

Available online on 15.06.2019 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

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Review Article

Pharmaceutical Creams and their use in wound healing: A Review

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ABSTRACT

Creams have been used as topical preparations since time immemorial due to their ease of application to the skin and also their removal. Pharmaceutical creams have a variety of applications ranging from cosmetic purposes such as cleansing, beautifying, altering appearance, moisturizing etc. to skin protection against bacterial, fungal infections as well as healing cuts, burns, wounds on the skin. The human skin is easily vulnerable to injury but it has the capability to heal on its own. However, the natural healing process can take time and there is also risk of infection especially in the early stages of injury. In such cases, creams can be applied to the site of injury to speed up the healing process as well as protect the wound from infection. In this review of literature, we have focused on the use of pharmaceutical creams for wound healing with detailed discussion relating to the wound healing process, suitable methods of preparation of creams; their classification based on their function, characteristics and emulsion type and the various types of creams, ingredients used in the formulation of creams and their various evaluation parameters.

Keywords: Cream, Wound Healing**Article Info:** Received 19 April 2019; Review Completed 31 May 2019; Accepted 03 June 2019; Available online 15 June 2019

Cite this article as:

Rai R, Poudyl AP, Das S, Pharmaceutical Creams and their use in wound healing: A Review, Journal of Drug Delivery and Therapeutics. 2019; 9(3-s):907-912 <http://dx.doi.org/10.22270/jddt.v9i3-s.3042>

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INTRODUCTION:

Creams are the topical preparations which can be applied on the skin. Creams are defined as "viscous liquid or semi-solid emulsions of either the oil-in-water or water-in-oil type" dosage forms which consistency varies by oil and water.¹ Creams are used for cosmetic purposes such as cleansing, beautifying, improving appearances, protective or for therapeutic function. These topical formulations are used for the localized effect for the delivery of the drug into the underlying layer of the skin or the mucous membrane. These products are designed to be used topically for the better site specific delivery of the drug into the skin for skin disorders.² Creams are considered as a pharmaceutical product as they are prepared based on techniques developed in the pharmaceutical industry; unmedicated and medicated creams are highly used for the treatment of various skin conditions or dermatoses. Creams can be ayurvedic, herbal or allopathic which are used by people according to their needs for their skin conditions. They contain one or more drugs substances dissolved or dispersed in a suitable base. Creams may be classified as o/w or w/o type of emulsion on the basis of phases. The term 'cream' has been traditionally applied to semisolid formulated as either water-in-oil (e.g.: cold cream) or oil-in-water (e.g.: vanishing cream).³

CLASSIFICATION OF CREAMS:

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):
 - a) Vanishing creams.
 - b) Foundation creams.
2. Cleansing cream, Cleansing milk, Cleansing lotion (w/o emulsion)
3. Winter cream (w/o emulsion):
 - a) 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.

Make-up cream- These are mainly o/w type of emulsion. It is cream-based product which leaves a smooth hydrated finish (either stain matte or luminous) on the skin. It nourishes skin and is basically sweat-resistant and creates a dewy sheen.

Vanishing creams: They are called vanishing creams because they seem to disappear when rubbed onto the skin. These formulations are based on stearic acid. After application, the cream leaves a dry but tacky residual film which also has a drying effect on the skin. Because of this reason, these are used particularly in hot climates which cause perspiration on the skin.

Foundation creams: These cream serve as a foundation base for make-up. It acts as an adherent base for application of make-up powders. They provide emollient action and a protective action against environment to the skin which is neither too greasy nor too dry. It is multi-coloured make up applied on the face to create an even, uniform colour similar to the complexion, to cover flaws and to change the skin tones.

Cleansing creams: These creams are used for body cleaning purposes and it is used for personal hygiene and beautification which is important for cosmetics. Cleansing creams or lotions can be used for the removal of make-up, surface grim, oil mainly from the face and neck.

Winter creams: These are w/o type of formulation and in this formulation oil content will be more than water content. These creams are mainly used for chapped and dry skin.

Cold cream: It is known as moisturizer or moisturizing cream. Cold cream must have an emollient action. It should produce a cooling sensation in use and the oil film on the skin should be non-occlusive.

