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A PROMISING FORMULATION FOR MANAGING DEEP BURN WOUNDS WITH SILVER-INFUSED ETHOSOMAL GEL

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ABSTRACT

The use of silver-infused ethosomal gel for the treatment of severe burn injuries. The formulation seeks to tackle issues in infection prevention, inflammatory regulation, and tissue regeneration by combining silver's antibacterial characteristics with the effective drug delivery of ethosomal gel. The controlled release of silver ions has a focused therapeutic impact, providing a complete approach to treating severe burn wounds. Drug release experiments were conducted in vitro for a length of five hours. It was found that formulation F4 exhibited the highest quantity of drug release during this time period, namely 76.80%. The research concludes that incorporating silver sulfadiazine into a hydrogel via the ethosomal method enables a more efficient and precise administration of the medication, resulting in persistent and targeted effects.

Keywords: - Sulfadiazine, Drug, Burn Wound, Silver, Ethosomal Gel.

I. INTRODUCTION

Effective management of severe burn wounds is a multifaceted and crucial component of contemporary healthcare, necessitating inventive strategies to expedite the healing process and minimize possible problems. A very promising formulation that has attracted much interest is the use of silver-infused ethosomal gel. Deep burn injuries provide significant difficulties since they penetrate numerous layers of the skin and underlying tissues. These injuries need specialist treatment to facilitate tissue regeneration, avoid infections, and limit scarring. The integration of silver, renowned for its ability to inhibit the growth of microorganisms, into an ethosomal gel delivery system provides a new and promising method to tackle many elements of managing severe burn wounds. The use of silver for wound healing has been recorded for millennia, due to its well-established antibacterial qualities in many medicinal disciplines. Scientific progress in recent years has provided us with a more profound understanding of how silver works, especially when it comes to treating wounds. Silver ions possess a wide range of antibacterial properties due to their ability to damage the cell membranes of bacteria and interfere with crucial biological processes. The antimicrobial properties of silver make it a desirable option for preventing and treating infections, which is particularly important in cases of extensive burn wounds when the weakened skin integrity provides a susceptible environment for microbial invasion. Ethosomal

gels are a complex medication delivery technology that improves the penetration of active substances into the skin. Ethosomes are vesicles composed of phospholipids that possess exceptional deformability, enabling them to enter the skin with more efficiency compared to traditional liposomes. By integrating ethosomal technology into gel formulations, the bioavailability and prolonged release of therapeutic chemicals are enhanced, making it an optimal method for delivering silver ions to severe burn wounds. The use of a silver-infused ethosomal gel shows significant potential in effectively managing the complex issues related to the treatment of severe burn wounds. An inherent benefit of silver-infused ethosomal gel is its capacity to provide a continuous and controlled release of silver ions directly to the site of the wound. The ethosomal vesicles function as carriers, enabling the regulated and protracted release of silver, which is essential for maintaining an optimal antibacterial concentration for a longer duration. The continuous release of medication not only prevents early infections but also provides continued protection to the site throughout the whole healing period. Moreover, the ethosomal gel matrix provides a shielding barrier that assists in retaining moisture, so establishing an ideal condition for cellular growth and tissue healing. Moreover, the malleable characteristics of ethosomal vesicles allow them to traverse the intricate composition of the skin, thereby accessing the underlying layers that are often impacted in severe burn injuries. The increased permeability facilitates the efficient transportation of silver ions to the specific location of the damage, guaranteeing a focused and potent therapeutic impact. Contrary to conventional topical treatments, which may have difficulties in reaching and treating the dead tissue and scabs that often occur with severe burn injuries, the silver-infused ethosomal gel has the ability to effectively enter and address these regions, so aiding in a more thorough healing process.

