IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

PHARMACEUTICALS USED IN WOUND HEALING: A COMPREHENCING REVIEW

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Abstract:

Wound is defined as the damage or disruption of living tissues cellular, anatomical, and functional integrity and wound healing is define as the complex process that is critical in restoring the skins barrier function. Wounding occurs when the epidermal layer of skin is ruptured and the underlying dermis is thus exposed to air. Wound repair consists of an orderly and complex process divides into four phases: coagulation, inflammation, proliferation and remolding. The management of wounds always requires additional effort for comprehensive healing and subsequent removal of the scar from the wound site. The present review article attempts to enlist the different formulations which have been reported to be effective in treatment of wounds.

Index Terms – Wounds, Wound healing, Marketed formulations.

INTRODUCTION

The skin is a fundamental part of the human body, the largest organ and the first defense barrier against the environment. This organ maintains homeostasis as a reservoir of nutrients, a defense mechanism and an injury response[1,2,3]. It is made up of multiple layers of ectodermal tissues that protect the muscles, bones, ligaments and internal organs of our body. A wound is defined as loss of the integrity and normal function of skin[4,5,6]. When skin structure is disturbed, its restoration and recovery of its functions must be carried out as soon as possible to guarantee the organisms homeostasis, so that the wound healing process begins almost immediately after the skin injury[7]. After injury, skin integrity must be promptly restored in order to maintain its functions. In this process, peripheral blood mononuclear cells, resident skin cells, extracellular matrix, cytokines, chemokines, growth factors, and regulatory molecules participate in the wound healing process[8].

WOUNF HEALING

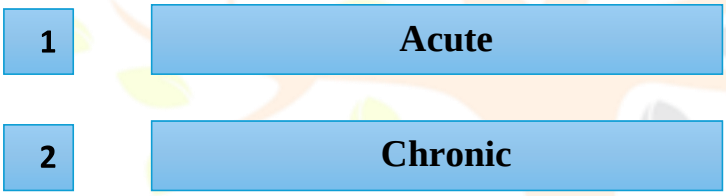
Wounds are occurs when epidermal layer of skin is ruptured and the underlying dermis is thus exposed to the air. Skin wounds or injuries may result from burns and other physical and chemical agent, genetic irregularities, skin diseases or removal of skin during surgery. Depending on the depth of the injury, skin wounds can be categorized as epidermal, superficial partial thickness, deep partial thickness and full thickness wounds[9].

Types of wounds

Based on depth of skin damage and area of skin affected.

1) superficial wound- when only the epidermal skin surface is injured.
2) Partial thickness wounds- when injury involves deeper dermal layers (ex-blood vessels, sweet glands and their hair follicles).
3) Full thickness wounds- when underlying subcutaneous fat or deeper tissues become ruptured.

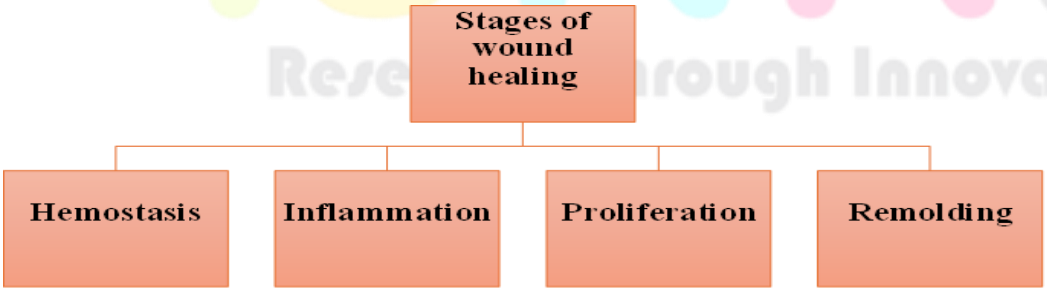
Based on healing time and etiology of wound



Acute: -These wounds heal within 7 to 10 days and are caused by small abrasions, burns, lacerations, puncture wounds, and surgical incisions. They heal through normal stages of hemostasis, inflammation, proliferation, and remodeling.
Ex- surgical incision, thermal injuries, abrasions and laceration

Chronic: - These wounds don't heal within four weeks and are caused by pressure, increased bacterial load, trauma, lack of blood supply, inappropriate treatment, and infections. They don't progress normally through the stages of healing and are often stuck in the inflammation phase.

