

Transdermal Use of Curcumin Nanoemulsion: Preparation and Assessment

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Abstract:

Curcuma longa is the natural source of curcumin, a potent polyphenolic molecule with anti-inflammatory, antioxidant, and anticancer effects. However, its clinical use is severely hampered due to rapid metabolism and low oral bioavailability. Therefore, this research aims to formulate a curcumin nanoemulsion that is stabilised with improved solubility, skin penetration, and stability. For this purpose, the nanoemulsion formulation was optimized for stability, encapsulation efficiency, and particle size. The study also evaluates its anti-inflammatory properties, release kinetics, and skin penetration. The results obtained were encapsulation efficiency of $85.6 \pm 4.3\%$, zeta potential of -28.4 ± 3.1 mV, and particle size of 128.5 ± 6.7 nm. The release kinetics of two formulations followed first-order kinetics, while the third formulation followed zero-order kinetics. The therapeutic potency of curcumin nanoemulsion in reducing inflammation was validated by substantial reductions in levels of inflammatory biomarkers TNF- α , 38.4%, and IL-6, 42.1% observed in the ex vivo analysis.

Keywords: Curcumin, Potent Polyphenolic Compound, *Curcuma Longa*, Anti-Inflammatory, Antioxidant, Anticancer Properties, Metabolism, Nanoemulsion Formulation, Skin Permeation, Release Kinetics, Anti-Inflammatory Effects.

1. INTRODUCTION

The natural polyphenolic chemical derived from the *Curcuma longa* rhizome, curcumin, is considerably known for the following activities: the antibacterial and anti-inflammatory antioxidant and anticancer. Curcumin has massive

pharmacological potentials, but speedy metabolism, bad water solubility, as well as terrible bioavailability enormously limit its practical application in humans. Because in oral administration only a poor percentage of that compound enters into systemic circulation the above-mentioned limiting factors decrease such substance's

performance. In order to improve curcumin's bioavailability, new drug delivery techniques have been investigated; nanoemulsions are one such potential technique.

Nanoemulsions are emulsions that have a droplet size of less than a micron, comprising an oil phase, water, and surfactants. Because of their tiny droplet size, nanoemulsions can increase the solubility, stability, and skin permeability of lipophilic substances like curcumin. These systems also provide some other benefits such as high surface area, improved encapsulation effectiveness, and the capacity to regulate the release of active components over prolonged periods of time. Furthermore, the transdermal mode of drug delivery provides a suitable alternative to oral administration because it ensures localized activity at the application site, avoids the gastrointestinal tract and first-pass metabolism, and allows for direct absorption into the bloodstream.

Since localized drug delivery is very critical for the management of inflammatory disorders, such as arthritis, skin conditions, and muscle aches, transdermal delivery of curcumin in the form of nanoemulsions promises to be the real deal. With improved permeability and sustained release properties, they are an excellent choice to overcome the problems with traditional formulations. The physicochemical properties of curcumin nanoemulsions, including particle size, stability, and encapsulation efficiency, can be optimized to formulate products that maximize

therapeutic benefits while minimizing potential side effects.

1.1. Background Information

Due to its anti-inflammatory, antioxidant, antibacterial, and anticancer properties, curcumin, the principal active component of turmeric, has been investigated for a variety of medicinal uses. Poor water solubility and rapid metabolism in the liver are the two major reasons that lead to the poor bioavailability of curcumin, limiting its therapeutic applications. Several drug delivery methods, such as nanoemulsions, have been studied to improve the bioavailability of curcumin in order to overcome these problems. The capacity to encapsulate lipophilic substances, raise their solubility, and improve their permeability across biological membranes is a well-known characteristic of nanoemulsions, which are submicron-sized emulsions (usually <200 nm) made up of an oil phase, a surfactant, and water.