The antibacterial properties of silver are especially important in the setting of burn wounds, where there is an increased risk of bacterial colonization and infection. Severe burn injuries weaken the skin's inherent protective processes, allowing germs to enter the body. The antibacterial impact of silver ions is exerted by breaking bacterial cell membranes and interfering with key cellular activities. This not only aids in the prevention of infections but also assists in resolving existing microbial issues inside the wound. The use of silver-infused ethosomal gel offers a proactive strategy for managing infection in severe burn wounds, thereby addressing a crucial part of their treatment. Furthermore, silver has shown anti-inflammatory properties, which might be advantageous in the case of burn injuries that are marked by severe inflammatory reactions. Excessive inflammation may hinder the healing process and lead to the formation of problems such as hypertrophic scarring. The silver-infused ethosomal gel has the ability to modulate the inflammatory cascade, which may produce a better environment for tissue regeneration. This reduces the chances of negative consequences that are linked to long-lasting and uncontrolled inflammation. Silver is acknowledged for its ability to promote tissue repair and regeneration, in addition to its antibacterial and anti-inflammatory qualities. Research has shown that silver ions may enhance the growth of fibroblasts, which are the cells responsible for generating the extracellular matrix and collagen that are crucial for the process of wound healing. The

regenerative property of silver enhances its antibacterial effects, making it a versatile therapeutic agent for treating severe burn wounds. By incorporating silver into an ethosomal gel, its potential is further enhanced since it enables precise delivery to the exact skin layers that need regeneration. It is crucial to acknowledge that while silver has various advantages, its therapeutic use must be carefully regulated to prevent possible toxicity. The ethosomal gel formulation's regulated release helps maintain equilibrium by limiting the excessive buildup of silver ions in the systemic circulation. This regulated administration technique reduces the likelihood of systemic adverse effects while optimizing the localized therapeutic benefit, so offering a safer and more effective approach for managing severe burn wounds.

The development of a gel containing silver-infused Ethosomes shows great potential as a novel method for treating severe burn injuries. This formulation effectively tackles the complex issues related to deep burn wound care by using the antibacterial properties of silver and the improved delivery capabilities of ethosomal technology. The controlled release of silver ions, together with the precise distribution to inner layers of the skin, makes silver-infused ethosomal gel an effective treatment for preventing infections, reducing inflammation, and promoting tissue regeneration in the case of severe burn wounds. As research advances in this area, more knowledge about the best combinations, amounts, and methods of using silver-infused ethosomal gel will probably improve and broaden its impact on the treatment and results of patients with severe burn injuries.

II. REVIEW OF LITERATURE

Qadir, Abdul et al., (2021) The skin, being the biggest organ of the human body, serves as a protective barrier against external threats, safeguarding the underlying organs and tissues. Any injury inflicted on the skin might potentially lead to significant repercussions in the underlying tissues of the body. Burns are a kind of injury that harm the layers of skin, making it more susceptible to the entry of foreign substances and the development of severe illnesses. An online literature study was conducted to examine the methods used for lipid nanoparticles, burn wound treatments, and other forms of Nano formulation. Data was extracted from several electronic scientific databases including Web of Science, Elsevier, Science Direct, Springer, PubMed, and Google Scholar. Supplementary information was condensed from textbooks, local publications, and manuscripts. Outcome The latest advancements in medication delivery systems based on nanotechnology have shown encouraging outcomes in mitigating the limitations associated with traditional therapy. Lipid-based nanoparticles have the ability to transport active substances to their intended location without the risk of degradation. The traditional approach to treating burn wounds is expensive and requires a lengthy treatment period, which may cause discomfort for the patient. Furthermore, it fails to provide adequate outcomes or specific impacts. The bioactive compound is enclosed inside the lipid core, providing protection from pH and enzymatic destruction. This review focuses on the limitations associated with traditional dose forms. Considerable attention is devoted to the development of nanomaterials via novel approaches in

wound care to expedite the healing process of burn wounds. This review paper focuses on the latest advancements in lipid-based Nano formulations for the treatment of burn wound injuries.

Abdelfattah, Sally et al., (2021) When the skin is harmed by physical, chemical, mechanical, or thermal means, a spontaneous sequence of events, known as the "cascade of healing," is initiated. This process aims to repair the injured tissues, replace the damaged structures, and prevent the entry of pathogens into the affected tissues. Various conventional wound healing treatments, including gels, creams, ointments, dressings, and solutions, rely on moisture absorption to facilitate tissue regeneration. However, these products may not provide the ideal circumstances necessary for effective wound recovery. Nanocarriers have a crucial impact on wound healing by enhancing the transport of medications into the skin. They do this by modifying the way pharmaceuticals are distributed and metabolized in the body, ultimately leading to an increased availability of drugs. Liposomes, noisome, Transfersomes, penetration enhancer containing vesicles (PEVs), and Ethosomes are types of vesicular systems that have been shown to improve the effectiveness of medications used for wound healing. This article provides a comprehensive overview of several vesicular systems used in wound healing. It covers their composition, benefits, drawbacks, preparation procedures, and processes of skin penetration.