Stages of wound healing



1) Hemostasis-

It occurs immediately.
Blood vessels constrict to stop bleeding.
Blood clots forms[11,12,13].

2) Inflammation-

The area around the wound becomes red, swollen, tender and slightly warm
Blood vessels open up to bring oxygen and nutrients to the wounds.
Infection prevention[14,15,16].

3) Proliferation-

Granulation tissue forms and the vascular network is restore.
This phase usually starts 3 to 10 days after injury.

Wound rebuilds connective tissue for protection[17,18].

4) Remodeling-

The internal wound heals and is replaced with strong skin.

This phase can last for a year or longer.

New epithelial tissue forms (new healthy skin)[19,20]

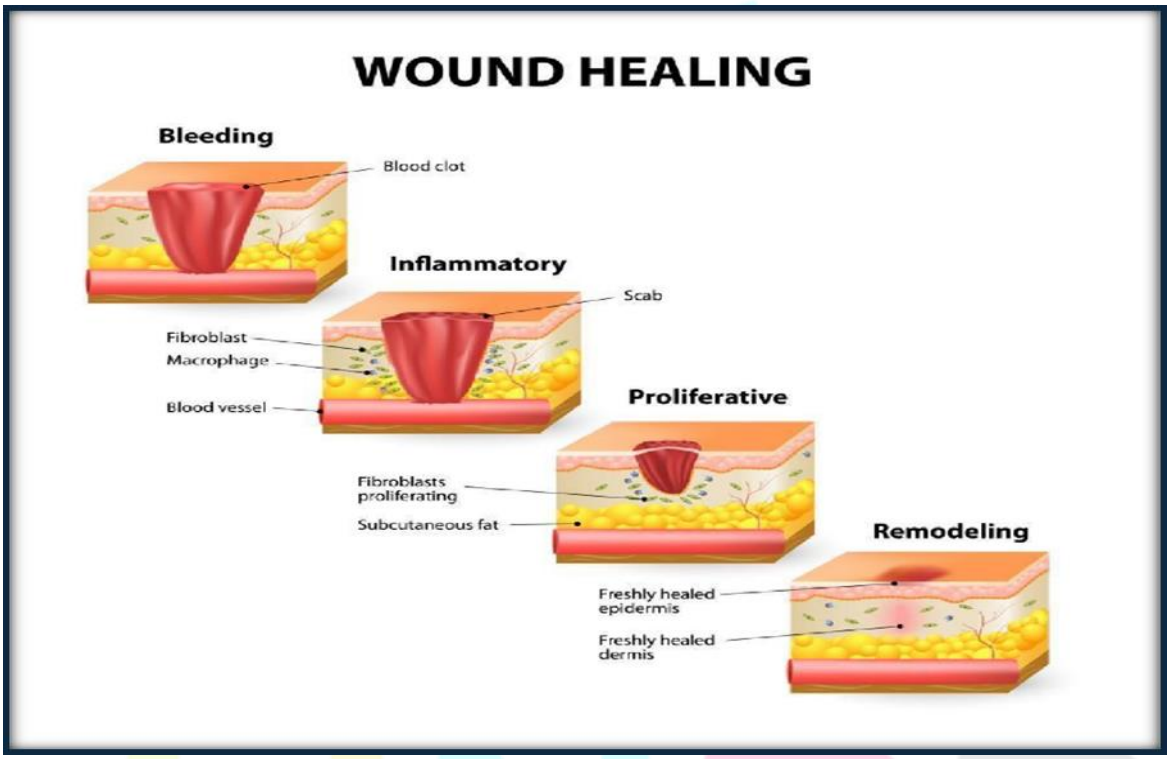


Figure:- Wound healing stages

WOUND HEALING PREPARATIONS:

[Marketed Formulations]

A] Povidone Iodine:-

The role of iodine in wound care is primarily as an antimicrobial agent. Povidone iodine has been used and tested in wound healing for many decades[21,22]. In vitro evidence suggests that iodine not only has broad spectrum antibacterial effects, but also counteracts inflammation elicited by both pathogens and the host response[23].These anti-inflammatory effects appear to be multifactorial[24,25,26,27] and have been shown to be clinically relevant[26,28].

