Nanoemulsion Based Transdermal Patch of Curcumin and Curcumin Analogue

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Received: 10-03-2020; Revised: 21-05-2020; Accepted: 28-05-2020.

ABSTRACT
The present study design to formulate nanoemulsion based transdermal patch of curcumin and curcumin analogue to enhance the solubility of curcumin and its permeability through biological membrane. A nanoemulsion was prepared by the high-pressure homogenization methods and evaluated for globule size, particle size, zeta potential, stability, pH determination, and drug content. FTIR spectrum of nitro derivative of curcumin exhibited the absorption bands 3223.88, 1628.01, 1596.02, 1429.16, 1542.51 cm⁻¹, assigned to –OH, C=O, aromatic C=O, phenol, enol and nitro stretching respectively. The DSC curve of nitro derivative of curcumin showed number of peak at 71.3, 175.1, 183.2 and 187. The curcumin and nitro derivative of curcumin nanoemulsion was prepared and evaluated by UV Spectrophotometric at 421nm. In HPLC analysis, the retention time of curcumin and nitro derivative of curcumin was 1.83 and 1.82. The % release of curcumin and curcumin from nanoemulsion was found to be 75.65 and 81.72% respectively. Moreover, the % release of curcumin and curcumin analogue from transdermal patches was 88.32 and 96.89% respectively indicated extended release. The developed nanoemulsion-based transdermal patches of curcumin and nitro derivative of curcumin have skin permeation for topical drug delivery and may be useful for the treatment of skin diseases.

Keywords: Curcumin, Curcumin analogue, nanoemulsion, transdermal delivery.

INTRODUCTION
Curcumin is a polyphenolic compound isolated from the rhizomes of Curcuma longa Linn. It is quite soluble in organic solvents such as dimethylsulfoxide (DMSO), dimethyl form amide, ethanol, methanol, chloroform, acetone and oils and having very poor solubility and low absorption3,4. It is insoluble in water under acidic or neutral condition (0.1 mg/ml) but dissolves in alkaline environment (3 mg/ml)³. Curcumin has wide medical use includes anti-septic, analgesic, anti-inflammatory, anti-oxidant, wound healing, diabetic wounds, certain tumors and psoriasis1,2. However, curcumin has extremely low aqueous solubility and rapid intestinal and hepatic metabolism, which result in poor systemic bioavailability, restrict its oral use7,8. Therefore, several approaches have been investigated to increase curcumin biological efficacy8.

The approaches have been investigated to increase curcumin biological efficacy, including chemical derivatization, complex formation or interaction with macromolecules and using nanoscale drug delivery system. Hence, the chemical modification and nanoemulsion are most promising approaches for solubility enhancement and dissolution of poorly water soluble drugs and hence, its bioavailability7. Synthetic chemical modifications of curcumin have been studied intensively in an attempt to find a molecule with similar but enhanced properties of curcumin. A series of novel curcumin analogues were synthesized and screened for anticancer activity. New analogues that exhibit growth-suppressive activity 30 times that of curcumin and other commonly used anticancer drugs were identified10. Several approaches in synthesis of curcumin derivatives for improve the chemical stability; solubility and permeability of curcumin have been taken in order to enhance the bioavailability of curcumin4.

A nanoemulsion is considered to be a thermodynamically or kinetically stable liquid dispersion of an oil phase and a water phase, in combination with a surfactant. It is also used as transdermal drug delivery and defines as a dispersion consisting to oil, surfactant, co-surfactant and aqueous phase, which is optically isotropic and thermodynamically stable liquid solution with a droplet diameter usually in the range of 10-200 nm. The ascendancies associated with the transdermal use of nanoemulsion which enhance drug solubility, good thermodynamic stability and enhance the effect of transdermal ability. The dispersed phase typically comprises small particles or droplets, with a size range of 5-200 nm, and has very low oil/water interfacial tension. Because the droplet size is less than 25% of the wavelength of visible light, Nanoemulsion are transparent11.