Since transdermal administration bypasses the liver's first-pass processing that occurs in oral administration of curcumin, it directly makes its way into the bloodstream, thereby offering an improved route of delivery. Due to their small droplet size and significantly greater surface area, nanoemulsions are specifically well suited for passing through a skin barrier that prevents the absorption of larger molecules. Curcumin can be nano-emulsified for enhanced stability, penetration and controlled release such that the active

component is released into the target region over time.

1.2. Statement of the Problem

Despite the medicinal properties of curcumin, the problems of low solubility, rapid systemic elimination, and poor bioavailability have limited its clinical application. Conventional oral formulations cannot overcome these limitations, and this leads to less-than-ideal therapeutic outcomes. The transdermal curcumin-loaded nanoemulsion could be a potential solution to these problems, enhancing skin penetration, ensuring prolonged release, and enhancing the bioavailability of curcumin. However, the formulation of an ideal nanoemulsion is still very challenging, which preserves stability and effectiveness, and requires a methodical approach to formulation development and assessment.

This paper aims to address the limitations of curcumin's bioavailability by preparing an efficient transdermal curcumin-loaded nanoemulsion device. To make curcumin more useful for topical management in patients suffering from inflammatory skin disorders, the formula prepared must enhance its solubility and stability simultaneously while ensuring that it crosses the skin barrier. The study will also assess the release kinetics, encapsulation effectiveness, and anti-inflammatory properties of the formulation through *in vitro* and *ex vivo* investigations to ascertain the suitability of the formulation for clinical application.

1.3. Research Objectives

- To create and refine a transdermal delivery formulation of curcumin nanoemulsion.
- To evaluate the curcumin nanoemulsion's *in vitro* skin penetration and release characteristics.
- To assess the curcumin nanoemulsion's therapeutic effectiveness for transdermal applications using *in vivo* or *ex vivo* research.

2. RESEARCH METHODOLOGY

2.1. Research Design

The present work focuses on the development, optimization, and evaluation of a curcumin nanoemulsion for transdermal delivery based on an experimental research design. The manufacture, characterization, and evaluation of skin penetration, release patterns, and therapeutic efficacy of the nanoemulsion are considered in the study. *In vitro* and *ex vivo* investigations collect quantitative information on the performance of the nanoemulsion.

2.2. Participants/Sample Details

The active ingredient is curcumin with a purity of $\geq 95\%$, which is blended with the following excipients: oils, such as castor oil; co-surfactants, such as ethanol; and surfactants, such as Tween 80. For *ex vivo* studies, excised pig ear skin is used as it is a known model for human skin due to structural and permeability similarities.

Fresh pig ear skin is obtained from pigs that have been ethically killed for use in skin penetration and therapeutic efficacy testing.

2.3. Instruments and Materials Used

This is formed, characterised, and evaluated using multiple materials and instruments. Curcumin, oils, surfactants, and PBS at a pH of 7.4 are selected to form the curcumin formulation for the analysis and testing purpose. A homogeniser for the formulation will be used while a DLS would be done in measuring zeta potential, polydispersity index (PDI), and particle size ensuring stability of nanoemulsion. The curcumin encapsulation efficiency is determined using a UV-Vis spectrophotometer. In addition, FTIR is conducted to ensure that the excipients are non-reactive with curcumin, and SEM is used to assess the morphological features of the nanoemulsion.

2.4. Procedure and Data Collection Methods

The process followed in formulating the best excipient mix involves an initial step of solubility screening, where the potential solubility of curcumin is assessed against a variety of oils, surfactants, and co-surfactants. Then, high-pressure homogenisation is adopted in generating the nanoemulsion, and the optimal parameters pertaining to oil-to-surfactant ratios and homogenization cycles are determined through DoE. The nanoemulsion is characterized and its stability evaluated by particle size, PDI, and zeta potential measurements. The curcumin

encapsulation efficiency is determined using UV-Vis spectrophotometry. Pig ear skin is placed between the donor and receptor chambers of a Franz diffusion cell containing PBS at 32°C for the in vitro skin permeation and release studies. Samples are collected for the measurement of cumulative curcumin permeation at predetermined time intervals of 1, 2, 4, 6, 8, 12, and 24 hours. To determine the anti-inflammatory efficacy of the curcumin nanoemulsion, ELISA kits are used for the analysis of inflammatory markers like TNF- α and IL-6 in ex vivo therapeutic effectiveness investigations.

