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# "A Review On Nanoemulsion Based Transdermal Patch Of Curcumin And Its Nitro Derivatives"

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**ABSTRACT:** Curcumin, a bioactive compound from *Curcuma longa*, is renowned for its therapeutic properties but suffers from poor water solubility and low bioavailability, limiting its clinical potential. This review explores the formulation and evaluation of nanoemulsion-based transdermal patches for curcumin and its nitro derivatives to address these limitations. Nanoemulsions were prepared using oil-in-water systems and were optimized for particle size, zeta potential, stability, and drug release properties. Ex-vivo permeation studies demonstrated enhanced skin penetration of nitro derivative nanoemulsions compared to plain curcumin formulations. Transdermal patches made from hydroxypropyl methylcellulose (HPMC) further enhanced bioavailability by bypassing first-pass metabolism, reducing dosing frequency, and improving patient compliance.

**KEYWORDS:** Curcumin, Nanoemulsion, Transdermal Patch

## 1. INTRODUCTION

A polyphenolic substance called curcumin was discovered in the rhizomes of Curcuma longa Linn. It has very weak solubility and low absorption and is very soluble in organic solvents such dimethylsulfoxide (DMSO), dimethyl form amide, ethanol, methanol, chloroform, acetone, and oils.[1] It dissolves in an alkaline environment (3 mg/ml) but is insoluble in water when neutral or acidic (0.1 mg/ml).[2] Curcumin is widely used in medicine for a variety of conditions, such as psoriasis, wound healing, diabetic wounds, analgesics, anti-inflammatory drugs, and antioxidants. Curcumin's fast metabolism in the intestines and liver, along with its extremely low water solubility and limited systemic bioavailability, limit its oral use.[3]

Several strategies, including as chemical derivatization, complex formation or interaction with macromolecules, and the use of nanoscale drug delivery systems, have been studied to improve curcumin's biological efficacy. Therefore, the most promising methods for improving the solubility and dissolving of medications that are poorly soluble in water and, consequently, increasing their bioavailability, chemical modification and nanoemulsion.[4] The bioavailability of curcumin has been significantly increased by encapsulating it in nanoscale carrier systems, such as nanoemulsion. High kinetic stability is possessed by nanoemulsions, which can serve as a carrier to shield active ingredients from harsh environments.[4] The advancements related to using nanoemulsion transdermally, which improve medication solubility, high thermodynamic stability, and transdermal effectiveness.

An intriguing substitute for topical administration that can produce local or systemic effects is transdermal distribution, which comes in the form of a gel or patch. It can enhance patient compliance while also providing certain benefits for curcumin, such as avoiding first-pass metabolism, reducing adverse effects, and maintaining stable blood levels over longer periods of time.

## 2. MATERIAL AND METHODS

### 2.1 Chemicals:

Curcumin, Concentrated Sulphuric acid, concentrated Nitric acid, Nitrobenzene, Chloroform, Methanol, Dibutyl phthalate, Dimethyl sulfoxide, Polyethylene glycol 400, Tween 80.

### 2.2 Preparation of Nitro Derivative of Curcumin

Curcumin was placed in a round-bottom flask, and then nitrobenzene and a mixture of concentrated sulphuric and concentrated nitric acids were added. The reaction mixture was then left to react for six hours. After 6 hours the mixture was filtered using a vacuum pump, cleaned and dried.[5]

### 2.3 Preparation of Oil in water (O/W) nanoemulsion

The water phase was additionally heated, either with or without an extra co-solvent and emulsifier. Next, using a magnetic stirrer set to 40°C, the oil phase and aqueous phase components were introduced gradually while being stirred and vortexed. Additional homogenization was done to give the emulsion the required small droplet size range. The ultra sonicator was finally utilized to produce the required range of scattered globules.[6]

### 2.4 Formulation of nanoemulsion

In an oil phase, surfactant, and co-surfactant, a spontaneously generated nanoemulsion of curcumin and its nitro derivative occurred. 20 ml of a basic nanoemulsion phase were mixed with 0.2 grams of curcumin and its nitro derivative. For three days straight, curcumin, oil, surfactant, and co-surfactant were continuously mixed at 4000-6000 rpm in a homogenizer. Deionized water was added to the oil phase and gently swirled on a homogenizer to create a nanoemulsion.