Barkat, Md et al., (2016) The objective of this study was to develop, refine, and evaluate a topical gel combining micronized Silver sulfadiazine (mSSD) and Aloe vera gel (AV-gel) for its therapeutic effects on second degree burn wounds in Albino Wistar rats. The concentration of Carbopol 940, a gelling agent, was chosen based on the observation of the ideal spreadability and consistency. Second-degree burn injuries were induced on the rear region of Albino Wistar rats while under anesthesia. The established wounds were treated by using mSSD gel once daily for 14 days after injury, and the progress was monitored until complete healing occurred. The observation demonstrated a difference in the rate of wound healing between the group treated with mSSD gel (Group II) and the control group (Group I). The group treated with mSSD gel had a greater degree of tissue hyperplasia in comparison to the control group. The animals treated with AV-gel in the MSSD topical gel exhibited a healing rate of 84.96% during a span of 14 days. In contrast, the animals in the control group showed a healing rate of 49.48% on the 14th day. No signs of inflammation or pus development were detected in the treated animals, but the control group exhibited clear indications of inflammation and pus formation throughout the first week. Overall, the use of mSSD gel incorporating AV-gel has shown promising results in the treatment of second degree burn wounds by reversing the process that delays wound healing.

Akbari, Hossein et al., (2015) Multiple experiments were conducted to create advanced dressings that may accelerate the healing process and reduce the amount of germs in burn wounds. This research evaluated the therapeutic efficacy of nettle extract in treating second degree burns in rats, comparing it to the effects of silver sulfadiazine and Vaseline. Forty rats were allocated randomly into four groups of equal size. A profound second-degree burn was induced on the dorsal region

of each rat using a conventional burning technique. In group 1, the burns were treated daily with nettle extract, in group 2 with silver sulfadiazine, in group 3 with Vaseline, while group 4 served as the control group without any medicine. The evaluation of treatment efficacy was conducted by the use of digital photography throughout the treatment period, up to day 42. Histological assessment was performed on scar tissue samples on days 10 and 42. Group 1 showed a statistically significant difference compared to the other groups in 4 scoring criteria after a period of 10 days. A considerable statistical disparity was seen in the fibrosis parameter after a duration of 42 days. The nettle group had the most wound surface area healing, whereas the control group showed the least amount of repair. The results of our study demonstrated that the nettle group had the highest rate of healing. Therefore, it might serve as a viable alternative to silver sulfadiazine and Vaseline, if they are not accessible.

Adhya, abhishek et al., (2014) For many years, Silver sulfadiazine (SSD) has been widely used as the primary topical antibacterial treatment for burn wounds. Currently, there are nanometer-sized silver particles that possess a high surface to volume ratio. These particles retain their effectiveness even at extremely low concentrations and reduce the risk of tissue toxicity caused by silver. Therefore, we performed a randomized controlled experiment to evaluate the efficacy of topical SSD and Nano-crystalline silver (AgNP) hydrogel in the treatment of burn wounds. The study was carried out in the Burn Unit of IPGME&R & SSKM Hospital Calcutta, spanning from January 2011 to August 2012. Subjects with second-degree burn injuries were randomly assigned to either the silver sulfadiazine (SSD) therapy group or the silver nanoparticle (AgNP) treatment group. Weekly clinical evaluations of the burn site were conducted until the fourth week, as well as upon completion of the therapy. Evaluation data were collected from 54 patients with second-degree deep-dermal cases, who had SSD therapy, and from 52 patients with second-degree deep-dermal cases, who received AgNP treatment. The healing progress of second-degree deep-dermal burns was more favorable in the group treated with silver nanoparticles (AgNP) compared to those treated with silver sulfadiazine (SSD) after 4 weeks. At the 4-week mark, 80.6% of patients who received AgNP treatment demonstrated a minimum of 50% recovery in 2° deep-dermal wounds, but only 48.1% of patients treated with SSD achieved the same level of healing ($P = 0.001$). The rates of full recovery at 4 weeks were 4% and 0% for the respective groups ($P = 0.116$). Silver nanoparticles (AgNP) may serve as a highly efficient and superior substitute for silver sulfadiazine (SSD) in the treatment of burn injuries, especially second-degree deep-dermal burns. The healing process typically takes 6 to 8 weeks, varying based on the degree of body surface affected.