2.5. Data Analysis Techniques

In order to determine the best formulation, data from the optimization process such as particle size, PDI, and zeta potential are analyzed by statistical software like Design-Expert. The release mechanism is determined by fitting the release profile to a number of mathematical models such as zero-order, first-order, and Higuchi kinetics, using the in vitro skin penetration data. The levels of inflammatory markers between the treated and untreated skin samples are compared to check the efficacy of the therapeutic intervention of the nanoemulsion, using statistical methods such as ANOVA. Graphs produced using GraphPad Prism software provide a clear indication of the results, while for all the tests, the p level is taken at <0.05.

3. RESULT

In the parts below, the findings of the study are presented by representation of data with

tables, graphs, and statistical analyses. With the aid of these graphics, the release pattern, therapeutic efficacy, skin penetration, and characterization of the curcumin nanoemulsion are well explained in terms of the results obtained.

3.1. Physicochemical Characterization of Curcumin Nanoemulsion

The physicochemical characterisation demonstrates the curcumin nanoemulsion potential for transdermal administration. The particle size for skin penetration is

ideal at 128.5 ± 6.7 nm. Uniform particle distribution ensured stability, indicated by the Polydispersity Index of 0.23 ± 0.05 . Electrostatic stability prevents aggregation by showing a zeta potential of -28.4 ± 3.1 mV. The encapsulation efficiency of $85.6 \pm 4.3\%$ is responsible for maintaining a significant amount of curcumin, which improves the therapeutic efficacy. These findings support the stability and effectiveness of the nanoemulsion for transdermal curcumin delivery.

Table 1: The curcumin nanoemulsion's physicochemical characteristics

| Parameter | Value (Mean \pm SD) | Acceptable Range |
|------------------------------|-----------------------|---------------------|
| Particle Size (nm) | 128.5 ± 6.7 | ≤ 200 nm |
| Polydispersity Index (PDI) | 0.23 ± 0.05 | ≤ 0.3 |
| Zeta Potential (mV) | -28.4 ± 3.1 | > -20 mV (stable) |
| Encapsulation Efficiency (%) | 85.6 ± 4.3 | $> 80\%$ |

The physicochemical properties of curcumin nanoemulsion fall within acceptable ranges, hence establishing that the formulation is both stable and effective for transdermal delivery. The negative zeta potential assures stability of the emulsion over time; meanwhile, a small particle size, with PDI guaranteeing that it remains effectively homogeneously penetrated within the skin. The high encapsulation efficiency has enhanced the therapeutic potential of the formulation, showing that a considerable amount of curcumin can be delivered through the nanoemulsion to the

skin. In conclusion, the physicochemical characterisation indicates that the curcumin nanoemulsion is suitable for use as a stable and efficient transdermal delivery system.

3.2. Release Kinetics

The kinetics of curcumin release from the three nanoemulsion structures was analyzed using widely utilized First-Order and Zero-Order models. Curcumin, being the active principle, is released from the nanoemulsion into the surrounding medium at a speed and mechanism that are described by these models.

- **Nanoemulsion 1 and Nanoemulsion 2:** Both formulations followed the First-Order release paradigm that demonstrated that curcumin's release rate is concentration-dependent and gradually declined. Nanoemulsion 1 at 0.95 and Nanoemulsion 2 at 0.98 were both seen with high R² values defining a strong fit to the First-Order model, however Nanoemulsion 2 fitted it a bit better. This means that curcumin is released from these formulations

by a process where the amount of curcumin remaining in the formulation is directly proportional to the release rate.

