



REVIEW ARTICLE

CURCUMIN-LOADED NANOEMULSION-BASED TOPICAL DRUG DELIVERY SYSTEMS FOR WOUND HEALING: FORMULATION STRATEGIES, EVALUATION, AND THERAPEUTIC POTENTIAL

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ABSTRACT: Wound healing is a complex process in which inflammation, followed by tissue regeneration, and then remodeling takes place. Curcumin, a natural polyphenolic compound extracted from *Curcuma longa*, presents antioxidant, anti-inflammatory and antimicrobial properties which can help wound healing. However, its poor aqueous solubility, lack of stability and poor skin penetration limit its therapeutic use. To address these limitations, nanoemulsion based topical drug delivery systems are emerging as a promising alternative, with the aim to improve drug solubilisation, facilitate topical delivery and potentially improve the therapeutic performance. The formulation strategies required to prepare curcumin loaded nanoemulsions including the selection of oil phases, surfactants, co-surfactant and preparation methods is discussed in the review. It also points out some key parameters for evaluation which include globule size, polydispersity index, zeta potential, pH, drug content, in-vitro drug release, skin permeation, and stability. In addition, published preclinical studies on the wound healing ability of curcumin loaded nanoemulsions and nanoemulgels are discussed. While the findings have been promising, additional work needs to be done to determine the long-term stability, formulation safety, reproducibility and clinical efficacy. In general, the use of curcumin loaded nanoemulsions is a promising formulation approach for topical wound treatment, but needs more clinical assessment studies.

Keywords: Curcumin, Nanoemulsion, Topical drug delivery, Wound healing, Formulation development, Drug release

I. INTRODUCTION

Wound healing is a complex, natural process in which the body attempts to heal the wound and restore the skin's barrier function. It is a process that has four overlapping stages: haemostasis, inflammation, proliferation and remodelling. While some wounds are self-healing, some other factors like microbial infection, chronic inflammation, oxidative stress, and various health-related issues can slow down the healing process. These difficulties have spurred the study of effective topically delivered drug delivery systems capable of assisting with the management of wounds [1,2]. Curcumin is a natural polyphenolic compound obtained from the rhizomes of *Curcuma longa* (turmeric). It is highly interesting due to its antioxidant, anti-inflammatory and antimicrobial activity. Preclinical research indicates that curcumin could play a role in wound healing through its anti-inflammatory effects, antioxidant properties, and effects on tissue repair processes. The application of this in pharmaceutical industry is, however, hindered because of its poor aqueous solubility, its chemical instability under some circumstances, and insufficient targeting to skin tissues. These restrictions can be expected to impact its use in traditional topical product applications [2–4].

Nanoemulsions are a colloidal drug delivery system made up of oil and aqueous phases and their stability is achieved through the use of surfactants. They are showing promise as carriers for poorly water-soluble compounds because they are small droplets and can be formulated in a variety of ways. These curcumin-loaded nanoemulsions could help the drug to be soluble in the oil phase, and the composition of the formulation can affect the rate of release and the permeation of the drug through the skin. However, they rely on the proper selection of excipients, preparation conditions, physico-chemical stability and need to be confirmed experimentally [3–5]. Systematic formulation optimization and detailed evaluation of the curcumin loaded nanoemulsions is necessary to develop. Globule size, polydispersity index, zeta potential, pH, drug content, *in-vitro* drug release, physical and chemical stability are some of the important parameters. The permeation through the skin, local tolerability and biological evaluation are also relevant to the question of whether these systems are suitable for topical use. Published preclinical studies have also shown promising results for curcumin-based nanoemulsions and nanoemulgels, but more studies are required to prove their safety, repeatability and effectiveness for clinical application [4–6].

This review focuses on formulation strategies, parameters used for evaluation of nanoemulsion loaded topical drug delivery system, and therapeutic applications of curcumin loaded nanoemulsion for wounds healing. It also covers the pertinent research results, formulation problems and future trends in the formulation of stable, safe and effective topical dosage forms.

2. Curcumin and Its Role in Wound Healing

Curcumin is a natural polyphenolic compound obtained from the rhizomes of *Curcuma longa* (turmeric). It has drawn considerable interest in wound healing study due to its antioxidant, anti-inflammatory and antimicrobial activity. Its aqueous solubility and chemical stability can however be limited in certain formulations, which can prevent it from being used in conventional topical formulations. The limitations have led to the development of advanced systems for drug delivery to enhance solubilisation and topical delivery of curcumin [7–9].

2.1. Antioxidant and Anti-inflammatory Activities

Oxidative stress and inflammation are important in wound healing. Reactive oxygen species (ROS) have normal functions in the cell but excess production of these can result in damage to adjacent tissues and wound healing delays.