### 2.5 Drug entrapment in nanoemulsion: By De novo emulsion approach

Nonetheless, a de novo procedure ought to be used to include the lipophilic medicinal molecules (thermo stable). The concentrations of curcumin and its nitro derivative were maintained constant throughout the formulations used in the current investigation. The drug was first dissolved or solubilized with an appropriate single-oil by heating it to 40ºC on a magnetic stirrer until the curcumin and its nitro derivative were completely dissolved. The dissolved curcumin and nitro derivative was found in the lipophilic portion (oil) of the nanoemulsion.[7]

### 2.6 Ex-vivo Skin Permeation Study by Franz Diffusion Cell

A modified Franz diffusion cell was used for an in vitro drug release investigation. With the stratum corneum facing the donor compartment, the removed goat ear skin was clamped into place between the diffusion cell's compartments. One milliliter of the nanoemulsion formulation was put in the donor compartment, and seventeen milliliters of phosphate buffer (pH 7.4) were put in the receptor compartment.Throughout the experiment, the diffusion cell was stirred at 600 rpm and kept at 37+0.5°C. For a 24-hour period, 1 milliliter of receptor fluid was removed from the receiving compartment at 1 hour and replaced with 1 milliliter of new phosphate buffer pH 7.4 solution. Following the appropriate dilution, the spectrophotometer measured the λ max at 271 nm against the blank.[8]

### 2.7 Preparation of Skin for Ex-vivo Skin Permeation Study

Using goat ear skin that was collected from the slaughterhouse within an hour after the animal's sacrifice, a few formulations were investigated for skin penetration. After utilizing an animal hair clipper to remove the hair from the upper and lower parts of the skin's surface, the entire thickness of the skin was then harvested. A surgical scalpel was used to remove the fatty layer that was sticking to the dermis side. These removed skins were then wrapped in aluminum foil after being carefully cleaned with distilled water. The skin samples were used within a week after being stored at -200ºC.[8]

### 2.8 Formulation of nanoemulsion based transdermal patch

Various patches, including simple curcumin and plain nitro derivative of curcumin, were made from the produced nanoemulsion. Additionally, a curcumin nanoemulsion patch and its nitro derivative were synthesized on the film former. HPMC was utilized as a polymer, dibutyl phthalate as a plasticizer, dimethyl sulfoxide (DMSO) as a penetration enhancer, and a 1:1 mixture of chloroform and methanol as a solvent in the creation of the nanoemulsion-based patch. After dissolving HPMC in a solvent, a medication was added. Add DMSO and dibutyl phthalate drop by drop once it has completely dissolved. Spread it on the film forming, which uses a spreader to keep the temperature at 30 degrees Celsius, after it appears to be a clear or fully dissolved solution. After 15 to 20 minutes, carefully remove the film with a cutter and scale, then dry it in an oven set to 40°C.[9]

## 3. EVALUATION PARAMETERS

### 3.1 Evaluation of nitro derivative of curcumin

- **Organoleptic properties of Nitro Derivative of Curcumin:**

The organoleptic properties of nitro derivative of curcumin were evaluated. According to its standard, the colour of nitro derivative of curcumin depend on its concentration, the taste of nitro derivative of curcumin has a modified bitter in nature, nitro derivative of curcumin has a characteristic odor.

- **UV Spectrophotometric Analysis:**

The UV spectrophotometric analysis of curcumin is typically performed in the wavelength range of 200-800 nm. The maximum absorbance (λmax) of curcumin is usually observed around 425-430 nm when dissolved in solvents like ethanol, methanol, or dimethyl sulfoxide (DMSO). This is where curcumin exhibits its characteristic yellow color due to the presence of its conjugated double-bond system, which absorbs light in this region. he absorbance of nitro derivatives of curcumin depends on the position and number of nitro groups ($-NO_2$) introduced into the curcumin structure, as the addition of nitro groups affects the electron density and the conjugated π-system of curcumin, thereby altering its UV-Vis absorption properties.
Generally, the introduction of nitro groups tends to cause a bathochromic shift (red shift), meaning the absorbance maximum (λmax) moves to a longer wavelength. For specific nitro derivatives:

1. Mononitro Curcumin: The λmax typically shifts slightly higher than that of native curcumin, possibly around 450-470 nm.

2. Dinitro Curcumin: With two nitro groups, the shift can be more pronounced, and λmax might be observed around 470-500 nm or higher.

