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A Review on Curcumin Loaded Nanoemulgel for Wound Healing Activity

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Abstract: *Wound healing is a natural process in which the body repairs damaged tissues through several stages, including inflammation, new tissue formation, and tissue remodeling. Curcumin, a natural chemical compound derived from turmeric (Curcuma longa), has attracted interest because of its antioxidant, anti-inflammatory, antimicrobial, and wound-repairing activities. It may help in wound healing by controlling inflammation, reducing oxidative damage, supporting collagen formation, promoting the development of new blood vessels, and improving wound closure. Despite these beneficial effects, the use of curcumin is limited by its poor solubility in water, low bioavailability, and lack of stability under certain conditions. To address these challenges, researchers are exploring advanced drug delivery systems, such as nanoparticles, nanoemulgels, and hydrogels, to improve curcumin's stability and effectiveness.*

This review focuses on the chemical characteristics of curcumin, its role and mechanisms in wound healing, its benefits and limitations, and the development of improved formulations. It also discusses future research opportunities and the need for further clinical studies to confirm its safety and therapeutic benefits in humans. Curcumin may be a useful candidate for wound management; however, more evidence is needed before its full clinical potential can be established..

Keywords: Curcumin, Wound Healing, Antioxidant Activity, Anti-Inflammatory Activity, Collagen Synthesis, Angiogenesis, Drug Delivery Systems

I. INTRODUCTION

The skin forms a protective covering for the body and helps protect it from harmful environmental factors, including microorganisms, foreign chemicals, and ultraviolet (UV) radiation. Because the skin is regularly exposed to the outside environment, it is more likely to experience injuries and damage.[1] Skin injuries occur worldwide due to surgery, accidents, burns, and long-term illnesses, making wound care an important public health concern. Wounds are generally divided into two types: acute and chronic. Acute wounds usually heal within a few weeks or months through the body's natural repair process. In contrast, chronic wounds take longer to heal and may be associated with complications such as persistent infection and delayed tissue repair.

Wound healing is the body's natural process of repairing damaged skin and restoring its normal structure and function. It occurs through four overlapping stages: stopping bleeding, inflammation, new tissue formation, and tissue strengthening. These stages depend on the coordinated action of different cells, growth factors, and signaling substances. However, conditions such as diabetes, ageing, infection, and long-lasting inflammation can slow healing and lead to chronic wounds. For this reason, developing effective creams and gels that support tissue repair and improve wound healing is an important area of pharmaceutical research.[2]

Curcumin is a naturally occurring compound obtained from the rhizome of *Curcuma longa*, commonly known as turmeric. It has attracted considerable research interest because of its antioxidant, anti-inflammatory, and other potential

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health benefits. In wound-healing research, curcumin may help regulate inflammation, limit oxidative stress-related damage, and promote collagen formation and tissue regeneration. However, its pharmaceutical application is restricted by its poor water solubility, limited stability under certain conditions, and inadequate delivery to injured tissues[3]
Nanotechnology-based drug delivery systems are being studied to improve the delivery of drugs that do not dissolve easily in water, such as curcumin. Nanoemulsions contain tiny oil and water droplets that are stabilized by surfactants. They may help distribute curcumin more evenly and improve its delivery into the skin. When a nanoemulsion is mixed with a suitable gel, it forms a nanoemulgel. This formulation combines the benefits of the nanoemulsion with the easy application, suitable thickness, and better retention of the gel on the skin.[4]

Overview of Wound Healing:

Wound healing is a physiological process through which the body restores injured skin and tissues. It consists of four interconnected phases: hemostasis, inflammation, proliferation, and remodeling. The healing process can be affected by several factors, including infection, age, nutritional status, and wound severity. Curcumin, a natural bioactive constituent derived from turmeric (Curcuma longa), exhibits antioxidant and anti-inflammatory properties that may help promote tissue repair. Curcumin-based nanoformulations are being explored to enhance drug solubility, improve delivery to the wound site, and potentially increase therapeutic effectiveness.[5]
Wound healing occurs through four interconnected stages: hemostasis, inflammation, proliferation, and remodeling. During hemostasis, a blood clot forms to control bleeding. The inflammatory phase helps eliminate microorganisms, damaged cells, and tissue debris. In the proliferative phase, new tissue develops through fibroblast activity, collagen formation, new blood vessel growth (angiogenesis), and re-epithelialization. Finally, the remodeling phase strengthens the repaired tissue and enhances its structural organization.[6] The wound-healing process is influenced by various factors, such as age, nutritional status, blood supply, infection, existing medical conditions, and the severity of the injury. Delayed healing can increase the likelihood of infection and chronic wound development, highlighting the importance of proper wound care and effective management.[7]Curcumin, a natural polyphenolic compound obtained from turmeric (Curcuma longa), has attracted considerable attention because of its antioxidant, anti-inflammatory, and potential wound-healing properties. However, its poor water solubility, limited bioavailability, and stability issues may restrict its therapeutic application.[8]