Transdermal patches define as an adhesive medicated patch that is placed on to the above skin to deliver an exact dose of the drug through the blood stream with a predetermine rate of release to reach in the body5. Transdermal delivery for poorly water soluble curcumin is believed to be the potential area of research as it delivers the drugs through the skin to the systemic circulation is variety of clinical indications. Transdermal delivery system is presently available for various disorders including skin cancer, Alzheimer’s disease, Parkinson’s disease, cardiovascular disease, depression, anxiety and attention
Deficit hyperactivity disorder (ADHD), female sexual dysfunction and postmenopausal dysfunction.

Transdermal delivery in the form of patch is an interesting alternative for topical route to give local or systemic effects. Low oral bioavailability of curcumin motivates us to study topical preparation. However, curcumin exhibits low skin penetration resulting in poor efficacy. Nanoemulsion formulation possess improved transdermal and dermal delivery properties in vitro, as well as ex vivo. Nanoemulsion have improved transdermal permeation of many drugs over the conventional topical formulations such as emulsions. This study describes a more effective and efficient strategy to deliver curcumin via the transdermal route.

**MATERIALS AND METHODS**

**Chemicals**

Curcumin was received as gift sample from the Oxford Laboratory. Con. Sulphuric acid, con nitric acid, nitrobenzene, chloroform, methanol, dibutyl phthalate, dimethyl sulfoxide, polyethylene glycol 400, Tween 80 were obtained from Merck Specialities Private Limited, Samar Chemicals Nagpur, HiMedia Laboratories, Loba Chemie Pvt. Ltd, National Chemical Pvt. Ltd.

**Preparation of Nitro Derivative of Curcumin**

In round bottom flask, curcumin was placed and mixture of concentrated sulphuric acid and concentrated nitric acid were poured in it, and also added nitrobenzene in it, then the reaction mixture was allowed to react for 6 h. The mixture was filtered through vacuum pump, washed and dried.

**Preparation of Oil in water (O/W) nanoemulsion**

The water phase with or without an additional emulsifier and co-solvent was also heated. Then the components of oil phase and aqueous phase added at a slow rate with gradual stirring and vortex mixing at 40°C on a magnetic stirrer. Further homogenization carried out to obtain the needed small droplet size range of the emulsion. Finally ultra sonicator used to achieve the desired range of dispersed globules.

**Formulation of nanoemulsion**

A nanoemulsion of curcumin and nitro derivative of curcumin formed spontaneously in an oil phase, surfactant and co-surfactant. 0.2 g of curcumin and nitro derivative of curcumin were added to 20 ml of plain nanoemulsion phase. Curcumin, oil, surfactant and co-surfactant were stirred at homogenizer at 4000-6000 rpm for continuous 3 days. Further to obtain nanoemulsion, deionized water was added to the oil phase and stirred gently on homogenizer.

**Drug entrapment in nanoemulsion: By De novo emulsion approach**

The lipophilic drug molecules (thermo stable) should however be incorporated by a de novo process. In present study, in all the formulation the concentration of Curcumin and Nitro derivative of curcumin was kept constant. The drug was initially solubilized or dispersed together with an in suitable single-oil by means of heating at 40°C on a magnetic stirrer, until Curcumin and Nitro derivative of curcumin was perfectly dissolved. The Curcumin and Nitro derivative of curcumin was dissolved in the lipophilic part (oil) of the nanoemulsion.

**Ex-vivo Skin Permeation Study by Franz Diffusion Cell**

An in vitro drug release study was performed using modified Franz diffusion cell. The excised Goat Ear skin was mounted between the compartments of the diffusion cell with stratum corneum facing the donor compartment and clamped into position. Nanoemulsion formulation 1ml was placed in donor compartment and the receptor compartment was filled with phosphate buffer pH7.4 (17ml). The diffusion cell was maintained at 37±0.5°C with stirring at 600rpm throughout the experiment. 1ml of receptor fluid were withdrawn from the receiving compartment at 1 hr for the period of 24 hours and replaced with 1ml fresh phosphate buffer pH7.4 solution and after the suitable dilution analyzed by spectrophotometer at 6max 271 nm against blank.