Mechanism of Action:

In povidone iodine, iodine forms a complex with the synthetic carrier polymer povidone, which itself has no microbicidal activity. In an aqueous medium, free iodine is released into solution from the povidone iodine complex and an equilibrium is established, with more free iodine being released from the povidone iodine reservoir as iodine-consuming germicidal activity proceeds[29,30]

How to use:-

Gently clean the wound with cotton soaked in the solution, allow it to dry and then cover with a sterile bandage.

Contraindication:-

povidone iodine should not be used by patients with hyperthyroidism or thyroid cancer. It should also be used with caution by pregnant or lactating women and infants.

Povidone Iodine is available in several formulations:

1) Solution:-

The most common commercial form is a 10% solution in water, which yields 1% available Iodine. It is an antiseptic that can be used to prevent and treat minor skin infections and Wounds and to prepare skin before surgery. Its effective against a wide range of microbes Including bacteria, fungi, viruses and protozoa.

Mechanism of action:-

Povidone iodine is a kind of iodine disinfectant which directly cause in vivo protein denaturation, precipitation of bacteria, and further resulting in the death of pathogenic microorganisms. Therefore, it is effective in disinfection and sterilization.

Precautions:-

Avoid contact with the eyes and nose, and rinse thoroughly if it gets in your eyes. Don't use it if you're allergic to povidone-iodine or any other ingredients.

How to use:-

Clean the affected area, apply a small amount of the solution, and let it dry before covering with a bandage.

Uses:-

It can be used to prepare the skin before surgery, or to treat minor wounds, cuts, scrapes, and burns. It can also be used to treat gynecological vaginal infections.

Figure- 10% Povidone-Iodine solution

2) ointment:-

It is an antiseptic and disinfectant used to treat and prevent skin infection in minor burns, laceration, wound and abrasions. It works by inhibiting the growth of infection causing microbes.

Mechanism of action:-

When formulated as a topical wound dressing, It adsorbs exudate and particulate matter from the surface of granulating wounds and, as the dressing becomes moist, iodine is released. The product thus has the dual effect of cleansing the wound and exerting a bactericidal action.

Uses:-

Povidone iodine ointment can be used to treat wounds and help them heal faster. It can be used on a variety of wounds, including cuts, burns, and minor nicks.

Precaution:-

Do not apply over large areas of the body; toxicity may occur if applied in large areas or prolonged periods. Ask a doctor in cases of deep or puncture wounds, serious burns, or animal bites.

Figure- Povidone iodine ointment

B] Mupirocin:-
Mupirocin is a secondary metabolite produced by the gram negative soil bacterium, pseudomonas fluorescens[31].It is used as a topical antibiotic, which act by inhibiting protein synthesis.[32]. Mupirocin can help promote wound healing. It's a topical antibiotic that can help treat wounds by: Killing bacteria- Mupirocin can kill bacteria or prevent their growth.
Stimulating growth factors: Mupirocin can stimulate the production of growth factors that promote wound healing. Increasing keratinocyte proliferation: Mupirocin can increase the proliferation of human keratinocytes, which can help wounds heal.

Mechanism of action:-
Mupirocin binds to the bacterial isoleucyl-transfer RNA synthetase, which prevents the formation of isoleucyl-tRNA. This stops the incorporation of isoleucine into the polypeptide chain, which eventually leads to bacterial cell death.

How to use:-
Wash your hands with soap and water before and after using this medicine.
Apply a thin layer to the affected area of the skin. Rub it in gently. After applying this medicine, the treated area may be covered with a gauze dressing if desired.