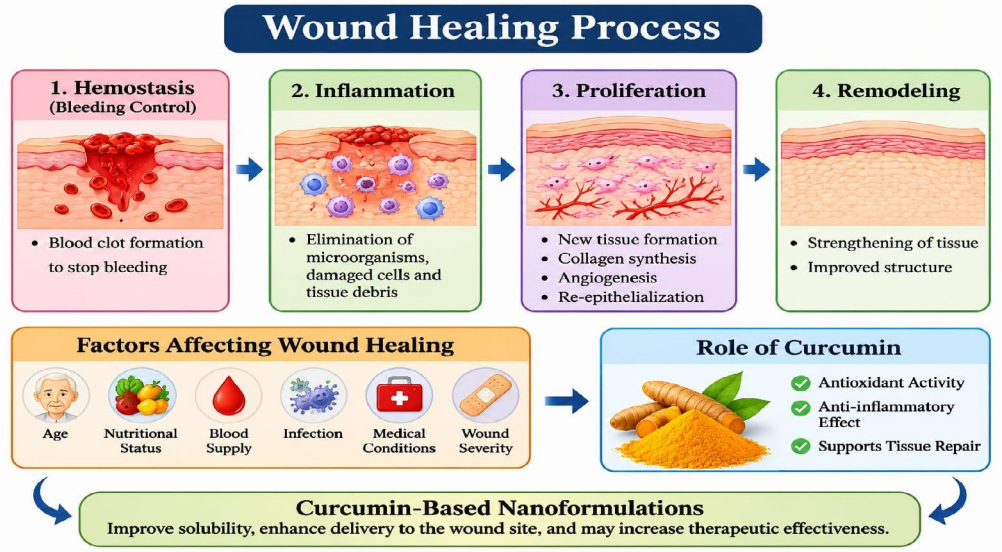


Figure 1: Wound healing process and potential role of curcumin based nanoformulation.

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Properties of Curcumin:

Chemical formula: Curcumin has the chemical formula $C_{21}H_{20}O_6$.

Molecular weight: Its molecular weight is about 368.38 g/mol.

Appearance: It is a yellowish-orange crystalline substance.

Solubility: Curcumin dissolves very poorly in water but dissolves in some organic solvents.

Stability: Curcumin may break down in alkaline conditions and under certain environmental conditions.

Chemical structure: Its structure consists of two aromatic rings joined by a seven-carbon chain containing a β-diketone group.

Curcumin is a plant-derived polyphenol primarily found in the rhizome of turmeric (Curcuma longa L.). It is chemically designated as (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, with a molecular formula of $C_{21}H_{20}O_6$ and a molecular mass of approximately 368.38 g/mol. Its chemical structure contains two aromatic rings joined by a conjugated carbon chain incorporating a β-diketone moiety.

The hydroxyl and methoxy functional groups influence its physicochemical characteristics and interactions with biological systems. Curcumin can occur in two different forms, called keto and enol forms, depending on its chemical surroundings. It does not dissolve well in water, making it difficult to prepare medicines using water-based formulations. Its solubility and stability can change with pH, temperature, and the type of solvent or carrier used. Curcumin may also break down in water, especially under neutral or alkaline conditions, which can reduce the stability of the formulation [9]

Sources and Composition of Curcumin:

Turmeric is obtained from the underground stem, known as the rhizome, of Curcuma longa, a plant belonging to the Zingiberaceae family. It mainly contains three curcuminoids: curcumin, demethoxycurcumin, and bisdemethoxycurcumin. The amount of each compound may differ depending on the plant source, growing conditions, extraction technique, and processing method.[10] In pharmaceutical research, curcumin can be used either as a purified compound or as an extract containing a mixture of curcuminoids. Differences in purity and composition may affect the consistency of formulation results and biological activity. Therefore, researchers should clearly mention the source of curcumin, its purity, and the analytical method used to measure its content.[11]