- **Differential Scanning Calorimetry (DSC):**

The DSC curve of nitro derivative of curcumin showed that indicated single sharp endothermic peak at $174.4^{O}$, which might be associated with the melting point of curcumin. The peak at 68.6 which may be associated with the impurity presence in the curcumin or may be associated with the presence of moisture.
The DSC analysis of nitro derivative of curcumin showed a sharp endothermic peak at 71.3, 175.1, 183.2 and 187.0. The DSC curve of nitro derivative of curcumin showed a single sharp endothermic peak at $187^{O}$C. This was due to the increase in the melting point of nitro derivative of curcumin which is associated with the nitro group attached to the curcumin. The DSC curve also showed a peak at 71.3 which might be associated with crystallinity. It also a peak at 175.1 which might be associated with the melting point of curcumin.[10]

- **High Performance Liquid Chromatography (HPLC):**

For estimation by HPLC, the linearity of the method for Curcumin was checked at five-ten concentration levels such as concentration range of 20-100 µg/ml. The typical equation describing the calibration curve is $y = mx + c$ where y is the peak area of Curcumin and x is the concentration of Curcumin, the value of correlation coefficient ($R^2$) should within the range of 0.995-0.999. The nitro derivative of curcumin had good peak shape in the mobile phase i.e., acetonitrile-5% acetic acid buffer (83:17, v/v) at 425 nm and the retention time of Curcumin is generally 8-10 minutes and for nitro derivative of curcumin it can vary depending on position of nitro group and generally it may have slightly different retention times as compared to curcumin

## 3.2 Evaluation of nanoemulsion

- **Particle size distribution analysis:**
According to reports, the emulsion droplets' reduced particle size may promote faster absorption and increased bioavailability. Transmission Electron Microscopy (TEM) or Dynamic Light Scattering (DLS) can be used to measure the particle size of curcumin nanoemulsion and its analogue. Particle sizes should normally fall between 20 to 200 nanometers.

- **Centrifugation:**
The Eppendorf Centrifuge is used to centrifuge nanoemulsion. This involves centrifuging a curcumin nanoemulsion for 30 minutes at room temperature at 10,000 rpm. The nanoemulsion is then checked for changes in homogeneity, such as phase separation and flocculation, or for lack thereof.[11]

- **Zeta potential determination:**
A zetasizer (1000 HS) can be used to perform photon correlation spectroscopy (PCS) in order to quantify the droplet surface charge, or zeta potential. In a volumetric flask, the formulation (0.1 ml) was distributed in 50 ml of water, vigorously mixed, and light scattering was observed at 25 °C at a 90 ° angle. The charge of the droplets is likewise determined by this angle. The droplet size distribution is wider the greater the polydispercity index (PDI). Using built-in software, zeta potential values were ascertained from the oil droplets' electrophoretic mobility. The emulsion formulations that were diluted were used for the measurements.
The higher negative a particle's zeta potential, the larger the net charge of its droplets and the more stable the nanoemulsion. A high level of physical stability is often indicated by a zeta potential value less than 30 mV. The system's zeta potential was negative (-) mV, indicating that the nanoemulsion droplets had a negative charge and were therefore closer to the range.[12]

- **pH Analysis:**
Using a digital pH meter, the pH of the nanoemulsion was measured at room temperature. The curcumin nanoemulsion's pH should be between 4.5 and 5.7.

- **Stability studies:**
For physical stability, the produced nanoemulsion was kept at room temperature (25°± 3°C, 28°C, 50°C, 75% RH, and 45°C) for 28 days. The observation was made visually, and the outcome was noted.[13] To ascertain the samples' temperature stability, prepared nanoemulsion was diluted with purified distilled water. Three distinct temperature ranges were used to store the samples, and they were checked for signs of phase separation, flocculation, or precipitation.[11]

- **Viscosity Study:**
By utilizing a Brookfield viscometer with spindleno.63, one can test the viscosity of an oil in water (O/W) nanoemulsion. The nanoemulsion's viscosity needs to be low and constant.[8]

- **Drug content of nanoemulsion:**
Accurately 0.1 ml of each formulation of the Oil in Water (O/W) nanoemulsion of curcumin and the Nitro derivative of curcumin were put in a 10 ml volumetric flask and diluted with methanol to the appropriate level. Following additional dilutions, the mixture was spectrophotometrically analysed at 421 nm using a spectrophotometer. The drug concentrations were computed at 421 nm using the Beer's plot, which was created with methanol as the solvent.[14] The nanoemulsion's curcumin concentration needs to be between 0.5 and 5%w/v.

- **Ex-vivo skin permeation study:**
Using a modified Franz diffusion cell and a goat's ear membrane as a permeation membrane, ex-vivo skin penetration tests for curcumin nanoemulsion and its nitro derivative were carried out. The permeation of both was then compared. As the time interval grows, the nitro derivative of curcumin nanoemulsion has greater penetration than curcumin nanoemulsion.