Studies in experimental models show that curcumin is anti-inflammatory and has antioxidant properties. Such effects could help to manage the wound environment and promote tissue repair. The size of these effects, however, varies depending on the formulation and concentration, the experimental model and the application conditions [8-10].

2.2. Role in Tissue Repair

The process of wound healing consists of several well-coordinated phenomena such as migration of fibroblasts, deposition of collagen, granulation tissue formation, angiogenesis and re-epithelialization. Preliminary research indicates that curcumin-containing formulations can affect these processes and promote the repair of tissues. Krausz *et al.* studied nanoparticles containing curcumin, which they found to have beneficial antimicrobial effects and wound healing in experimental models. There are other experimental studies that have studied the effect of nano-formulated curcumin on wound repair and inflammatory responses. However, results of laboratory and animal experiments cannot be taken as evidence of efficacy in humans [11-13].

The possible mechanisms by which curcumin could promote wound healing are listed in Figure 1.

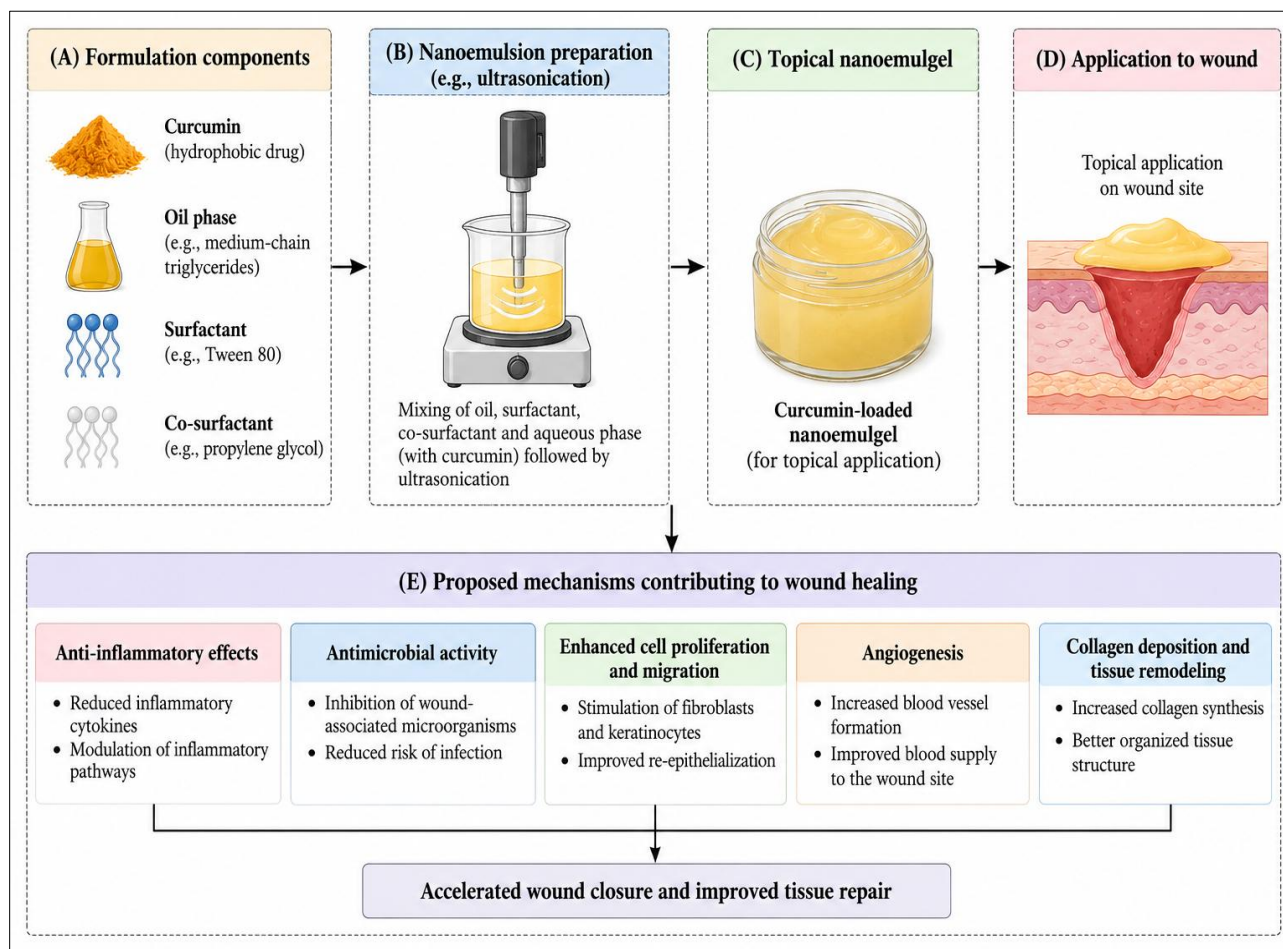


Figure 1: Mechanisms of curcumin-loaded nanoemulsion-based topical drug delivery for wound healing

2.3. Need for Nanoemulsion-Based Delivery

However, curcumin's poor water solubility is a challenge for conventional topical delivery because of its therapeutic potential. One potential strategy is to form curcumin nanoemulsions, which involves the inclusion of curcumin in an appropriate oil phase, and could have an effect on the solubilization of the drug, as well as its release or permeation through the skin. They are effective depending on composition of the formulation, size of the droplet and physical and chemical stability [9,14,15].