Contraindication:-
This drug is contraindicated in individuals with a history of sensitivity
Reaction to any of its components. Avoid application to the eyes. ointment contains polyethylene glycol which may be absorbed from open wounds and damaged skin. Caution is needed in moderate or severe renal impairment, in neonates and burns patients.

Mupirocin is available in several formulations:

1) Foam:-
A pressurized foam that can be applied to burn wounds with minimal touch. The foam collapses when tapped, making it easy to apply with medical gauze. Studies on subjects suffering from dermatological diseases such as psoriasis and eczema concluded that the foam delivery system is easy to apply, provides a cooling or emollient effect, increases patient acceptance, and displays faster absorption than traditional topical dosage forms [33], [34], [35], [36], [37], [38], [39]. It contains the active ingredient and surfactant, co-solvent, and gelling agent in the form of emulsion, suspensions or solution. This pre-foam formulation is sealed inside a pressurized canister that dispenses the foam upon actuation by incorporating air bubbles inside the liquid due to rapid evaporation of the propellant [40],[41],[42].

Mechanism of action:-
Mupirocin is believed to exert its antimicrobial activity by inhibiting isoleucyl-transfer RNA, thereby obstructing bacterial protein and RNA synthesis, ultimately resulting in cell death.

Uses:-
1]Quick collapse time: The foam collapses when touched, which is useful for burn patients with microbial infections. 2]Good antibacterial activity: The foam has a minimum inhibitory concentration against E. coli, P. aeruginosa, and S aureus. 3] Non-sticky: The foam is non-sticky and has good spreadability.

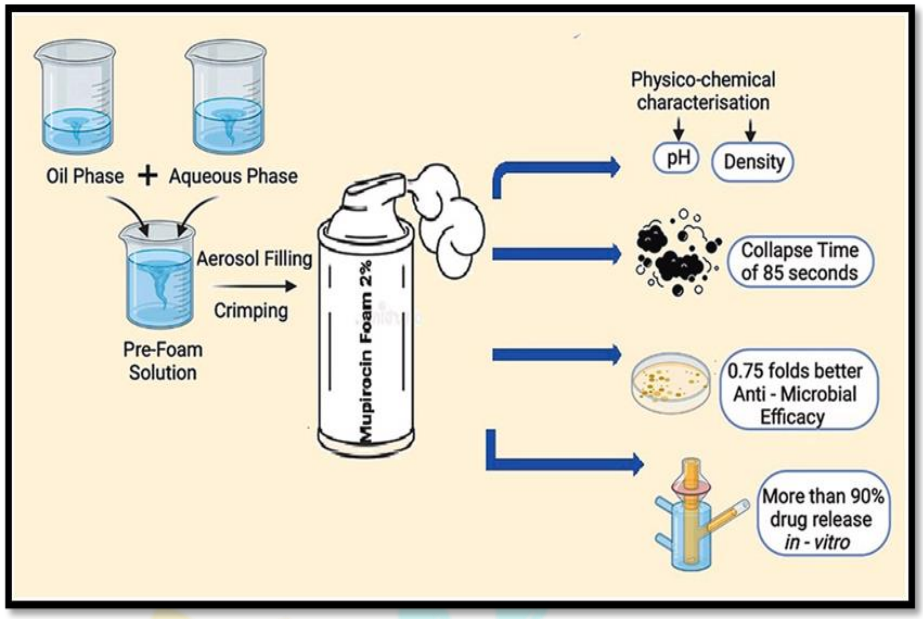


Figure-Mupirocin Foam 2%

2) ointment:-

Mupirocin ointment is a medication that treats bacterial skin infections. It prevents bacteria growth and kills existing bacteria on your skin. You can rub this medication on your affected skin. Make sure you wash your hands before and after using the ointment. The brand names of this medication are Bactroban® and Centany®. It treats skin infections caused by bacteria. It works by killing or preventing the growth of bacteria on the skin.

