated lecithin, isopropyl palmitate, polysorbate 80, triethanolamine, vitamin E, Water.

Evaluation Parameters of Creams:¹⁰

1. **pH Determination:** The pH of the formulation is measured using a digital pH meter at room temperature after dilution with a suitable solvent.
2. **Physical Appearance:** Assessed based on color, texture, and overall visual characteristics.
3. **Spreadability:** Evaluated by placing the sample between glass slides under a fixed weight, calculated as:
4. **Saponification Value:** Determined by refluxing the sample with alcoholic KOH, followed by titration with HCl.
5. **Acid Value:** Measured by dissolving the sample in an alcohol-ether mixture, heating, and titrating with NaOH.
6. **Viscosity:** Assessed using a Brookfield viscometer.
7. **Homogeneity:** Examined through visual and tactile assessment.
8. **Ease of Removal:** Evaluated by washing with tap water.
9. **Dye Test:** Determines emulsion type using a scarlet dye and microscopic observation.
10. **After Feel:** Assesses emolliency, slipperiness, and residue post-application.
11. **Smear Type:** Observes the film formed on the skin after application.
12. **Irritancy Study:** Conducted by applying the cream to a marked area and monitoring for erythema or edema over 24 hours.
13. **Accelerated Stability Study:** Accelerated stability study is conducted for formulation according to ICH guidelines.

Conclusion

The skin, as the body's primary protective barrier, plays a crucial role in maintaining homeostasis. Pain, a multifaceted physiological response, can be effectively managed through topical formulations such as creams. These semisolid preparations offer localized action, ease of application, and improved patient compliance. Proper formulation, classification, and evaluation are essential to ensure their efficacy and stability. Advancements in topical drug delivery systems may further enhance the therapeutic potential of analgesic creams.

Conflicts of Interest: The authors declare that there are no conflicts of interest.

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