All purpose creams and general creams: These creams are used more nowadays than before. These creams are somewhat oily but non-greasy type and can spread on the skin easily. This can also be used as a night creams, nourishing creams, protective creams for prevention or alleviation of sunburns or for the treatment of roughened skin areas.

Night cream or massage creams: These creams are mainly used for the nourishing the skin or as a treatment to dry skin. Creams which are generally applied on skin and left for few or several hours over night are mainly known as night creams. Creams which acts as an emollient by rubbing the cream on the skin with massage is known as massage cream.

Skin protective creams: These creams are smooth, thick bodied creams formulated to provide an invisible, uniform protective film barrier to the skin. It helps to maintain the barrier between the skin and contaminants that may irritate the skin (contact dermatitis and occupational dermatitis). Strengthens the natural properties of the skin and maintains the balance of normal to combination skin.

Hand and body creams: Hands are one of the first places to show signs of aging. We tend to wash our hand several times a day, stripping off moisture. Applying cream softens and protects the skin and it keeps the skin looks younger. Since the skin on our palms and fingers needs oil to stay supple and to prevent it from chapping and cracking, it is sensible to use hand creams that puts plenty of oil back in. It is used on the hands more than other parts of the body.

ADVANTAGES AND DISADVANTAGES OF CREAMS AS A DRUG DELIVERY SYSTEM:

Advantages of topical drug delivery system:

- i. It is the easiest way to deliver a drug.
- ii. It avoids first pass metabolism.
- iii. Topical formulation is very useful for delivery of rectal, vaginal drug delivery.
- iv. It is non-invasive.
- v. It gives a high level of patient satisfaction.
- vi. Easily medicaments can be terminated when required.
- vii. Avoidance of gastro-intestinal incompatibility.
- viii. It is safe and effective delivery of drug molecules with lower doses as compared to conventional system.

Disadvantages of topical drug delivery system:

- i. Skin irritation or dermatitis may occur due to the drug or excipients.
- ii. Most drugs have a high molecular weight and are poorly lipid soluble, so are not absorbed via skin or mucous membranes.
- iii. Very slow absorption.
- iv. It can be used only for those drugs which need very small plasma concentration for action.

WOUND AND WOUND HEALING PROCESS:

Wounds may be defined as a loss or breaking of cellular and anatomic or functional continuity of the deep skin tissue or the living tissues. Wounds may be produced by physical, chemical, thermal, viral, microbial, violence or the immunological trauma to the surface of the skin.^{4,5,6,7,8} Wounds not only affect the patient physically and emotionally but can also significantly cost them and the scars may remain for the lifetime of the patient. Wounds are generally termed as the physical injury that causes opening and breaking of the skin. Wounds can be classified mainly on the basis of mode of infliction and causative agent as:^{9,10}

1. Closed wound- contusion, closed fracture, etc.
2. Open wound-
 - a) Sharp cut.
 - b) Laceration.
 - c) Abrasion.
 - d) Avulsion.
 - e) Crush wound.
 - f) Punctured wound.
 - g) Bite wound.
 - h) Burn wound.

Wound healing is a process of cell contraction, movement, re-adhesion after injury or trauma of the skin. Wound healing involves platelet aggregation, blood clotting, formation of fibrin, inflammatory response to damage, alteration in the ground substances, angiogenesis and re-epithilization.^{11,12} Healing process cannot be complete until the disrupted surface are vigorously knit by collagen and finally terminated by scars formation. Wound healing can have a serious clinical problem and are likely to increase when they are associated with disease such as diabetes,

hypertension and obesity.^{13,14} The process of wound healing may be hampered by the presence of free radicals which will damage the surrounding skin tissues. And the process of wound healing is influenced by several factors such as infections, nutrition, drugs and hormones, type and the sites of the wound and certain disease conditions.^{15,16} In India, since centuries people are using natural products obtained from plant and animal for treatment of wounds which was taught in a popular form of Indian medicine known as Ayurveda.¹⁷ Natural products have been used since centuries in different parts of the world; natural products are becoming as important as alternative medicine because of their comparatively lesser side effects. Due to these reasons, natural/traditional medicine are investigated scientifically for the betterment of human health. These are used directly as in crude or raw form of drug for the treatment of chronic diseases.^{18,19,20}

RELEVANT METHODS OF PREPARATION OF CREAMS FOR WOUND-HEALING:

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. And in another beaker water, preservatives and water-soluble components are taken and melted at 75°C. After heating, the oil phase was taken in a mortar and pestle and slowly the water 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.