Figure 2: Curcuma Longa

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Pharmacological Activities of Curcumin:

Curcumin has been studied for its ability to reduce oxidative stress, control inflammation, and act against certain microorganisms. These properties have led researchers to explore its use in formulations designed to support wound healing. However, the reported benefits may vary depending on the type of study, the amount of curcumin used, the formulation method, and the overall study design

Antioxidant Activity:

Curcumin contains phenolic groups that can react with free radicals and help reduce oxidative stress. Studies have shown that it may help maintain the balance between oxidants and antioxidants under certain conditions. This is important in wound healing because excessive oxidative stress can damage cells and delay tissue repair. However, reactive oxygen species also support the body's immune response and normal cell signalling. Therefore, their role in wound healing depends on their concentration and biological function.[12]

Anti-inflammatory Activity:

Curcumin has been studied for its potential to reduce inflammation by affecting certain inflammatory substances and cell signalling pathways, including nuclear factor kappa B (NF-κB). These effects may help explain its anti-inflammatory properties. Curcumin may be useful when inflammation continues for too long, as prolonged inflammation can delay wound healing. However, the early inflammatory response is also important for removing harmful microorganisms and damaged tissues, so it is necessary for normal wound repair[13]

Antimicrobial Activity:

Laboratory studies have shown that curcumin may act against certain microorganisms. However, its effectiveness depends on factors such as the type of microorganism, the concentration of curcumin, the duration of exposure, and the formulation used. Although these findings are promising, results from laboratory experiments alone cannot confirm that curcumin-loaded nanoemulgel can prevent or treat wound infections in humans. Further clinical studies are needed to establish its safety and effectiveness[14]

Mechanism of curcumin in Wound Healing:

Curcumin is a natural compound found in turmeric (Curcuma longa). It has been studied for its possible benefits in wound healing because it may help reduce oxidative damage and inflammation and act against some microorganisms. Wound healing occurs in different stages, including inflammation, the formation of new tissue, and tissue repair. Curcumin may help these processes, but its effects depend on the amount used, the type of formulation, and the conditions of the study. Most evidence comes from laboratory and animal studies, so more research in humans is needed to confirm its benefits.[15]

Antioxidant Effect:

Curcumin may help protect cells from damage by reacting with free radicals and supporting the body's natural antioxidant systems. Excessive oxidative stress can harm cells and slow down the healing of wounds. By helping maintain a balance between oxidants and antioxidants, curcumin may support the wound-repair process. However, reactive oxygen species also help the body fight infections and support normal cell communication, so they are important for healthy wound healing when present at appropriate levels.[16]

Anti-inflammatory Effect:

Curcumin has been studied for its ability to control inflammation by affecting signalling pathways such as nuclear factor kappa B (NF-κB), which helps regulate the release of inflammatory substances called cytokines. By influencing

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these pathways, curcumin may help reduce excessive inflammation that can slow wound healing. However, the early inflammatory response is important because it helps remove damaged tissue and protects the wound against infection [17]

Stimulation of fibroblast activity and collagen formation:

Fibroblasts are cells that play an important role in wound healing by producing collagen and other materials needed to build and support new tissue. Experimental studies suggest that curcumin may help fibroblasts function and increase collagen formation, which can support the growth of new tissue and improve wound repair. However, too much collagen production may lead to excessive scar formation, so the effects of curcumin on collagen production require further investigation[18]

Angiogenesis and re-epithelialization:

Angiogenesis refers to the development of new blood vessels, which help deliver oxygen and nutrients to damaged tissues during wound healing. Research using diabetic animals suggests that applying curcumin to wounds may encourage the growth of new blood vessels and affect factors involved in this process, such as vascular endothelial growth factor (VEGF). Therefore, curcumin may have potential for supporting the healing of wounds with poor blood circulation. However, these findings are mainly based on preclinical studies, and further research is needed to confirm its effects in humans. Re-epithelialization is the process in which skin cells, mainly keratinocytes, move and multiply to cover the wound and rebuild the skin's protective layer. Some animal studies have reported better skin regeneration and faster wound closure following curcumin treatment. These benefits may be linked to curcumin's effects on inflammation and the formation of new tissue. However, the results may vary depending on the type of wound and the formulation used [19]