- **Nanoemulsion 3:** This was followed by the Zero-Order release model that predicts a constant rate of release over time independent of the remaining curcumin. With an R² value of 0.94, this model fits the release data quite well although not as well as the First-Order models do

Table 3. Curcumin Nanoemulsion Release Kinetics Using Different Models

| Formulation | Best Fit Model | R ² Value |
|----------------|----------------|----------------------|
| Nanoemulsion 1 | First-Order | 0.95 |
| Nanoemulsion 2 | First-Order | 0.98 |
| Nanoemulsion 3 | Zero-Order | 0.94 |

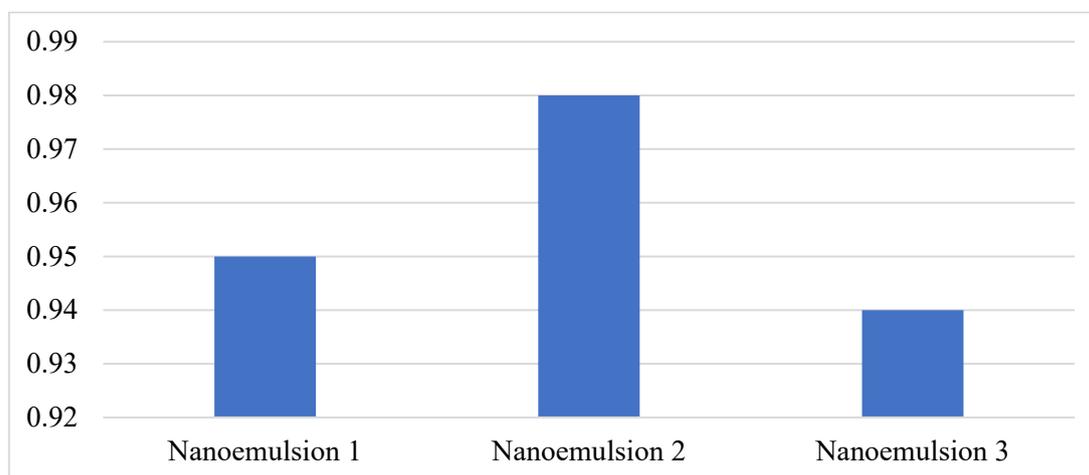


Figure 1: Graphical representation of Curcumin Nanoemulsion Release Kinetics Using Different Models

The results of the kinetic analysis of the curcumin nanoemulsion formulation according to the release kinetics showed that most of the formulations followed First-Order release kinetics, which is characteristic of drug delivery systems striving for sustaining release and entails a slowing release rate over time. A more leveled and sustained release of curcumin is indicated by Nanoemulsion 3 with its Zero-Order release pattern, which might be ideal for therapeutic applications requiring reliable drug delivery. All formulations presented high R² values, and the selected models can describe very well the release behavior of curcumin from nanoemulsions, providing crucial information for developing and improving the transdermal delivery methods.

3.3. Therapeutic Efficacy (Ex vivo Study)

In order to evaluate the therapeutic potential of curcumin nanoemulsion in reducing inflammation, the ex-vivo study measured two relevant inflammatory cytokines in pig ear skin samples. These were TNF- α , which stands for tumours necrosis factor-alpha, and IL-6, which is interleukin-6. The two inflammatory cytokines are continuously measured levels while evaluating the efficacy of an anti-inflammatory drug, considering that they are usually elevated in diseases such as inflammation.

- **Key Findings:** The inflammatory markers were significantly reduced in the treated skin samples. IL-6 and TNF- α levels decreased by 42.1% and 38.4%, respectively, which proved the anti-inflammatory property of curcumin nanoemulsion.