Chen, Jiong et al., (2006) The objective is to investigate the impact of silver nanoparticle dressing on the prevention of infection and the healing process of second degree burn wounds. A total of 191 burn patients, who had second-degree burns involving both superficial and deep burn wounds, were randomly assigned to three groups. Group A, consisting of 65 patients, received treatment with silver nanoparticle dressing for their wounds. Group B (63 cases) and group C (63 cases) were treated with 1% silver sulfadiazine cream and vaseline gauze, respectively, for their wounds.

The dressing was replaced on a daily basis, and bacterial cultures of wound swabs were conducted both before and after each dressing change. Additionally, the time it took for the wounds to heal was documented for each patient. Both Group A and Group B exhibited comparable bacterium colonization on the wound following treatment with the silver nanoparticle dressing and 1% silver sulfadiazine cream. Additionally, both groups demonstrated a similar ability to reduce bacterium colonization on the wound after treatment. In contrast, the Vaseline gauze group experienced an increase in bacterium colonization on the wound after treatment. The wound healing period of superficial second degree injuries in group A was considerably shorter compared to group B and group C ($P < 0.01$). The healing period for deep second degree wounds was significantly shorter in group A compared to group C ($P < 0.01$), however there was no significant difference when compared to group B ($P > 0.05$). The use of silver nanoparticle dressing is effective for treating second degree burn wounds since it reduces the likelihood of wound infection and expedites the healing process.

III. RESEARCH METHODOLOGY

Solubility analysis

Solubility refers to the capacity of a salute to completely dissolve in a liquid (solvent) and create a uniform mixture. The solubility of a substance is influenced by many factors, including the nature of the solvent, the temperature, and the pressure. The primary objective of the solubility study was to identify an appropriate solvent capable of dissolving the active pharmaceutical ingredient (API), lipid, and excipients used in the formulation production.

Preparation of silver sulfadiazine loaded ethosomal suspension

An Ethanolic suspension of silver sulfadiazine was made using the hot approach proposed by Elka Touitou for the use of ethosomal nanocarriers. A solution of silver sulfadiazine was diluted using a 25% ammonia solution. Six distinct compositions, namely F1, F2, F3, F4, F5, and F*, were created by altering the concentrations of ethanol and propylene glycol, in addition to including the necessary quantity of medication (500µg). This was achieved by heating the mixture to 40°C and thereafter subjecting it to mechanical stirring at 400rpm. The lecithin was mixed with the necessary amount of water and left undisturbed for several hours. It was then vigorously agitated using a mechanical device at a speed of 900-1100 revolutions per minute. Subsequently, the mixture was heated to a temperature of 40°C to ensure that it was fully activated before being used. The lipid phase was gradually added to an ethanol mixture while continuously and securely stirring with a magnetic stirrer at room temperature for a duration of 30 minutes, maintaining a speed of about 300 revolutions per minute, in order to ensure thorough and consistent blending. The formulation was ultimately subjected to sonication using a probe sonicator (Frontline Sonicator) for about 5-8 minutes while being maintained in an ice bath at a temperature of 4°C. A uniform suspension of SSD Ethosomes was achieved. The Nano-ethosomal formulation was kept in an

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opaque container at ambient temperature, shielded from light, in preparation for further experiments.

Table 1. Composition of SSD ethosomal formulations is given in Table 2 below.