Nanoemulsion: Principles and Formulation:

A nanoemulsion is a mixture of two liquids that do not normally mix, such as oil and water, in which one liquid is present as very small droplets within the other. Surfactants and sometimes co-surfactants are used to help form and stabilize these droplets. Depending on the formulation, the oil droplets may be dispersed in water or water droplets in oil. Nanoemulsions are being studied for topical drug delivery because they may help dissolve and distribute poorly water-soluble substances, such as curcumin, and improve their delivery into the skin. Curcumin does not dissolve well in water, making it challenging to prepare conventional water-based medicines. Adding curcumin to the oil phase of a nanoemulsion may help improve its solubility and allow it to spread more evenly throughout the formulation. When this nanoemulsion is mixed with a gel, the resulting product is called a nanoemulgel. It combines the ability of a nanoemulsion to carry the drug with the ease of application and longer contact time provided by the gel. Therefore, curcumin-loaded nanoemulgel is a potential option for topical wound treatment, but its performance and safety must be confirmed through suitable testing.

Types of nanoemulsions:

Nanoemulsions are divided into two main types based on how oil and water are distributed in the system.

Oil-in-water (O/W) nanoemulsion: In this type, tiny oil droplets are spread throughout a water-based phase. It may be suitable for topical formulations containing curcumin because curcumin dissolves poorly in water.

Water-in-oil (W/O) nanoemulsion: In this system, small water droplets are dispersed throughout an oil-based phase. Its use depends on the drug's properties and the purpose of the formulation. The choice between these types depends on the drug's solubility, the selected ingredients, and the intended route of administration

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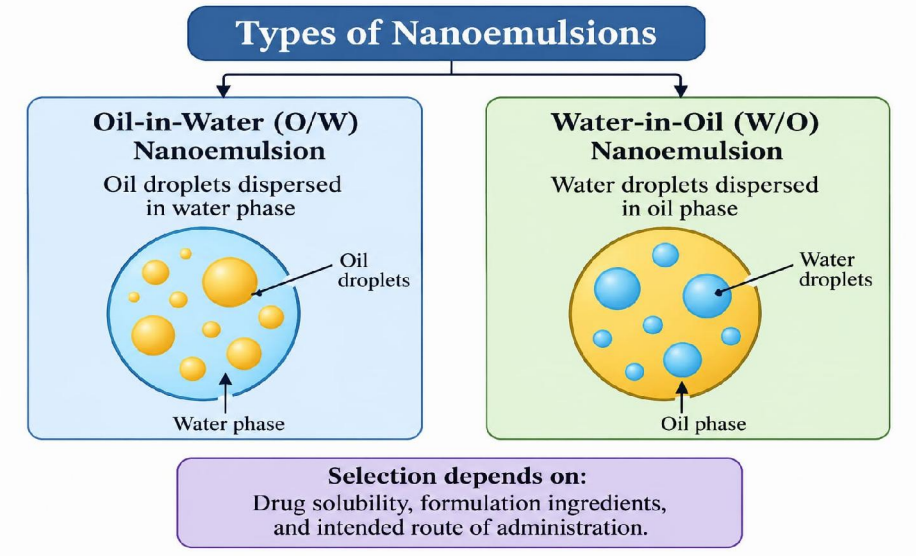


Figure 3 : Types of nanoemusion

Main components of the Nanoemulsion:

The formulation generally consists of the following components-

- **Aqueous phase:** Purified water is commonly used as the water-based part of an oil-in-water nanoemulsion.
- **Oil Phase:** Oil phase is commonly used as the oil-based part of an oil-in-water nanoemulsion.
- **Surfactant:** It lowers the surface tension between oil and water, helping form and maintain stable droplets.
- **Co-surfactant:** This ingredient may be added to improve flexibility at the oil–water interface and assist in forming small droplets.
- Ac**tive pharmaceutical ingredient (API):** Curcumin is added in an appropriate amount according to its solubility and the requirements of the formulation.