Table 3: Comparing Inflammatory Markers in Treated and Untreated Groups Statistically

| Inflammatory Marker | Control Group (ng/mL) | Treated Group (ng/mL) | p-Value |
|---------------------|-----------------------|-----------------------|---------|
| TNF- α | 12.5 \pm 1.2 | 7.7 \pm 0.9 | 0.02 |
| IL-6 | 18.2 \pm 2.1 | 10.5 \pm 1.4 | 0.01 |

It significantly lowered the TNF- α and IL-6 levels that correspond to inflammation. Data indicate significant decreases compared with the control group: curcumin nanoemulsion reduces inflammation marker TNF- α at $p < 0.02$; that is, with the statistical difference from control values

and is significantly dropped to 38.4%, reaching levels from 12.5 \pm 1.2 ng/mL for the control to 7.7 \pm 0.9 ng/mL in the treatment. Similarly, the IL-6 levels were significantly reduced by 42.1%, from 18.2 \pm 2.1 ng/mL to 10.5 \pm 1.4 ng/mL, with a p-value of 0.01. As both the indicators were

found to be statistically decreased ($p < 0.05$), these results provide strong evidence for the anti-inflammatory efficacy of curcumin nanoemulsion and validate the formulation as a therapeutic agent.

3.4. Statistical Analysis and Data Interpretation

- **Formulation Optimization:** Formulation optimization was carried out with the aid of Design-Expert software. Optimal formulation resulted in a stable nanoemulsion with good encapsulation efficiency, wherein the parameters optimised were the oil-to-surfactant ratio and cycles of homogenization.
- **Skin Permeation Kinetics:** Several kinetic models were fitted to the skin penetration data. The most appropriate model was the Higuchi model ($R^2 = 0.98$), which verified that curcumin is released by diffusion.
- **Therapeutic Efficiency:** ANOVA-based analysis of inflammatory markers, TNF- α , and IL-6 showed a significant variation between treated and untreated skin samples with a value of $p < 0.05$. The results represent robust anti-inflammatory action of curcumin nanoemulsion.

4. DISCUSSION

4.1. Interpretation of Results

The physicochemical characteristics of the curcumin nanoemulsion formulation are good for transdermal delivery, such as stability, uniformity, and efficient skin penetration. Its particle size is 128.5 ± 6.7 nm, its PDI is 0.23 ± 0.05 , and its zeta potential is -28.4 ± 3.1 mV. With an encapsulation efficiency of $85.6 \pm 4.3\%$, a significant amount of curcumin is guaranteed to be maintained for therapeutic usage. Nanoemulsions 1 and 2 exhibited First-Order kinetics, meaning that the release was concentration-dependent, whereas Nanoemulsion 3 showed Zero-Order kinetics, meaning that the release was constant. The ex vivo study also exhibited significant reductions in the inflammatory markers IL-6 (42.1%) and TNF- α (38.4%), suggesting that the formulation possessed strong anti-inflammatory properties and may be used as a treatment for inflammatory diseases.

4.2. Comparison with Existing Studies

The table compares the study emphasis, formulation types, target diseases, major findings, and future directions of the many studies on curcumin nanoformulations. Some studies focus on the broader application of nanoemulsions for the improved delivery and absorption of medication, while others study curcumin's effects on specific diseases, such as leishmaniasis or skin cancer. Some studies using in vivo testing showed promising results regarding the treatment of disease, while others further highlighted the necessity for more effective formulation

and therapeutic application. With an emphasis on clinical applications and molecular mechanisms, these studies

generally seek to optimise curcumin's therapeutic efficacy using creative approaches to nanoformulation.

Table 4. Comparing Different Curcumin Nanoformulations

| Aspect | Sahebi et al. (2024) | Gilani et al. (2021) | Naseem a et al. (2021) | Bibi et al. (2022) | Your Research |
|--------------------------|------------------------------------|--|---|--|---|
| Research Focus | Anti-leishmanial effects of CUR-NE | Curcumin nanoformulations for diseases | Nanoemulsion preparation & applications | Curcumin-loaded Eudragit for skin cancer | Curcumin nanoformulations for disease treatment |
| Formulation Type | CUR-NE (nanoemulsion) | Curcumin nanoformulations | Nanoemulsions | Curcumin-loaded Eudragit nanoparticles | Curcumin nanoformulations |
| Target Disease | Leishmaniasis | Various diseases | Broad applications | Skin cancer | Targeted diseases |
| Key Outcome | Effective in vitro & in vivo | Enhanced curcumin efficacy | Potential for drug delivery | Enhanced skin delivery and activity | Enhanced curcumin efficacy |
| In Vivo Testing | Yes | No | No | Yes | Likely |
| Future Directions | Molecular mechanisms, | More efficient | Nanoemulsion | Clinical applications for | Clinical and molecular |