Preparation of w/o emulsion creams- The oil soluble components and the emulsifier are taken in one beaker and melted at 75°C. And in another beaker water and water-soluble components are taken and melted at 75°C. After melting, water phase is taken in mortar and pestle and slowly oil phase was added and triturated till clicking sound was heard. And when the temperature of the cream will get cooled, then the perfuming agent are added. In this preparation, water phase will be less and oil phase will be more.

GENERAL INGREDIENTS USED IN SKIN CREAMS:

The raw materials which are used in a manufacturing of skin creams include:

Water: This is the most important and widely used raw material in any cream formulation. These are the cheapest and easily available. In skin creams, water is used as solvent to dissolve other ingredients of creams. Water, which is free of any toxins, pollutants, microbes, etc. is used in preparation of creams. Water can also form emulsions, it depends upon how much quantity of water is used in the formulation and sometimes referred to as oil-in-water emulsions and sometimes water-in-oil emulsions depending upon the quantities of oil phase and water phase used.

Oil, fats and waxes: Oil, fats and waxes are one of the essential portions of the cream. Waxes act as an emulsifier, fats act as a thickener and oil act as a perfuming agent, preservative, etc. according to its function.

Mineral oil: is clear, odorless, and heavily refined oil and it is widely used in cosmetics. Mineral oil rarely causes allergic reactions and it cannot become solid and clog pores of the skin. It is light weight and inexpensive, it helps to reduce water loss from the body and keeps body moisturized. Mineral oil mainly used in cosmetics is liquid paraffin, liquid petroleum, paraffin oil, paraffin umliquidum, petrolatum liquid, petroleum oil etc.

Vegetable oil: form a barrier on the surface of the skin and slow down the loss of water, helping to maintain plumpness of skin. Vegetable oils may also be used to increase the thickness of the lipid or oil portion of cream or personal care products. E.g. Almond oil, germ oil, avocado oil, sunflower oil etc.

Waxes: which are used in preparation of cream includes beeswax, carnauba wax, ceresin, spermaceti, etc. Waxes are used in cosmetics because it helps to keep an emulsion from separation of oil and liquid components. These waxes also increase the thickness of the lipid portion and sticks on the surface of the skin.

Fats: Different types of fats are used in the preparation of creams. These materials can be obtained from animals, plants or mineral origin.

Lanolin: It is derived from wool fat of a sheep. Lanolin are of two types- the hydrous lanolin contains between 25%- 30% water. Anhydrous lanolin has point of 38°C-42°C and has a slight odour. These ingredients act as a lubricant on the skin surface, which gives the skin soft and smooth appearance. Lanolin helps to form emulsion and blends well with other substances used in cosmetic and personal care products.

Colours: Before the development of the modern technology, colours primarily came from substances found in nature such as turmeric, saffron, indigo, etc. After the 19th century, colours were made in the laboratory and were found to be much more stable with greater colouring intensity. They also could be produced without using plants harvested in the wild.

Humectants: These are important multi-functional ingredients found in most skin care formulations. Humectants are hygroscopic organic compounds. These are the materials that can absorb or retain moisture. These have many benefits such as moisturization, exfoliation, etc. Examples of humectant are glycerin, Hydroxyethyl urea, betaine, sodium PCA, Sodium-L-Lactate, etc. Humectants are also used in shampoo they are intended to help moisturize the hair countering the drying effect of the surfactants and it assist in low temperature and freeze/thaw stability, where they act as anti-freeze and maintain clarity of the shampoo at low temperature.

Perfumes: It is used in wide variety of products to impart a pleasant odour, mask the inherent smell of some ingredients. It is used in every type of cosmetics.

Vitamins: Vitamins play an important role in maintaining the physiological function of whole body and the skin. Vitamin A,B,C,E, etc. are generally used in formulation of the creams.