**Preparation of Skin for Ex-vivo Skin Permeation Study**

Selected formulations were studied for skin permeation using goat ear skin, obtained from the slaughter house after sacrificing the animal within 1 hour. Then the hair was removed from the upper portion and lower portion of skin surface using an animal hair clipper and subsequently, full thickness of the skin was harvested. The fatty layer, adhering to the dermis side, was removed by surgical scalpel. Finally, these excised skins were thoroughly rinsed with distilled water and packed in aluminum foils. The skin samples were stored at −20°C and used within a week.

**Formulation of nanoemulsion based transdermal patch**

From the prepared nanoemulsion, different patches were prepared such as plain curcumin patch, plain nitro derivative of curcumin patch. Then also prepared curcumin nanoemulsion patch and nitro derivative of curcumin nanoemulsion patch on the film former. For preparation of nanoemulsion based patch, HPMC used as a polymer, dibutyl phthalate used as a plasticizer, dimethyl sulfoxide (DMSO) used as a penetration enhanced and Chloroform and methanol in 1:1 ratio used as a solvent. HPMC was dissolved in solvent, then add drug in it. When it is completely dissolved, add drop wise dibutyl phthalate and DMSO. When it seems as a clear or completely dissolved solution then spread it on the film former which maintain the temperature 30°C through spreader. Leave the film for 15-20 min, then remove it slowly with the help of cutter and scale and dry it in oven at 40°C.
Evaluation of prepared Nitro Derivative of Curcumin

*Organoleptic properties of Nitro Derivative of Curcumin*

The prepared nitro derivative of curcumin was studied for color, odor and appearance.

**UV Spectrophotometric Analysis**

Analysis of curcumin and nitro derivative of curcumin analogue in methanol, water and pH 7.4 phosphate buffer was carried out using UV Spectrophotometer\(^2\).  

**Fourier Transform Infrared Spectrophotometric Analysis (FTIR)**

Nitro derivative of curcumin& potassium bromide dried in hot air oven at 50°C for 2 hr. The sample was prepared by mixing thoroughly with potassium bromide. This physical mixture was compressed under pressure of 10 Ton/nm\(^2\) and converted in a circular disc. This disc was then placed in the scanning slot of Fourier Transform Infra-red (FT-IR) Spectrophotometer and scanned at range from 4000 to 500 cm\(^{-1}\) to obtain the FTIR of nitro derivative curcumin. An FTIR spectrum of nitro derivative of curcumin compared with reference spectrum of curcumin\(^1\).  

**Differential Scanning Calorimetry (DSC)**

DSC analysis of nitro derivative of curcumin was performed using SII Nanotechnology (SIECKO) Model=EXSTAR DSC 6220, SOFTWARE=Muse, Measurement 6.9U. Samples were accurately weighed (10 mg) in aluminum pans, sealed and thermograms were obtained at the heating rate of 10°C per min up to a temperature of 300°C. Ultrahigh purity nitrogen was used as the purge gas at a flow rate of 50 ml/min\(^1\).  

**High Performance Liquid Chromatography (HPLC)**

The analysis was carried out on a JASCO HPLC system consisting of a JASCO LC-NET II/ADC and JASCO PU-2089 Plus (Quaternary Gradient Pump). The system also included a Photodiode Array (PDA) detector and a computer running JASCO CHROMNAV software for data acquisition and processing\(^2\).  

**Evaluation of nanoemulsion**

**Particle size distribution analysis**

Particle size of prepared curcumin nanoemulsion and curcumin’s analogue nanoemulsion was analyzed on motic microscope.  

**Zeta potential determination**

The droplet surface charge (zeta potential) was determined by photon correlation spectroscopy (PCS) using a zetazizer (1000 HS, Malvern Instruments). The formulation (0.1 ml) was dispersed in 50 ml of water in a volumetric flask, mixed thoroughly with vigorous shaking and light scattering was monitored at 25 °C at 90 ° angle. This angle is also used to identify the charge of the droplets. The higher the polydispersity index (PDI), the wider is the droplet size distributed. Zeta potential values were determined from the electrophoretic mobility of the oil droplets via in-built software. The measurements were carried out on diluted emulsion formulations\(^2\).  