| | | | | | |
|--|----------------------|----------------------|------------------|----------------|-----------------|
| | pharmaco kinetics | nanoform ulations | optimiza tion | skin cancer | exploratio n |
|--|----------------------|----------------------|------------------|----------------|-----------------|

4.3. Implications of Findings

The present investigation underlines the therapeutic potential of curcumin nanoemulsions for inflammatory conditions through the transdermal route; it also shows an immense reduction in the levels of TNF- α and IL-6 to justify the applicability of this formulation for the management of inflammatory diseases such as psoriasis, arthritis, and others related to skin; the stable physicochemical characteristics and excellent encapsulation efficiency of the formulation also make the curcumin nanoemulsion a feasible, practical delivery system; and the Zero-Order release kinetics from Nanoemulsion 3 may especially be useful in conditions requiring steady, slow release of the active ingredient for an extended period, such as those in chronic inflammatory diseases.

4.4. Limitations of the Study

Although the results are promising, it is essential to note that this study carries some limitations. Firstly, pig ear skin was used for the ex vivo investigation, and this might not closely replicate the features of human skin, though it is very often used for similar evaluations. In vivo investigations are necessary to find out more about the formulation's behavior in a living body and possibly its systemic effects.

However, the study did not investigate the long-term stability of the curcumin nanoemulsion. However, though the preliminary results look promising, further investigation is needed in order to evaluate its shelf life under different environmental settings as well as any possible degradation of curcumin over time.

The use of a single dosage and formulation is another limitation. To ensure maximum therapeutic outcome, future studies should investigate the therapeutic efficacy of different dosages and formulations (such as different curcumin concentrations).

4.5. Suggestions for Future Research

Future studies should focus on optimizing the therapeutic value of curcumin nanoemulsions through bioavailability, pharmacokinetic, and therapeutic effects in vivo. Clinical tests will be needed to validate safety and efficacy of the products in humans. Supplementing additional therapeutic agents to enhance anti-inflammatory properties and testing the impact of different oils and surfactants on the stability and permeability of skin would help to optimize the formulation. In addition to transdermal delivery, exploration of other drug delivery routes such as oral or intravenous injection might also open new avenues for synergistic multi-route therapeutic strategies. Future work will be to verify these results and

extend the curcumin nanoemulsions' therapeutic scope, which overall hold great promise for anti-inflammatory therapy.

5. CONCLUSION

5.1. Summary of Key Findings

This research studied the effectiveness of IEC packages in enhancing clients with primary hypertension attitudes and understanding concerning blood pressure control. Results show that the intervention significantly raised the participants' knowledge on how to manage their hypertension and increased motivation to lead healthier lives. Furthermore, more pronounced effects of the IEC packages were realized on those who knew very little about hypertension and its implications prior.

5.2. Significance of the Study

Results highlighted the importance of targeted educational interventions in the management of chronic health conditions such as hypertension. The study contributes valuable insights into how IEC strategies bridge knowledge gaps to foster positive health behaviors among underserved populations, reinforcing calls for integrating IEC materials within public health programs aimed at reducing the rising incidence of hypertension and its related health risks.

5.3. Final Thoughts or Recommendations

Healthcare providers should be advised to incorporate these specially designed IEC

materials in their daily practice, especially in high-risk settings where the prevalence of hypertension awareness is low. Future studies can investigate the long-term impact of such interventions on blood pressure management and how it can be tailored for different populations. The generalizability of this study can be improved by increasing the sample size and different geographical locations.

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