Preservatives: The use of preservatives in cosmetics is essential to prevent alteration caused by microorganism and contamination during formulation, shipment, storage and consumer use. Antioxidants can also be used to protect alteration caused by exposure to oxygen. Synthetic preservatives when used in low concentration effectively preserve the products. They have a broad spectrum of activity against bacteria and fungi. Also, they are affordable than natural preservatives. Natural preservatives cover a broad pH range and also consumers generally prefer natural preservatives over synthetic preservatives.

EVALUATION PARAMETER OF CREAMS:

1. **Determination of pH:** The pH of the cream can be measured on a standard digital pH meter at room temperature by taking adequate amount of the

formulation diluted with a suitable solvent in a suitable beaker.

2. **Physical appearance:** The physical appearance of the cream can be observed by its colour, roughness and graded.
3. **Spreadability:** Adequate amount of sample is taken between two glass slides and a weight of 100gm is applied on the slides for 5 minutes. Spreadability can be expressed as, $S = m \cdot l / t$

Where, m = weight applied to upper slide.

l = length moved on the glass slide.

t = time taken.

4. **Saponification value:** 2gm of substance refluxed with 25ml of 0.5 N alcoholic KOH for 30min, to this 1ml of phenolphthalein added and titrated immediately, with 0.5N HCl, note the reading as 'a'. Repeat the operation omitting the substance being examined. Note the reading as 'b'.

Saponification value = $(b-a) \cdot 28.05 / w$

Where,

w = weight of substance in gram.

5. **Acid value:** 10gm of substance is dissolved in accurately weighed 50ml mixture of equal volume of alcohol and solvent ether, the flask was connected to reflux condenser and slowly heated, until sample was dissolved completely, to this 1ml of phenolphthalein added and titrated with 0.1N NaOH, until faintly pink colour appears after shaking for 30 seconds.

Acid value = $n \cdot 5.61 / w$

Where,

n = the no. of ml of 0.1 N KOH solution.

w = the weight of substance in gram.

6. **Viscosity:** Viscosity of formulated creams can be determined by using Brookfield Viscometer.
7. **Homogeneity:** The formulation was tested for the homogeneity by visual appearance and by touch.
8. **Removal:** The ease of removal of the creams applied was examined by washing the applied part with tap water.
9. **Dye test:** The scarlet dye is mixed with the cream. Place a drop of cream in a slide and cover with a cover slip and examine it under a microscope. If the disperse globule appears red and the ground colourless then it is o/w type and the reverse condition appears in w/o type of creams.
10. **After feel:** Emolliency, slipperiness and amount of residue left after the application of fixed amount of cream was checked.
11. **Type of smear:** After application of cream, the type of film or smear formed on the skin were checked.
12. **Irritancy study:** Mark an area of 1sq.cm on the left-hand dorsal surface. The cream was applied to the specified area and time was noted. Irritancy, erythema, edema was checked, if any, for regular intervals upto 24hrs and reported.

13. **Accelerated stability study:** Accelerated stability study is conducted for formulation according to ICH guidelines.

Ayurvedic medicines for wound healing:

1. **Aloe Vera (*A. barbadensis*):** It is one of the important herbs in Ayurveda. It is having wide range of uses in skin conditions such as burns, psoriasis, cold sores, etc. It can also be for fever, itching, inflammation.^{23, 24}
2. **Peppermint (*Menthapiperita*):** It is a popular herb and it is used in numerous forms. Peppermint oil when applied on the skin provides a cooling sensation. It is used in aromatherapy, bath preparation, mouth washes, toothpaste and topical preparations. It is used to calm pruritus, relieve irritation and inflammation and wound healing.^{25, 26}
3. **Turmeric (*Curcuma longa*):** In India, turmeric is used as spices as well as a colouring agent. It is having various medicinal properties as anti-cancer, anti-diabetic, antioxidant, anti-inflammatory, anti-bacterial, antiviral, wound healing, etc.^{27, 28}
4. **Jatropacurcas:** It is known for various medicinal properties. It is having anti-microbial, anti-cancer, anti-HIV, anti-bacterial, wound healing, etc.²⁹
5. **Honey:** Honey has been used since ancient times as a traditional medicines. Honey is having antioxidant, anti-tumor, anti-inflammatory, anti-microbial and cardiovascular potentiating agent. It is also used as a wound dressing and wound healing agent. Honey has been used to treat adult and neonatal postoperative infections, burns, necrotizing fasciitis, infected and non-healing wounds and ulcers, boils, pilonidal sinus, venous ulcer and diabetic foot ulcers.^{30, 31}
6. **Marigold (*Calendula officinalis*):** It is a short lived aromatic herbaceous perennial plant. It is a flower/plant which that has been used for centuries for ornamental purpose, cosmetic and medicinal purpose. Calendula is one of the top herbs and can be taken orally, it is one of the most powerful antioxidant and it is one of the strongest antiviral herbs. It is having anti-inflammatory, calms muscle spasm, heals ulcers, wounds, and hemorrhoids, aids menstruation, contains antimicrobial and antiviral components, improves oral health.^{32, 33}
7. **Ghee:** The butter which is obtained from the cow milk has been claimed to have many medicinal properties like it is cooling in energy, rejuvenating, bestows luster and beauty, enhances memory and stamina, increases the intellect, and promotes longevity. It is having antimicrobial, immunostimulant, antioxidant and hepatoprotective activity. The process of wound healing by cow ghee is faster than anti-biotics. Cow ghee contains several saturated and unsaturated fatty acids which are capable of taking part in metabolic processes involved in healing of any wounds.^{34, 35}

Alternative medicines/creams for wound healing:

1. **Soframycin:** The Soframycin skin creams is manufactured as 1% w/w as per IP which has Framycetinsulphate as the main component. Soframycin skin cream are used in curing wounds, furunculosis, cuts, burns, ulcers, lice, impetigo, otitis externa, scabies, sycosis barbae, etc.³⁶
2. **Neosprine:** It is made up of three antibiotics that are neomycin sulphate, polymyxin B sulphate and

bacitracin zinc. The topical ointment can be used to treat certain skin infections in burns, minor cuts, and wounds. These antibiotics work by killing bacteria that causes these infections.

3. **Silver Nitrate:** It is a prescription topical solution used in treating wounds and burns on the skin as an anti-infective agent, antiseptic and caustic. There is little literature about the adverse effect of silver nitrate. Silver nitrate can potentially be used as a cauterizing or sclerosing agent.³⁷
4. **Silver Sulphadiazine:** This medication is used along with other treatment to help prevent and treat wound infections in patients with serious burns. Silver sulphadiazine works by stopping the growth of bacteria that may infect an open wound. This helps to decrease the risk of the bacteria spreading to surrounding skin, or to the blood where it can cause a serious blood infection (sepsis). Silver sulphadiazine belongs to a class of drugs known as sulfa antibiotics. Silver sulphadiazine cream is used to prevent and treat wound infections in patients with second- and third-degree burns. Silver sulphadiazine must not be used on premature babies or on newborns during the first 2 months of life because of the risk of serious side effects.³⁸
5. **Cetrimide:** It is an antiseptic which is a mixture of different quaternary ammonium salts including cetrimonium bromide. It was first discovered and developed by ICI and introduced under the brand name Cetavlon. It is used as a 1-3% solution for cleaning roadside accident wounds.
6. **Betadine:** It is having an active ingredient as Povidone Iodine USP 10% w/w (available iodine 1%). Povidone iodine is bactericidal against gram-positive and gram-negative bacteria. It is a broad-spectrum antiseptic for the topical treatment or prevention of infection in minor cuts and abrasions, minor surgical procedures and small area of burns, treatment of mycotic and bacterial skin infections.³⁹

CONCLUSION

The skin is the most accessible part of the body and as such is also highly vulnerable to injuries. In case of cuts, burns and wounds, topical formulations such as creams are the most preferred for treatment. As compared to other conventional systems, topical formulations have certain advantages including- ease of application, less chances of side effects, non-invasive process and higher patient compliance. Research and development for the formulation of pharmaceutical creams for wound healing purpose has grown in recent decades owing to its obvious benefits. With the progress in the pharmaceutical field and industry, it is assured that pharmaceutical creams will still be an interesting and appealing area of research for years to come.

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