**Stability studies**

The prepared nanoemulsion was placed on room temperature (25± 3°C, 28°C, 50°C, 75% RH and 45°C) for physical stability for 28 days. The observation was taken by visual observation and result was observed\(^2\).  

Prepared nanoemulsion was diluted with purified distilled water to determine the temperature stability of samples. Sample were kept at three different temperature ranges and observed for any evidences of phase separation, flocculation or precipitation\(^2\).  

**Centrifugation**

The samples was placed in ependroff and then nanoemulsion was centrifuged at 10,000 rpm for 30 minute at room temperature and observed for any change in homogeneity of nanoemulsion\(^2\).  

**pH Analysis**

pH of nanoemulsion was determined at room temperature using digital pH meter, model NIG-333\(^3\).  

**Viscosity study**

The viscosity of Oil in water (O/W) liquid nanoemulsion was measured by model (DV-E) Brookfield viscometer using spindle no. 63\(^3\).  

**Drug content of nanoemulsion**

An accurately 0.1 ml of each formulation of Oil in water (O/W) nanoemulsion of Curcumin and Nitro derivative of curcumin was placed in a 10 ml of volumetric flask and diluted to the mark with methanol and after making further dilutions it was analyzed spectrophotometrically at 421 nm, using a spectrophotometer (Model UV JASCO). The drug concentrations were calculated with reference to the Beer’s plot prepared using the methanol as solvent and at 421nm \(^2\).  

**Evaluation of nanoemulsion based transdermal patch**

**Weight of the patch**

Three patches from each batch were taken and weight of each patch was observed by using electronic balance. Then average weight of single patch was determined\(^1\).  

**Thickness of the patch**

The thickness of the patch was assessed by using Digital Thickness Guage at different points of the patch. From each formulation three randomly selected patches were used. The average value for thickness of a single patch was determined\(^1\).  

**Percentage of Moisture Content**

The prepared film was weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 hours. The film was again weighed and
the percentage moisture content was calculated using the formula.%

\[
\text{Percentage moisture content} = \frac{\text{initial weight} - \text{final weight}}{\text{final weight}} \times 100
\]

**Moisture Uptake**

The weighed films were kept in a desiccators at room temperature for 24 hours and then exposed to 84 % relative humidity using a saturated solution of potassium chloride. Finally, the films were weighed and the percentage moisture uptake was calculated using the formula.

\[
\text{Percentage moisture uptake} = \frac{\text{Final weight} - \text{initial weight}}{\text{initial weight}} \times 100
\]

**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.

**RESULT AND DISCUSSION**

**Characterization of Curcumin and nitro derivative of Curcumin**

**Melting Point**

The melting point of the Curcumin was found to be in the range 174°C - 176°C.

**UV Visible Spectrophotometric determination**

The calibration curve of the drug was plotted in methanol (421nm), water (271nm) & pH 7.4 phosphate buffer (271nm).

**Fourier Transform Infrared Spectrophotometric Analysis (FTIR)**

All the prominent and primary peaks were observed in FTIR spectrum of Curcumin compared with the reference spectrum as per United State Pharmacopoeia 2011. The stretching region of hydroxyl group, O-H was showed at the band range of 3200-3600 cm⁻¹. The band at 3502.31 cm⁻¹ indicates the presence of hydroxyl group in the curcumin. The band for carbonyl group (C=O) peaks appeared at the band range of 1620-1650 cm⁻¹. The band of (phenol) alkanes (C=O) observed at 1350-1512 cm⁻¹.