Mechanism of action:-

Mupirocin ointment works by binding to bacterial isoleucyl-tRNA synthetase, an enzyme that's responsible for converting isoleucine and tRNA into isoleucyl-tRNA. This binding prevents the formation of isoleucyl-tRNA, which stops isoleucine from being incorporated into polypeptide chains. This in turn inhibits bacterial protein and RNA synthesis, which eventually leads to cell death.

Uses:-

Mupirocin topical cream is used to treat secondarily infected traumatic skin lesions due to specific bacteria. Mupirocin topical ointment is used to treat impetigo. used when infection occurs in skin damaged by eczema, dermatitis, psoriasis,herpes (cold sores), wounds, cuts, grazes, insect bites, minor burns.

Precaution:-

Before using mupirocin, tell your doctor or pharmacist if you are allergic to it; or if you have any other allergies. This product may contain inactive ingredients (such as polyethylene glycol found in some brands), which can cause allergic reactions or other problems. Talk to your pharmacist for more details.

Figure:- Mupirocin Ointment

C] Silver Nanoparticles:-

Silver nanoparticles (Ag-NPs) are metal nanoparticles that have antimicrobial properties and are being studied for their potential to help with wound healing. The use of silver in wound management is very ancient. In Egypt, in 1850 BC, silver was applied to wounds; in addition, the textbooks by Hippocrates described the positive effects of silver in wound healing [43]. Today, due to their broad-spectrum antibacterial capability, silver-based creams and ointments, as well as AgNPs-based biomedical products, such as wound dressings, are commercially available for different medical applications [44].

Mechanism of action:-

Antibacterial properties- AgNPs have a large surface area that allows for better contact with microorganisms. They can interact with the cell membrane and penetrate the cell, where they can damage the cell's respiratory chain and cell division. AgNPs are effective against multi-drug-resistant organisms.

Anti-inflammatory properties- AgNPs can reduce the production of cytokines by initiating neutrophil apoptosis. This reduces the inflammatory response and helps the wound heal faster.

Increased collagen deposition- As the amount of AgNPs in a dressing increases, more collagen is deposited in the wound area. This is linked to increased fibroblast and macrophage migration.

Reduced bacterial colonization- AgNPs can prevent bacterial colonization in the wound site.

Silver nanoparticles is available in several formulations:

1) Gel:-

Silva Kollagen Gel is a hydrolyzed collagen gel wound dressing with silver oxide. The silver preservative in the dressing controls microbial growth within the gel. Silva Kollagen Gel provides a physiologically favorable environment that encourages wound healing while protecting the wound bed and its newly formed granulation tissue; soothes and deodorizes; conforms to any wound site; is naturally highly absorbent; is biocompatible and biodegradable, and is easy to use.

Mechanism of action:-

Controlling microbial growth: The gel contains 1% silver oxide as a preservative to prevent microbial growth.

Absorbing drainage: The gel can absorb drainage from wounds that are exuding fluid.

Donating moisture: The gel can donate moisture to dry wounds.

Supporting autolysis: The gel can rehydrate and soften devitalized tissue, which supports autolytic debridement.

Conforming to wound sites: The gel can conform to any wound site.

Providing a favorable environment: The gel provides an environment that supports wound healing.

Uses:-

1% silver oxide as a preservative controls microbial growth within the gel. Provides a physiologically favorable environment that encourages wound healing. Maintains a moist wound environment. Supports natural autolysis by rehydrating and softening necrotic tissue and eschar thereby encouraging autolytic debridement. Silver collagen wound gel contains natural materials that contain the proteins and amino acids that constitute the major building blocks of normal skin and connective tissue. Conforms to any wound site. Biocompatible and biodegradable. Easy to handle and deliver. Absorbs wound exudate.

Precaution:-

Should not be used on patients with a known sensitivity to silver; Do not use on patients with a known allergy or sensitivity to Bovine collagen.

Figure:- Silva kollagen Gel

D] Polyhexanide:-

Polyhexanide, also known as polyhexamethylene biguanide (PHMB), is an antiseptic and antimicrobial agent that can be used to treat wounds. Polyhexanide has been identified as a highly effective antiseptic for clinical wound care in various studies.