### 3.3 Evaluation of nanoemulsion based transdermal patch

- **Weight of the patch:**
  Take three patches from each batch, then use an electronic scale to weigh each patch. Next, the single patch's average weight was calculated.[15] The transdermal patch's weight is permitted to fall between 50 to 800 mg (0.05 and 0.8 g).

- **Thickness of the patch:**
  Digital Thickness Gauge was used at several locations along the patch to determine its thickness. Three patches were chosen at random, and the thickness of each patch was then measured. The average value for thickness of a single patch was determined.[15] The transdermal patch's thickness can vary between 50µm and 500µm (0.05mm and 0.5mm).

- **Drug content determination:**
  An accurately weighed portion of film (about 0.5 cm) will be dissolved in 10 ml of suitable solvent in which drug is soluble and then the solution is sonicate for 15 min. After sonication and subsequent filtration, 0.2 ml of solution was withdrawn and again diluted up to 10 ml solvent, then drug in solution will be then estimated spectrophotometrically at 421 nm.[14]

- **Percentage of Moisture Content:**
  Each film was weighed separately and stored for a full day at room temperature in a desiccator filled with fused calcium chloride. After weighing the film once more, the formula was used to determine its percentage moisture content.[15]

$$Percentage\ Moisture\ content = \left[\frac{Initial\ Weight - Final\ Weight}{Final\ Weight}\right] \times 100$$

  The percentage moisture content is allowed within the range of 2% to 10%.

- **Moisture Uptake:**
  After being stored for 24 hours at room temperature in a desiccator, the weighted films were subjected to 84% relative humidity using a potassium chloride saturated solution. Lastly, the films were weighed, and the formula was used to determine the percentage of moisture uptake.[15]

$$Percentage\ Moisture\ uptake = \left[\frac{Final\ Weight - Initial\ Weight}{Initial\ Weight}\right] \times 100$$

  The percentage moisture uptake is allowed within the range of 5% to 10%.

## 4. APPLICATION OF CURCUMIN NANOEMULSION BASED TRANSDERMAL PATCH

- **Arthritis:** The transdermal patch can be used to deliver curcumin directly to inflamed joints, reducing pain and inflammation associated with conditions like osteoarthritis and rheumatoid arthritis.

- **Muscle Pain:** For conditions involving muscle pain or soreness, the curcumin patch can provide localized relief by reducing inflammation and oxidative stress.

- **Wound Healing:** Curcumin is known to promote wound healing by reducing inflammation and preventing bacterial infections. A curcumin patch could be applied to chronic wounds or ulcers to enhance healing and prevent infection.

- **Burns and Scars:** The patch can also be used to treat burns and reduce scar formation by delivering curcumin directly to the affected area, helping in tissue regeneration and reducing oxidative stress.

- **Topical Chemotherapy:** The patch can be used for localized treatment of skin cancers or precancerous lesions. Curcumin has been shown to induce apoptosis in cancer cells and inhibit tumor growth, making it a potential candidate for topical chemotherapy in skin cancers

- **Anti-Aging:** Curcumin's antioxidant properties can help in reducing the appearance of fine lines and wrinkles by neutralizing free radicals. A transdermal patch could be used as part of an anti-aging skin care regimen to deliver curcumin directly to the skin.

- **Oxidative Stress-Related Disorders:** Curcumin is a powerful antioxidant, and its continuous delivery through a transdermal patch could be beneficial in managing conditions related to oxidative stress, such as cardiovascular diseases, diabetes, and chronic fatigue syndrome.

- **Acne Treatment:** The antimicrobial and anti-inflammatory effects of curcumin make it a potential treatment for acne. A transdermal patch could be used to reduce inflammation and bacterial load on the skin, leading to clearer skin.

- **Psoriasis and Eczema:** Curcumin's anti-inflammatory and antioxidant properties can help manage chronic inflammatory skin conditions such as psoriasis and eczema. The transdermal patch can deliver curcumin directly to the affected area, promoting healing and reducing symptoms like itching and redness.

## 5. CONCLUSION

The study underscores the potential of nanoemulsion-based transdermal delivery systems for curcumin and its nitro derivatives in overcoming solubility and bioavailability challenges. Nanoemulsions improved drug stability and penetration, while transdermal patches ensured sustained release and better therapeutic outcomes. Nitro derivatives showed superior skin permeation, highlighting their promise in topical applications. These findings support the development of innovative delivery systems for poorly soluble drugs, paving the way for more effective and patient-friendly treatments. Further clinical evaluations are recommended to validate their efficacy and safety for large-scale applications.

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