Ahmad *et al.* formulated the curcumin based nanoemulsion with clove oil, PEG 400 and Tween 80 and studied its physiological properties and the effect on wound healing in experimental models [6]. This paper offers an example of the possibilities of this nanoemulsion based delivery formulation. Additionally, long-term stability, local safety, reproducibility, and clinical efficacy need to be established in further research [16].

3. Topical Drug Delivery Systems based on Nanoemulsion

Nanoemulsions are colloidal dispersion of oil and water stabilized by the use of surfactants, and the droplet size is typically in the nanometer range. They have been the subjects of topical drug delivery research due to their ability to entrap poorly water-soluble compounds, to improve formulation uniformity and to modify the drug release and/or skin permeation. The properties that nanoemulsions have, make them a suitable carrier for curcumin, which has low solubility in water and low bioavailability in itself [17,18].

But it is not enough to say that a nanoemulsion can be good for wound healing because it has small droplets. This performance is related to excipients composition, physicochemical properties, distribution, stability and compatibility with the intended application. Thus, formulation design and experimental testing become vital to test the suitability of the formulation for wound care [17–19].

3.1. Types of Nanoemulsions

Typical classification of nanoemulsions is based on the structure of oil and aqueous phase. The oil droplets are suspended in a continuous water phase in an oil-in-water (O/W) nanoemulsion. This type could be used if lipophilic drugs like curcumin are to be applied topically in the oil phase, which will dissolve the drug, and the aqueous external phase will help in spreading and will not be greasy. The real delivery performance will be determined by the oil, surfactant system and formulation characteristics of the final formulation [18,19].

A water-in-oil (W/O) nanoemulsion consists of a continuous oil phase, in which water droplets are dispersed. Its external phase is rich in oil which can be beneficial if a more occlusive formulation is needed. During formulation selection, however, the spreading ability, washability, skin tolerability and

suitability for the intended wound should be taken into account [18,20].

The conceptual representation of an O/W nanoemulsion is given in figure 2. The diagram is schematic and not a representation of the actual droplet dimensions as they may be measured in an experiment.

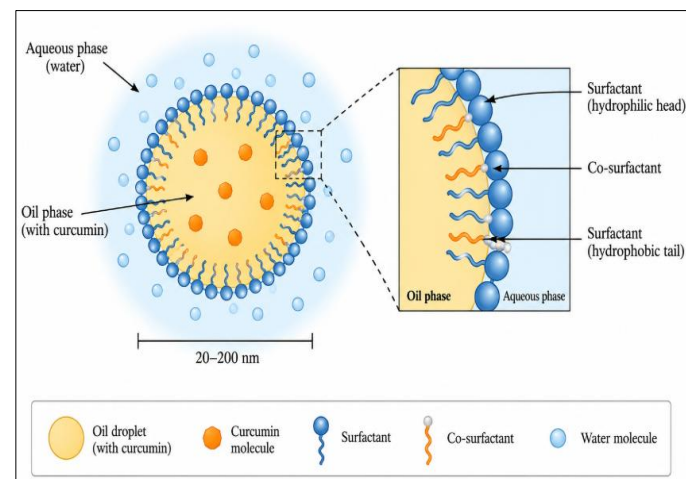


Figure 2: Schematic of an oil-in-water nanoemulsion.

3.2. Major Components of Curcumin-Loaded Nanoemulsions

The selection of the nanoemulsion formulation components, namely the oil phase, surfactant, co-surfactant (if it is needed) and aqueous phase, is of crucial importance. The function of the oil phase is to ensure a sufficient degree of solubilization of curcumin, and the role of the surfactant is to lower the interfacial tension and keep the dispersed oil droplets steady. Depending on the formulation design, a co-surfactant can facilitate the formation of droplets or change the interfacial properties [17–19].

In a directly relevant study, Ahmad *et al.* used clove oil, Tween 80 and PEG 400 to formulate a curcumin nanoemulsion by ultrasonication and optimization of formulation. The optimized system had a mean hydrodynamic diameter of about 94 nm and was tested for the permeation through skin, anti-inflammatory activity and wound healing in experimental models [11]. These results show that the selection of excipients as well as process optimization is of paramount importance, rather than simply selection of ingredients.