The type and quantity of each ingredient can affect droplet size, formulation stability, the amount of curcumin incorporated, and the suitability of the product for application to the skin.[20]

Advantages of Nanoemulsions:

- Enhances the solubility of poorly water-soluble drugs.
- Promotes uniform distribution of curcumin throughout the formulation.
- Improves drug–skin contact, potentially enhancing topical drug delivery.
- Acts as an efficient carrier system for the formulation of curcumin-loaded nanoemulgels

Limitations of Nanoemulsions:

- Physical stability may vary according to storage temperature, environmental conditions, and formulation composition.
- Some surfactants and co-surfactants may induce skin irritation when used at unsuitable concentrations.
- Nanoemulsion preparation and characterization require appropriate equipment and validated evaluation techniques.
- Improved drug solubility does not necessarily guarantee enhanced wound healing or established therapeutic efficacy in humans.

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Methods of Preparation of Nanoemulsion:

1. Nanoemulsions can be prepared using two main approaches:

High-energy methods: Techniques such as high-pressure homogenization and ultrasonication apply mechanical force to break larger droplets into smaller ones.

Low-energy methods: These techniques use changes in the formulation composition or surrounding conditions to help produce small droplets.

The choice of preparation method depends on the ingredients, desired droplet size, available equipment, and stability of the final formulation.

2. Curcumin-Loaded Nanoemulgel: Formulation Strategies

Curcumin-loaded nanoemulgel is a topical preparation made by combining a curcumin-containing nanoemulsion with a suitable gel. The nanoemulsion helps carry curcumin, which does not dissolve well in water, while the gel makes the product easier to apply and helps it stay on the skin. This formulation is being studied for its possible use in wound healing.

Preparing nanoemulgel involves choosing appropriate ingredients, forming the nanoemulsion, mixing it with the gel base, and testing the final product. The ingredients and preparation method can affect the formulation's stability, drug release, delivery into the skin, and overall quality.

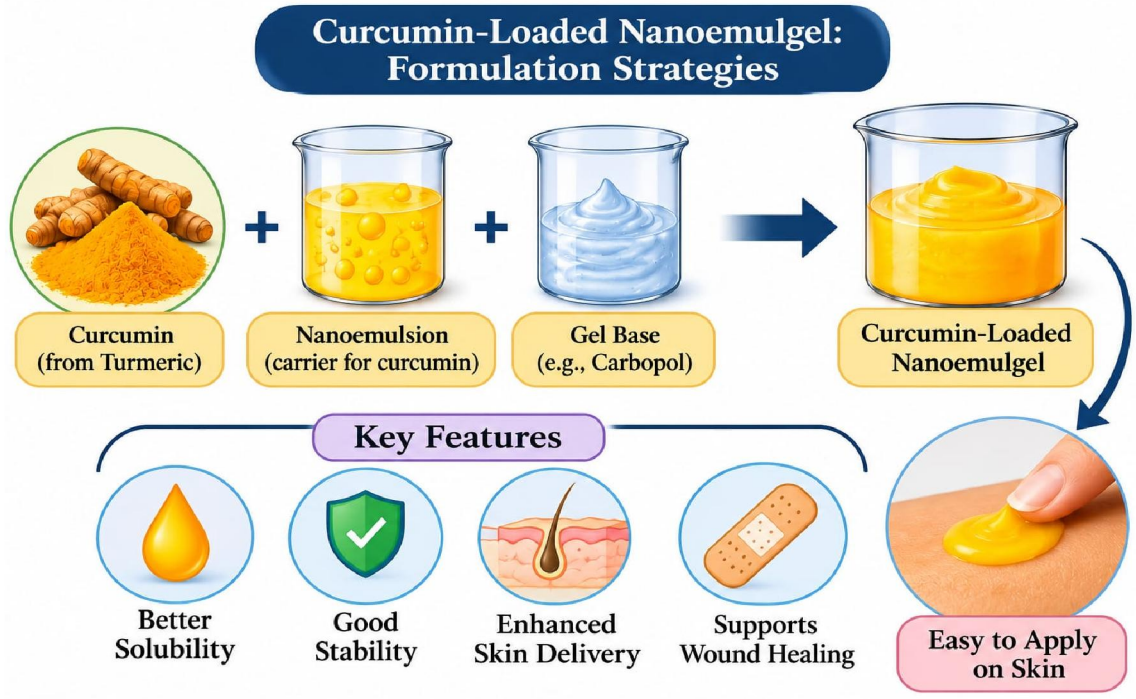


Figure 4: Diagrammatic overview of curcumin loaded nanoemulgel preparation and its potential role in wound healing.