FTIR spectrum of curcumin exhibited the absorption peaks 3502.31, 1625.64, 1601.78, 1427.26 and 1231.54 cm⁻¹ assigned to –OH, C=O, phenol, enol and C-O-C stretching respectively. The results were found to be concurrent with a reference spectrum of curcumin. FTIR spectrum of the nitro derivative of curcumin exhibited the absorption bands 3223.88, 1628.01, 1596.02, 1429.16, 1542.51 cm⁻¹ assigned to –OH, C=O, aromatic C=O, phenol, enol stretching respectively. The C=O peak observed at 1429.16 cm⁻¹, enolic group observed at 1123.58 in nitro derivative. In these, all the functional groups of curcumin retained by its nitro suggested its chemical stability. Additionally, the peak at 1542.51 cm⁻¹, observed assisted with N-O, suggested the formed derivative of curcumin was observed as chemically stable.
Differential Scanning Calorimetry (DSC)

The DSC curve of nitro derivative of curcumin showed that indicated single sharp endothermic peak at 174.4°C, which might be associated with the melting point of curcumin. The peak at 68.6°C 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°C. The DSC curve of nitro derivative of curcumin showed a single sharp endothermic peak at 174.4°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°C which might be associated with the melting point of curcumin.

Table 1: FTIR spectrum of Curcumin and Nitro derivative of curcumin

<table>
<thead>
<tr>
<th>Functional Groups</th>
<th>Wave number of curcumin (cm⁻¹)</th>
<th>Wave number of nitro derivative of curcumin (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-H stretching</td>
<td>3502.31</td>
<td>3223.88</td>
</tr>
<tr>
<td>C=O</td>
<td>1625.64</td>
<td>1628.01</td>
</tr>
<tr>
<td>Aromatic C=O</td>
<td>1601.78</td>
<td>1596.02</td>
</tr>
<tr>
<td>Phenol, C=O</td>
<td>1427.26</td>
<td>1429.16</td>
</tr>
<tr>
<td>Enol</td>
<td>1231.54</td>
<td>1123.58</td>
</tr>
<tr>
<td>N-O</td>
<td>–</td>
<td>1542.51</td>
</tr>
</tbody>
</table>

High Performance Liquid Chromatography (HPLC)

The linearity of the method for Curcumin was checked at ten concentration levels over the concentration range of 20-100 µg/ml. The typical equation describing the calibration curve is y=707.75x where y is the peak area of Curcumin and x is the concentration of Curcumin, with a mean correlation coefficient (R²) of 0.9984.

It was observed that, 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 421 nm and had same retention time as that of curcumin and short run time. It was also observed that the curcumin and nitro derivative of curcumin had nearly same retention time, same elution time and the same run time only the difference is that, there is a decreased intensity in case of nitro derivative of curcumin compared to curcumin. The peak area and retention time of curcumin and nitro derivative of curcumin was found to be 36942 and 1.83, 32580 and 1.82 respectively. The peak observed at 421 nm in the mobile phase.

Figure 2: DSC spectrum of Curcumin and Nitro Derivative of Curcumin

Table 1: FTIR spectrum of Curcumin and Nitro derivative of curcumin

Figure 3: Chromatogram of Curcumin and Nitro derivative of Curcumin

Solubility determination

It was observed that Curcumin was found to be more soluble in Castor oil (3.08mg/ml) and found to be less soluble in olive oil (2.19 mg/ml). This has been attributed to presence of medium chain triglyceride and monoglycerides in these lipids which have greater affinity for the lipophilic compounds.

Evaluation of Nanoemulsion

Particle size distribution analysis

It has been reported that the smaller particle size of the emulsion droplets may lead to more rapid absorption and improve the bioavailability. Particle size analysis was carried out for base of nanoemulsion and was found to be 0.1-0.4 (mean diameter). Particle size of nanoemulsion was found to be in the range of nanoemulsion. Moreover, Particle size analysis suggested improper distribution and larger particle size. Zeta sizer which measures the Brownian motion of the droplet and its relation to the droplet size based on the principle that larger droplets have a slower motion. Particle size analysis was carried out for plain base.
of nanoemulsion and found to be 291.5 d nm. Base of
nanoemulsion showed particle globule size and proper
distribution of particles which might be reduces particle
size in formulation.

**Zeta potential determination**

Particles with zeta potentials, the more negative zeta
potential, greater the net charge of droplets and more
stable the nanoemulsion. Zeta potential value lower than
-30 mV generally indicate a high degree of physical stability.
Zeta potential of the system negative (-) mV, which
indicated the droplets of nanoemulsion having negative
charge, which is closer to range. These results indicated
decrease in droplet size in base of nanoemulsion i.e., -22.6
mV. The negative zeta potential of nanoemulsion
suggested stability.