The other ingredients can be added if necessary for the desired dosage form. For instance, a gelling agent can be used to transform a liquid nanoemulsion to a nanoemulgel, which can enhance the acceptable application and site residence time. Other ingredients such as preservatives, antioxidants, humectants and pH-adjusting agents can also be used, if appropriate for the formulation. All ingredients need to be evaluated for their compatibility and tolerability at the site of application, especially if the product will be applied to irritated skin (Table 1) [14,19,21].

Table 1: Major components and their functions in topical nanoemulsion formulation [12-14]

Component	Primary function	Important consideration
Curcumin	Active pharmaceutical ingredient	Solubility and chemical stability
Oil phase	Solubilizes curcumin and forms droplets	Drug solubility and skin compatibility
Surfactant	Stabilizes the oil-water interface	Concentration and local tolerability
Co-surfactant	May facilitate droplet formation	Compatibility and irritation potential
Aqueous phase	Continuous phase in O/W systems	pH and formulation compatibility
Purified water	Aqueous vehicle	Microbiological quality
Gelling agent	Increases viscosity in nanoemulgels	Effect on spreadability and drug release
Humectant	Helps maintain moisture in the formulation	Concentration and tolerability
Preservative	Controls microbial growth when required	Compatibility and preservative efficacy
Antioxidant	May reduce oxidative degradation	Compatibility with curcumin and excipients
pH-adjusting agent	Adjusts formulation pH	Suitability for the intended application
Chelating agent	May limit metal-catalysed degradation	Need and compatibility in the formula

3.3. Potential Advantages and Limitations

Table 2: Potential advantages and limitations of topical nanoemulsions [17-22]

Parameter	Potential advantage	Limitation or consideration
Drug solubilization	May improve curcumin incorporation	Depends on the selected oil phase
Droplet size	Fine dispersion may be achievable	Requires instrumental measurement
Formulation uniformity	May support uniform drug distribution	Must be confirmed experimentally
Drug release	Composition can modify release behaviour	Requires in-vitro release testing
Skin permeation	May influence drug partitioning and delivery	Increased permeation is not guaranteed
Spreadability	O/W systems may spread readily	Depends on viscosity and composition
Sensory properties	May provide a less greasy feel	Must be assessed for the final formulation
Gel incorporation	May improve residence and handling	Gel may alter droplet characteristics
Physical stability	Optimized composition may improve stability	Droplet growth or phase separation can occur
Chemical stability	A suitable vehicle may help protect the drug	Curcumin may still degrade
Local tolerability	Excipients can be selected for the application	Irritation potential requires assessment
Manufacturing	Several preparation methods are available	Process parameters affect product quality
Scalability	Formulation processes may be adapted	Scale-up requires process validation
Storage	Appropriate packaging may protect the product	Temperature and light sensitivity need study
Wound-care application	Provides a platform for further investigation	Safety and efficacy must be established

The advantages of Nanoemulsions for topical delivery of the poorly water soluble drug Curcumin include better incorporation into the formulation, uniformity of dispersion, and the capabilities of controlling the release of the drug and its permeation through the skin. The composition can be varied to suit the intended application and they can be

converted to a nanoemulgel to enhance handling and residence time at the application site [17-19, 21].

However, there are some drawbacks of these systems. Nanoemulsions are usually not thermodynamically stable and physical appearance cannot be used to guarantee long term stability. Growth and/or coalescence, phase separation, and/or chemical degradation can occur during storage. Furthermore, excipients that improve permeation may lead to irritation at inappropriate concentrations, as can surfactants. It is also necessary to demonstrate improved permeation of the skin during experiments as this depends on the formulation and condition of the skin [18-20,22].

In developing a curcumin-containing topical nanoemulsion, the main potential benefits and limitations listed in Table 2 should be taken into account.

4. Formulation Strategies for Curcumin-Loaded Nanoemulsions

The preparation of a curcumin loaded nanoemulsion involves optimization of critical formulation variables, systematic selection of excipients and an appropriate preparation method. The main goal is to generate a physiologically stable system that possesses appropriate drug incorporation, acceptable topical properties and reproducible performances. Apart from droplet size, polydispersity, drug content, pH, viscosity, chemical stability and compatibility with intended use should be taken into consideration for formulation development [17,18,27,28].

4.1. Selection of the Oil Phase, Surfactant, and Co-Surfactant

Within the dispersed systems, an important role is played by the solubilisation of curcumin in the oil phase and the properties of the dispersed droplets. To screen candidate oils, the solubility of curcumin in the oil should be determined under controlled conditions. The oil chosen should meet the following criteria: good drug solubilization, good compatibility, oxidation stability and topical compatibility. The solubility of drugs in an oil phase may be desirable but it is not enough to ensure the preparation of a stable or effective nanoemulsion [27-29].