3. Selection of formulation Ingredients:

Aqueous phase: **Purified water is commonly used as the water-based component in an oil-in-water nanoemulsion.**

Gel base: A compatible gelling agent, such as Carbopol or another suitable polymer, is used to provide the desired thickness and consistency.

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Curcumin: The amount of curcumin incorporated is determined by its solubility and the requirements of the formulation.

The appropriate selection and proportion of these components are important for obtaining a stable nanoemulgel suitable for topical application.

4. Preparation of Curcumin-loaded Nanoemulgel:

The formulation can be prepared through the following steps:

- **Solubilization of C urcumin:** Curcumin is dissolved in an appropriate oil or another suitable ingredient that supports its solubilization.
- **Preparation of the gel base:** The selected gelling agent is mixed with a suitable medium and allowed to hydrate or disperse properly.
- **Incorporation into the gel:** The prepared nanoemulsion is gradually blended with the gel base until a uniform formulation is obtained.
- **Final evaluation:** The prepared nanoemulgel is assessed for physical appearance, pH, viscosity, droplet size, drug content, and other important quality parameters.[21]

Factors affecting formulation of Curcumin-Loaded Nanoemulgel:

- **Droplet size:** The size of the droplets influences the physical characteristics, uniformity, and distribution of the nanoemulsion.
- **Surfactant concentration:** The amount of surfactant can affect droplet formation, formulation stability, and the possibility of skin irritation.
- **Gel viscosity:** The thickness of the gel affects its ease of application, spreadability, and ability to remain on the wound surface.
- **Drug concentration:** The quantity of curcumin incorporated determines the drug-loading capacity and influences the amount of drug available for release.
- **pH and formulation stability:** These parameters help assess the compatibility of the formulation with the skin and its suitability for topical application.
- **Storage conditions:** Storage temperature and duration can influence the physical and chemical stability of the prepared nanoemulgel.

Characterization and Evaluation of Curcumin-Loaded Nanoemulgel:

Curcumin-loaded nanoemulgel requires a series of physicochemical and performance assessments to verify its quality, stability, and suitability for topical wound care. These evaluations help determine the consistency of the formulation, the release behavior of curcumin, and its potential for effective delivery into the skin.

Droplet Size and Polydispersity Index (PDI):

Droplet size analysis is performed to measure the average diameter of droplets present in the nanoemulsion. The polydispersity index (PDI) describes the variation in droplet size throughout the formulation. A smaller droplet size and lower PDI may indicate a more uniform dispersion, depending on the formulation characteristics and testing method

Zeta Potential:

Zeta potential measurement determines the electrical potential associated with the nanoemulsion droplets. It helps evaluate the likelihood of droplet aggregation and provides useful information about the physical stability of the formulation. However, the results should be interpreted in relation to the composition of the formulation, particularly the surfactants and other excipients used

pH Measurement:

The pH of the prepared nanoemulgel is determined to evaluate its suitability for application to the skin. Maintaining an appropriate pH may help minimize skin irritation and support the stability of curcumin and the formulation components

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Viscosity and Spreadability:

Viscosity refers to the resistance of the nanoemulgel to flow, while spreadability describes how easily it can be applied across the skin or wound surface. These characteristics affect the ease of application, consistency, and ability of the formulation to remain at the intended site

Drug Content and Content Uniformity:

Drug content analysis is carried out to quantify the amount of curcumin contained in a specific quantity of the nanoemulgel. Content uniformity assessment helps determine whether curcumin is distributed evenly throughout the formulation

In Vitro Drug Release:

In vitro drug release testing is performed to measure the quantity of curcumin released from the nanoemulgel over a defined period. The findings help characterize the drug-release pattern and compare the performance of different formulations under specified experimental conditions

Ex Vivo Skin Permeation:

Ex vivo skin permeation testing is conducted using excised skin tissue to evaluate the extent to which curcumin penetrates into or passes through the skin.