Mechanism of action:-

Attracting to bacterial cell surfaces- Polyhexanide is attracted to the negatively charged phospholipids on the surface of bacterial cells.

Disrupting bacterial cell structure- This attachment disrupts the bacterial cell's biological structure.

Destabilizing the cytoplasmic membrane-This leads to the leakage of macromolecular components, which kills the microbe.

Binding to DNA-Once inside the cell, polyhexanide can bind to DNA, which may block DNA replication or activate DNA repair pathways.

Polyhexanide is available in several formulations:

1) Spray:-

Hansaplast Wound Spray is an easy to use spray for the antiseptic cleansing of minor acute wounds such as cuts, abrasions, first and minor second-degree burns and open blisters, by mechanical irriation. It is free of alcohol and does not cause stinging during application or dry the skin. Hansaplast Wound Spray is a pain-free* and effective way to cleanse wounds from dirt and bacteria and prevent from wound infections.

Figure- Hansaplast wound spray

Working:-

Skin sprays that form a thin layer over the wound to protect it from infection and fluid loss. Hydrogels can also enhance the healing process, and some have antibacterial properties.

Uses:-

Hansaplast Wound Spray is a pain-free* and effective way to cleanse wounds from dirt and bacteria and prevent from wound infections. The Hansaplast Wound Spray also helps to remove crusts or clotted dressings.

Evaluation parameters of spray:

1. **pH**
2. **Viscosity**
3. **Tonicity**
4. **Bioadhesive strength of the film**
5. **Water washability**
6. **Fluid affinity**
7. **Rheological properties**

1) pH

The pH value is measured and adjusted to improve the stability of the active substance or make it suitable for the area of application. For skin pH ranging from 4–6, the pH of diabetic wounds ranges from 6.5–8, whereas faster healing time for burns occurs below pH

2) Viscosity

Each type and concentration variation of the polymer will result in a different viscosity. The viscosity of the film forming solution will affect its spray ability, so this is an important parameter, especially in MDS.

3) Tonicity

The application of film-forming solution to certain parts of the body such as wound and eye mucosa requires the tonicity adjustment of the film-forming 0 solution. Nonisotonic preparations can cause mucosal irritation and eye pain. For this reason, the tonicity of the preparations needs to be calculated and adjusted using the Kahar method.

4) Bio adhesive strength of the film

Measurement of the bio adhesive strength of the film can be done by attaching a film to the surface of the mouse skin (2 x 5 cm). Then, the skin is hydrated with 0.5 mL distilled water. The film is allowed to interact with the tissue surface for 5 minutes the total force (F) To detach the film from the surface of the skin is recorded. The Bioadhsive strength (Fb) is calculated per unit area (A) of the film.

5) Water washability

The ease of film wetting is assessed in the dried film. The film is washed with water and Assed in ordinal scale, i.e. easily washed, moderately washed, and poorly washed. The ease of sprinkling with water will be useful if the film-forming solutions contact with sensitive areas in the body such as eyes and mouth.

6) Fluid Affinity

This test is carried out to see how the ability of the film formed to absorb wound or provide moisture to the wound. An adequate supply of moisture to the injury will speed healing, but excess moisture can cause erosion of the wound tissue.

7) Rheological Properties

Flow testing aims to determine whether a compound is thixotropic or not. A mixture can easily pass through the sprayer nozzle repeatedly if it has these flow properties. This flowing property allows thinning of the film-forming solution as it shifts along past the nozzle (stressed) and returns to its original viscosity after being sprayed.

Evaluation parameters of ointment:-

1. Color and odour- Physical parameters such as color and odour were examined

by visual examination.

2. Consistency-Formulation was smooth and greediness is observed.

3. pH- The digital pH meter is used to measure the pH of preparation. Ointment solution was prepared by using 100ml of distilled water and set aside for 2 hrs. pH was determined three times for the solution and average value was determined.