Surfactants help to form droplets by lowering the interfacial tension between the oil and aqueous phases. The choice of their selection should be based on emulsification efficiency, concentration, compatibility and tolerability in the area. When needed to promote droplet formation or to change the properties of the interface, a co-surfactant can be added. High concentrations of surfactants or co-surfactants can, however, have a negative impact on skin tolerability and this may be particularly problematic if the formulation is to be applied to damaged tissue [18,29-31].

In case of formulations directed towards the wound, the selection of excipients will need to take into account the drug's

solubility as well as physical stability while not compromising the local safety of the product. Before optimization, the compatibility between each ingredient and the other ingredients in the formulation and between them and curcumin should be evaluated.

4.2. Preparation Methods

Nanoemulsions may be formed by either high or low energy methods. The selection depends on the composition of the formulation, availability of equipment, the desired droplet characteristics and the manufacturing requirements [28–31].

High energy methods involve mechanical energy to reduce the size of bigger droplets. Common methods are ultrasonication, high pressure homogenization and high shear homogenization. During the development in the lab, the processing time and amplitude may be tested and varied to study the effect on droplet size and dispersion and thus, ultrasonication may be useful. But, the sonication time may be too long and the temperature may rise, which can cause instability in curcumin. It is therefore important to regulate the processing time and temperature [28–30]. Low energy methods make use of composition changes or environmental changes in order to encourage the creation of fine droplets. Examples of such techniques are phase-inversion techniques and spontaneous emulsification techniques. These techniques may also be beneficial to some oil–surfactant–water systems, however, depending on the phase behaviour of the ingredients and the desired characteristics of the product [29–32].

To check the physicochemical characteristics and biological potential of the ultrasound assisted curcumin loaded into the nanoemulsion, Ahmad *et al.* formulated curcumin containing nanoemulsion using ultrasonication method [11]. The importance of the selection of the preparation method coupled to physicochemical characterization and biological assessment is here showcased. However, the best method of preparation needs to be carefully assessed for each formulation and not assumed to apply to all.

4.3. Development of formulation variables for optimization

Optimization is the determination of the formulation composition and the processing conditions which gives the desired product properties. The following parameters are important: oil concentration, surfactant to co-surfactant ratio, proportion of the aqueous phase, sonication time, processing temperatures, and homogenization conditions. These parameters can affect the droplet size, polydispersity index (PDI), drug content, physical stability and drug release [27–32].

Using a systematic experimental design can assist in assessing the impact of each variable and the interaction between variables. Factorial designs can be used to screen influential factors while response surface methodology can be used to investigate the relation between the formulation variables and measured responses. The design should be selected depending on the number of factors, experimental resources and objectives of the study (Table 3) [33–35].

Table 3: Critical formulation variables and their relevance to curcumin nanoemulsion development [27-35]		
Formulation variable	Potential effect	Suggested evaluation
Oil type	Influences curcumin solubilization and droplet properties	Drug-solubility screening
Oil concentration	Affects drug loading and dispersed-phase volume	Droplet size and drug content
Surfactant type	Influences interfacial stabilization	Emulsification and compatibility studies
Surfactant concentration	May affect droplet formation and stability	Size, PDI, and tolerability
Co-surfactant type	May modify interfacial properties	Formulation screening
Co-surfactant concentration	May affect droplet formation and drug distribution	Size, PDI, and stability
Oil-to-surfactant ratio	Influences emulsification behaviour	Phase screening and droplet characterization
Aqueous-phase proportion	Affects phase composition and product characteristics	Appearance and size distribution
Sonication time	May influence droplet size and heating	Size, PDI, and temperature monitoring
Sonication amplitude	Influences the energy delivered during processing	Size distribution and reproducibility
Processing temperature	May affect emulsification and drug stability	Temperature monitoring and drug assay
Homogenization conditions	Influence droplet breakup and uniformity	Size, PDI, and batch consistency
Storage temperature	May affect physical and chemical stability	Stability studies
pH	Affects product compatibility and potential local tolerability	pH measurement and safety assessment