Stability Studies:

Stability testing is performed to determine whether the nanoemulgel maintains its quality and properties during storage. Evaluation may include monitoring changes in physical appearance, droplet size, pH, viscosity, and drug content, as well as identifying phase separation or possible degradation of curcumin

Wound-Healing Evaluation:

The wound-healing potential of curcumin-loaded nanoemulgel can be investigated through preclinical studies by examining wound contraction, tissue repair, collagen deposition, inflammatory responses, and re-epithelialization. These assessments provide preliminary evidence of the formulation's therapeutic potential; however, findings from laboratory and animal studies alone are insufficient to establish its effectiveness in humans[22]

Advantages of Curcumin in Wound Healing:

Curcumin is a natural substance obtained from turmeric. It may support wound healing due to its ability to reduce inflammation, protect cells from damage, and fight certain bacteria. It also helps in the repair of injured skin tissues and supports the overall healing process.

- **Reduces inflammation:** Curcumin helps reduce inflammation by lowering the levels of substances in the body that cause swelling and irritation. This may help the wound heal properly.
- **Provides antioxidant protection:** Curcumin helps protect skin cells from damage caused by harmful molecules called free radicals. It also supports the body's natural antioxidant defense system, helping protect damaged tissues during wound healing.
- **Helps in collagen formation:** Curcumin may help the body produce more collagen, a protein needed to repair damaged skin. This helps form new tissue and may make the healing wound stronger.
- **Supports new blood vessel formation:** Curcumin may help the growth of new blood vessels around the wound. These blood vessels supply oxygen and nutrients needed for tissue repair.
- **Helps wounds close faster:** Curcumin may help wounds close by supporting the growth of new skin cells and the repair of damaged tissues
- **Fights certain bacteria:** Curcumin has antibacterial properties that may help control the growth of some bacteria and reduce the risk of infection at the wound site[23]

Disadvantages of Curcumin in Wound Healing

Curcumin has several benefits in wound healing, but some limitations may reduce its effectiveness in wound treatment.

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- **Poor water solubility:** Curcumin does not mix easily with water, making it difficult to prepare some types of wound-healing formulations.
- **Low absorption:** Curcumin is not easily absorbed by the body, which may reduce its effectiveness when taken orally.
- **Stability problems:** Curcumin may break down when exposed to light or certain pH conditions, which can reduce its effectiveness.
- **Rapid breakdown in the body:** Curcumin is quickly broken down and removed from the body, so its effects may not last long.
- **Possible skin irritation:** Some topical formulations containing curcumin may cause skin irritation, depending on their concentration and other ingredients.
- **Limited human studies:** Most research on curcumin for wound healing has been conducted in laboratories and animals. More studies in humans are needed to confirm its safety and effectiveness.[24]

Future Perspectives of Curcumin in Wound Healing:

Curcumin is a natural compound that may be useful in wound healing because it reduce inflammation, protects cells from damage, and fights certain bacteria. In the future researchers may develop better formulations to improve its effectiveness and overcome its limitations.

- **Use of nanotechnology**: Nanoparticles and nanoemulgels may help improve the solubility, stability, and delivery of curcumin to the wound.
- **Improved topical formulations:** New creams, gels, and ointments may help deliver curcumin directly to the affected skin.
- **Combination with other drugs**: Curcumin may be combined with other wound-healing agents to improve treatment outcomes.
- **Treatment of chronic wounds:** Future studies may investigate the use of curcumin for diabetic wounds, burns, and wounds that take a long time to heal.
- **Development of advanced wound dressings:** Curcumin may be incorporated into hydrogels, films, and biodegradable dressings to support wound protection and healing.
- **Further clinical research:** More studies in humans are needed to confirm the safety, suitable dosage, and effectiveness of curcumin in wound treatment.

II. CONCLUSION

Curcumin, which is derived from turmeric (Curcuma longa), is a promising natural compound for wound management due to its antioxidant, anti-inflammatory, and antimicrobial activities. It may help repair damaged tissues by controlling inflammation, protecting cells from oxidative damage, enhancing collagen production, encouraging new blood vessel formation, and supporting wound closure. However, its practical application is restricted by poor water solubility, limited absorption, and instability under certain conditions. To improve its therapeutic potential, advanced drug delivery systems, including nanoparticles, nanoemulgels, and hydrogels, are being explored to enhance its stability and delivery to the affected area.

Although existing experimental studies have reported encouraging results, more research is needed to confirm its safety and effectiveness in humans. Further clinical investigations are also required to determine suitable formulations and appropriate dosing. Overall, curcumin may offer useful opportunities for developing improved wound-care products, but its clinical benefits must be established through stronger scientific evidence.

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