Formulation	Cholesterol (%w/v)	Ethanol (% v/v)	Propylene Glycol (% v/v)	Lecithin (%w/v)	Water (ml)
F1	0.3	15	1	2	26.4
F2	0.3	20	3	3	19
F3	0.3	25	2	4	13.6
F4	0.3	30	4	5	6
F5	0.3	40	3	6	1.4
F*	0.3	20	4	7	13.4

IV. DATA ANALYSIS AND INTERPRETATION

Identification of pure drug

- **Melting point determination**

The melting point of silver sulfadiazine was found to be 284◦C. The observation revealed that the melting point of Silver Sulfadiazine aligns with the USP standard, therefore confirming the absence of any contaminants in the medicine.

- **Solubility analysis**

Silver sulfadiazine is insoluble in distilled water, mildly soluble in acetone, essentially insoluble in alcohol, chloroform, ether and is easily soluble in 30% ammonia.

- **Partition coefficient**

The Log P of Silver Sulfadiazine was determined to be about 2.1 suggesting that the medication is very lipophilic in nature.

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- **Standard calibration curve of silver sulfadiazine**

The calibration curve of Silver Sulfadiazine was developed by utilizing the 2-18µg/ml concentration of Silver Sulfadiazine in 0.05% ammonia solution. The absorbance was measured at 254nm. The calibration curve which was drawn was linear in the range of 2-18µg/ ml at λmax 254nm. The correlation coefficient was determined to be 0.996. The calibration curve is given in Table 2 and Figure 1.

Table 2: Silver sulfadiazine calibration curve (λ_{max} = 254 nm)

S.NO	Concentration (µg/ml)	Absorbance
1	2	0.135
2	4	0.17
3	6	0.37
4	8	0.394
5	10	0.478
6	12	0.554
7	14	0.621
8	16	0.717
9	18	0.754

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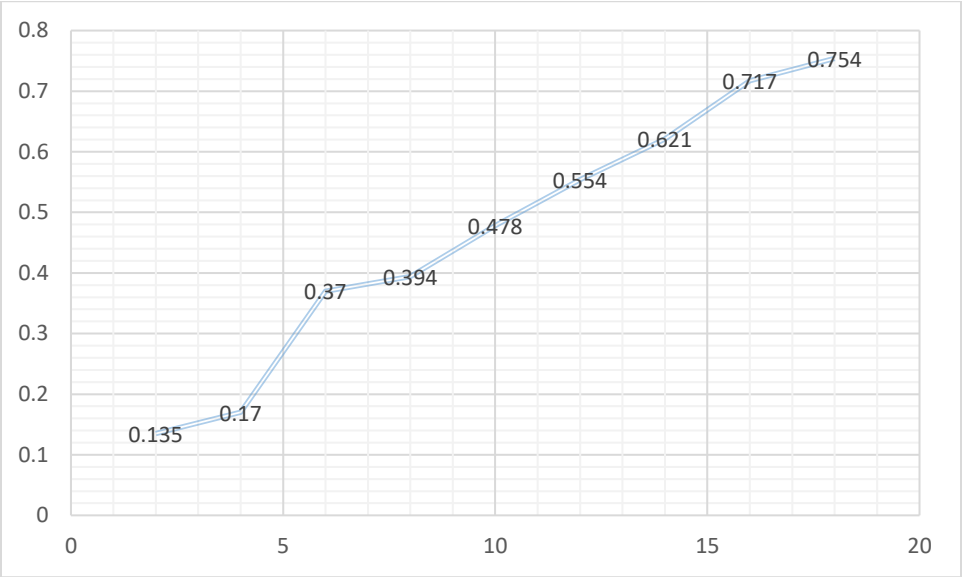

Figure 1. Calibration curve for silver sulfadiazine

V. CONCLUSION

The treatment of severe burn wounds is a vital component of healthcare, needing creative ways to accelerate healing and reduce consequences. A potential strategy includes the use of silver-infused ethosomal gel. Deep burns provide unique issues, affecting numerous skin layers and necessitating expert treatment. Silver's antibacterial characteristics, paired with ethosomal gel's effective drug delivery method, provide a revolutionary technique. This introduction discusses the logic behind silver-infused ethosomal gel, stressing its unique properties and possible advantages in deep burn wound care, addressing infection prevention, inflammation management, and tissue regeneration.

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