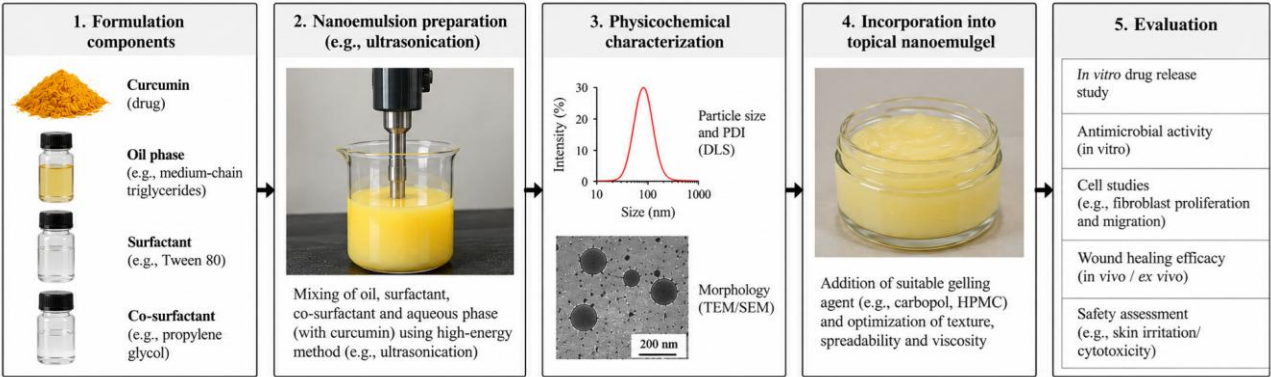


Figure 3: Proposed workflow for the development and evaluation of a curcumin-loaded topical nanoemulsion

4.4. Formulation Development Workflow

A stepwise development strategy can enhance the reproducibility and minimize the amount of needless experiments. Excipient compatibility and solubility of curcumin should be determined in initial studies. Preliminary batches can then be produced to determine acceptable composition ranges to be used for systematic formulation and processing optimization. Prior to claiming wound-healing benefits, the selected formulation should be characterized by physicochemical properties, *in-vitro* drug-release testing, suitable skin-delivery studies, stability testing, and safety testing [11,14,27–35].

Figure 3 is a summary of a proposed workflow from preliminary excipient screening to biological evaluation. The workflow is designed to be a development framework and not to imply that each step has been completed for a specific formulation.

5. Evaluation of Curcumin-Loaded Nanoemulsions

A thorough evaluation is necessary to decide if the nanoemulsion loaded with curcumin is suitable for topical application. Characterization aids in maintaining formulation consistency, evaluation of physicochemical stability, drug incorporation, release behaviour, and possible skin delivery performance. None of the parameters alone can define formulation quality, so they must be assessed together and compared to the particular intended use [27,28,36].

5.1. Globule Size and Polydispersity Index

An important property of globules is size as it gives information regarding the dispersed droplets which can affect the appearance of the formulation, physical stability and drug-release behaviour. The hydrodynamic diameter of droplets in a nanoemulsion is often measured by dynamic light scattering (DLS) technique. Samples should be diluted in the same way and measured in controlled conditions which should help to ensure the measurements are repeatable [36,37]. The polydispersity index (PDI) is used to describe the width of the particle size distribution measured. A low PDI tends to represent relatively limited distribution while a high PDI can be a sign of more heterogenous distribution. The acceptance criteria shouldn't just be a single cutoff figure for all systems, however, and should be chosen based on the formulation and the use. The mean size, in conjunction with PDI and measurement conditions, is a more informative description [36,37].

5.2. Zeta Potential, pH and Viscosity

Zeta potential gives information on the electrical potential of the particles or the droplets in the dispersion. It can aid in the interpretation of physical stability and can be used to describe electrostatic interactions. But, most of the nanoemulsions are stabilised partially or even mainly with non-ionic surfactant and steric effect. Based on this information, it is not necessary

that a low value of the absolute zeta-potential is synonymous with poor stability; the result must be de-interpreted in the context of the overall formulation [37,38].

The pH of a topical formulation should be tested as this may affect the stability of the drug, compatibility of excipients and tolerability of the formulation at the site. If a product is used in wounds, the pH should be taken in conjunction with the condition of the wound and the use made of it. It is also important to consider the rheological behaviour and viscosity, especially if the nanoemulsion is added to a gel base. Such properties can impact spreadability, handling characteristics, and residence time and drug release. Measurements taken should be made by an appropriate method and should be recorded with the appropriate conditions [38,39].

5.3. Drug Content and Entrapment or Incorporation Efficiency

Drug-content analysis is used to determine the amount of curcumin in a known quantity of the formulation. When the specificity and suitability for the formulation has been established, then the analytical method can be validated, for example, using UV-visible spectrophotometry or high-performance liquid chromatography (HPLC). HPLC can prove very useful in specific cases where separation of curcumin from excipients or degradation products is required [39,40].

Care should be taken in using the terms entrapment efficiency and incorporation efficiency. The curcumin can be dissolved in the oil phase or distributed between the formulation regions, rather than physically trapped in a solid carrier, in a conventional nanoemulsion. If a value of efficiency is given, the technique used to separate the free or nonincorporated drug must be suitable to the particular system being used and the method of calculating the efficiency must be clearly indicated. There is a correlation between drug content and drug incorporation efficiency, but the two cannot be equated. [40,41].