4. Spreadability- For the determination of spreadability the amount of sample is placed in between two slides and which compressed to uniform thickness by placing definite weight for definite time. Time required for the separation of two slides was known as spreadability. Spreadability is better when time taken for the separation of two slides is less. Spreadability was calculated by the

formula: S=MxL/T

Where,

S = Spreadability

M = Tide weight on upper slideL = Length of glass slide

T = Time taken for the separation of slides

5. Extrudability- Collapsible tube was used to fill the formulation. Extrudability was determined as weight of ointment required to extrude 0.5cm ribbon in 10 sec

6. Diffusion Study- Agar nutrient medium was prepared for diffusion study. A hole board was placed in the center Time taken by ointment to get diffused through it was noted after 60 minutes.

7. Loss on Drying- For the determination of loss on drying the formulation was placed in petri-dish on water bath and dried at the temperature of 105*C.

8. Solubility-Miscible with chloroform and soluble in boiling water.

9. Washability- The formulation was applied on the skin and then the washing of ease extend of formulation with water was checked.

10. Non irritancy testing- Herbal ointment preparation was applied on human skin and the effect was observed.

11. Stability Study- Testing of physical stability of herbal ointment was carried out for four weeks at various temperature conditions like 2*C, 25*C, and 37*C. Herbal ointment was found to be physically stable at various temperatures 2*C,25*C and 37*C within four weeks.

Evaluation parameters of Gel:-

1) **Physical evaluation**: A visual inspection was conducted to verify physical characteristics such color, odor, and consistency.

Colour: The formulation's colour was examined by visual examination Consistency: The formulation's consistency was verified by putting on skin.

Odour: The formulation's odor was assessed by combining the gel with water and smelling it.

2) Measurement of pH: The glass electrode was fully submerged in the gel system three times to determine the pH of the formulation. The average values are provided.

3) Homogeneity: Visual examination was used to verify each manufactured gel composition for homogeneity. Once the gels have been placed within the holder. We examined them to see if any aggregates were visible or present.

4) Viscosity: The produced gel's viscosity was measured at 25°C using the Brookfield Viscometer. The gels were spun at 0.3, 0.6, and 1.5 revolutions per minute, and the dial reading for each speed was noted. Next, the viscosity of the generated gels was calculated by multiplying the dial reading by a number found in the Brookfield Viscometer catalogs.

5) Spreadability: When a particular stress is applied, the amount of time it takes for two slides to separate from gel placed in their interstices is known as the spreadability. If two slides can be separated in less time, then spreadability is enhanced. Spreadability is calculated using the following formula:

$M \times L / T = S$

M = is the weight attached to the top slide.

L= is the glass slide's length.

T = amount of time needed to divide the slides

6) Clarity: A visual inspection is used to assess the gel's clarity.

7) Stability study: Stability studies were carried out to see how formulation was impacted by storage or environmental factors. In accordance with ICH recommendations, the formulation was maintained in an accelerated stability condition for three months at25°C temperature 60 ± 5% relative humidity, 30°C temperature 65 ± 5% relative humidity, and 40°C temperature 75 ± 5% relative humidity.

Evaluation Parameters of foam:-

1)- R5:-The ratio of the foam's height at five minutes after formation to its initial height. Foams with an R5 value higher than 50% are considered metastable, while foams with lower R5 values are less stable.

2)-Foam overrun: The ratio of foam volume to solution volume, divided by the solution volume. This parameter can be used to evaluate foaming capacity and stability.

3)-Initial foaming volume, half-life, comprehensive index, and liquid carrying rate: These parameters can be used to evaluate foam drainage agents.

Conclusion:-

Though the wound healing process maintains the skin integrity, most of the investigations have been done to speed up this process. However, rapid recovery in severe wounds is still a major challenge. Wound dressing has been a major segment of wound management where, many different type of formulations are prepared to treat wound healing fastly and more effectively. In the current times , different types of dosage forms are being researched for developing economical, sustainable, stable and effective delivery system for the treatment of wounds. The present review article attempts to enlist marketed formulations which have been reported to be effective in the treatment of wounds.

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