5.4. In-Vitro Drug Release and Skin Permeation

An *in vitro* drug release study aids in the characterization of the release of curcumin from the formulation under a set of controlled experimental conditions. The method should ensure suitable sink conditions (where applicable), ensure appropriate temperature and result in a sampling procedure that does not significantly disturb the system. The analytical method needs to be appropriate for the quantitation of curcumin in the release medium. When the experimental conditions are the same, release profiles can be compared between formulations [41,42].

Skin-permeation studies answer a different question: is curcumin permeable through or it is retained in the skin under certain experimental conditions? Excised skin and the validated diffusion-cell method are both possible depending on the research objective. The study should differentiate between the drug which remains in the skin and the drug which has

permeated through it. However, higher permeation is not always a desired property for the topical wound product, and there may be a need for the product to remain at the targeted site of the application. Experimental model be explicitly described along with its limitations [42,43].

5.5. Physical and Chemical Stability

Stability testing is used to assess if a formulation remains stable over time. Physical assessment could be appearance, phase separation, globule size changes, PDI, pH and viscosity. Chemical evaluation should be performed to check whether the content of curcumin is retained and if degradation occurs during storage. Chemical degradation cannot be solely identified by changes in colour, and if possible, an appropriate analytical method should be employed to establish the chemical degradation [36,44].

Stability studies should be performed in specified storage conditions, with sampling at specified time points. The results may be affected by packaging, light exposure and temperature which should be recorded. The length of study and conditions applied must reflect the stage of formulation development; a short term stability in the lab should not be construed as commercial stability (Table 4) [44,45].

Table 4: Key evaluation parameters for curcumin-loaded topical nanoemulsions [36-45]

Parameter	Purpose	Common approach
Appearance	Detect visible changes or separation	Visual inspection
Globule size	Characterize the dispersed droplets	Dynamic light scattering
Polydispersity index	Assess size-distribution breadth	Dynamic light scattering
Zeta potential	Characterize electrokinetic properties	Electrophoretic light scattering
pH	Assess formulation acidity or alkalinity	Calibrated pH meter
Viscosity	Characterize flow behaviour	Suitable viscometer or rheometer
Drug content	Quantify curcumin in the formulation	Validated UV-visible or HPLC method
Incorporation efficiency	Estimate the fraction incorporated according to a defined method	Validated separation and assay procedure
In-vitro drug release	Characterize drug-release behaviour	Suitable release-testing setup
Skin permeation	Evaluate drug passage through skin	Appropriate diffusion-cell method
Skin retention	Estimate drug retained in skin tissue	Tissue extraction and drug assay
Physical stability	Monitor changes in formulation characteristics	Scheduled storage studies
Chemical stability	Assess curcumin content and degradation	Stability-indicating analytical method
Microbial quality	Assess microbiological suitability	Appropriate microbiological tests
Local tolerability	Investigate potential irritation or tissue effects	Appropriate validated or ethically approved testing

These tests together give complementary data on the quality of the formulation. Small globule size and high drug content are no justification for the use of a curcumin nanoemulsion for wound application. Overall assessment should also take into

account the reproducibility, stability, the rate of drug release, skin delivery and local tolerability [36-45].

6. Skin Delivery, Stability, and Safety Considerations

The therapeutic efficacy of the curcumin loaded topical nanoemulsion is not only related to the physicochemical properties of the nanoemulsion but also to the behavior of the formulation post application. Wound care potential is indicated by drug release, skin permeation, stability in the formulation and tolerability at the site of application. The properties must be studied with complementary methods, as there is not a single test that can provide information on the overall suitability for therapy [46-48].

6.1. Skin Permeation and Local Drug Retention

The studies of skin delivery help in determining whether curcumin is released from the formulation and reaching the intended tissue. The composition of the nanoemulsion can alter the partition of the drug between the vehicle and skin, and the presence of surfactants and other excipients in the nanoemulsion may alter the barrier properties of the skin. The strength and direction of these effects, however, will vary depending on the formulation and experimental model; it is not assumed that improvements in permeation are to be expected unless supported by data [42,48,49].

In the case of wound-directed topical preparations, retention at the site of application can be significant, if not more important than permeation into the skin. A locally acting formulation should therefore be tested for both the amount that stays in the tissue of interest and the amount that transits through the tissue. Comparative data obtained by *ex-vivo* diffusion experiments may be helpful, but it is important to recognise that discrepancies exist between models and real skin [43,49].

6.2. Formulation Stability and Storage Conditions

The product quality must be maintained during storage and this is achieved by having both physical and chemical stability. Physical instability can manifest as droplet size changes, increase in polydispersity, creaming, coalescence, or phase separation. Chemical instability can be a loss of curcumin or production of degradation products. Such changes may impact the consistency of the product and reduce the reliability of biological testing results if the formulation is not properly characterized [44,50,51].

The potential for storage should be defined (storage conditions in the stability study) and the time should be determined (sampling intervals in the stability study). Appearance, globule size, PDI, pH, viscosity and curcumin content will be considered as some relevant parameters. Other factors to consider are temperature, light exposure, packaging material and formulation compatibility with container. Depending on the study design, accelerated tests can give information on formulation behaviour, but cannot replace proper long term stability information [50-52].

6.3. Local Safety and Biocompatibility

Safety of a topical nanoemulsion is dependent on the active ingredient, the concentration of the excipients, the formulation properties and condition of the application site. Surfactants or permeation enhancing agents can be irritating if used at inappropriate concentration. The protective skin barrier might be broken for wound application, for which this consideration is important. Hence, individual excipients should not be assumed to be safe, just because they are part of a complete formulation [53,54]. Evaluation can include appropriate in-vitro cytotoxicity testing and irritation assessment, and additional biological studies based on the formulation and intended use. If scientifically justifiable, animal studies should comply with appropriate ethical guidelines and controls. It is important to consider the concentration level, exposure time, and the experimental model when interpreting the safety results and not to make blanket statements about all curcumin nanoemulsions [53–55].

6.4. Understanding Preclinical Wound-Healing Evidence

Preliminary evidence of biological activity, such as changes in wound closure, inflammatory responses, tissue organization or microbial outcomes, can be obtained from preclinical studies. The endpoints, however, each represent different facets of wound repair, and should not be considered synonymous. Although wound closure is important, such as in the case of wounds, it does not ensure that barrier function and tissue structure are fully restored [48,55,56].

The design of the study, the number of subjects in the study, the comparator groups used, the length of the study, and whether the experimental model is similar to the intended clinical use should also be considered when interpreting the study. The outcomes from acute wounds do not necessarily apply to chronic wounds, which may be characterized by chronic inflammation and/or decreased perfusion, infection, or underlying disease. Thus, laboratory and animal studies do not demonstrate clinical efficacy and should be referred to as “preclinical evidence” [54–57].

In conclusion, more research is required to ensure that manufacturing is reproducible, stability is acceptable, clinical safety is ensured, and clinically significant benefits are demonstrated. A nanocurcumin capable formulation should be developed and further tested in suitable studies that optimally assess the formulation quality and biological performance.

7. Therapeutic Potential, Current Challenges and Future Perspectives

Curcumin loaded nanoemulsions are promising topical wound care products as they could enhance curcumin solubilization and affect its delivery at the site of application. In the preclinical studies, nano-curcumin formulations have shown beneficial antimicrobial, anti-inflammatory and wound repair properties with their formulation composition, drug concentration and experimental conditions; however, with

varying conditions, different outcomes have been reported [8,11,14,55,58,59]. The nanoemulgel systems could also provide some advantages in terms of their spreadability and residence time, however, the addition of a gelling agent can also influence the properties of the droplets, the release of the drug and the stability of the formulation [14,60]. Although these benefits may be appealing, there are still issues that need to be addressed when formulating curcumin in excipients, its chemical stability, long-term stability, excipient compatibility, and manufacturing reproducibility and scale-up [27–32,61,62]. Moreover, many of the studies available are in-vitro and animal studies, which alone cannot prove efficacy in humans. Therefore, further studies are needed to develop a standardized formulation, analytical methods with validation, safety evaluation, reproducible manufacturing, and well-designed clinical studies with relevant wound-healing outcome measures [55–57,63–65]. In summary, the therapeutic potential of curcumin in nanoemulsions will rely on the stability, safety, reproducibility of the final formulation and its ability to deliver clinically relevant therapeutic effects compared to the conventional topical formulations.

8. CONCLUSION

The topical delivery of curcumin with a nanoemulsion-based system is a promising strategy to overcome the formulation challenges of curcumin's poor aqueous solubility and low chemical stability. The selection of excipients, the methods and conditions of preparation can enhance the ability to incorporate the drug and maintain the formulation properties important for topical drug delivery. But the size of globules and the amount of the drug in the globule doesn't necessarily determine the quality of the formulation or effectiveness of the therapy. Extensive assessment of physicochemical properties, drug release, skin permeation and retention studies, stability studies and local tolerability studies are all important. While the preclinical evidence is promising, there is a need for consistent preclinical studies and good clinical research to confirm efficacy and safety in humans. In summary, the use of curcumin nanoemulsions for topical wound care system needs to be explored in further research, if their beneficial effects can be replicated in formulation development and adequately substantiated by sound experimental data.

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