**Centrifugation**

In order to estimate metastable systems, the optimized
nanoemulsion formulation was diluted with purified water.
Then nanoemulsion was centrifuged at 10,000 rpm for 30
minutes at room temperature and observed that there was
no phase separation, no flocculation and there were no
change in homogeneity of nanoemulsion.

**pH Determination**

The pH of base of nanoemulsion, curcumin nanoemulsion
and nitro derivative of curcumin nanoemulsion was found
to be 7.00±0.2000, 7.5±0.1000, 6.10±0.2646 respectively.
The observation revealed that all the formulations were
near to neutral pH.

**Viscosity**

The results of nanoemulsion indicate that increasing shear
rate decreases the viscosity of formulation. Therefore, all
these formulations represent the pseudo plastic flow (Non-
Newtonian system). In 60 rpm the viscosity of curcumin
nanoemulsion, nitro derivative of curcumin nanoemulsion
and base of nanoemulsion was found to be 783.3±3.215,
773.7±3.512 and 781.3±1.155.

Viscosities of all the formulation were found to decrease
with the increase of shear rate. At a same shear rate, the
formulations of Nitro derivative of curcumin Nanoemulsion
having more viscosity than the formulation of Curcumin
Nanoemulsion and Base of formulations. At same shear rate
(rpm) viscosity increases with decreasing in oil proportion
and simultaneously increasing in S/CoS because the
surfactant / co-solvent changes the turbidity of the system.

**Drug content determination**

The curcumin content determinations were found for
curcumin nanoemulsion and Nitro derivative of curcumin
nanoemulsion. The results of curcumin content of different
nanoemulsion were found to be 1.03 and 1.19.

**Ex-vivo skin permeation study**

Ex-vivo skin permeation test for all formulations were
performed using a modified Franz diffusion cell and goat’s
ear membrane used as a membrane for permeation. From
the result of skin permeation study of nanoemulsion, it was
found that there was more permeation of nitro derivative
of curcumin through skin than curcumin nanoemulsion in
increase order at the particular time interval.

The nanoemulsion was found to be stable at room
temperature and at freeze temperature (4°C) and found to
be stable at elevated temperature. This attributes that all
the components of the system observed compatible with
each other and form a single homogeneous phase. This
may be due to nearly same density of all the ingredients
which leads to physical compatibility, suggested stable
nanoemulsion formation. The results obtained from
temperature stability studies indicated that the
Nanoemulsion was found to be stable.

**Stability Study**

The nanoemulsion was observed visually for 28 days at
room temperature and no phase separation was observed.
It indicates that the nanoemulsion was stable at room
temperature for 28 days.

**Table 2: Temperature stability of Nanoemulsion**

<table>
<thead>
<tr>
<th>Time (Day)</th>
<th>Room temp. (25±3°C)</th>
<th>Cool temp. (At 4°C)</th>
<th>Elevated temp. (At 45°C)</th>
<th>At RH of 75%, 45°C</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>Stable</td>
</tr>
<tr>
<td>2</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>Stable</td>
</tr>
<tr>
<td>5</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>Stable</td>
</tr>
<tr>
<td>7</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>Stable</td>
</tr>
<tr>
<td>9</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>Stable</td>
</tr>
<tr>
<td>12</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>Stable</td>
</tr>
<tr>
<td>28</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>No separation of phase</td>
<td>Stable</td>
</tr>
</tbody>
</table>

**Figure 5: % Release of curcumin and curcumin nanoemulsion**
Evaluation of nanoemulsion based transdermal patch

The patches obtained were examined and characterized for the parameters like weight uniformity, thickness and drug content where,

F3-Curcumin nanoemulsion patch shows 0.3115±0.1118 weight uniformity, 0.4700±0.1411 thickness and 1.64% of drug content.

F4-Nitro derivative nanoemulsion patch shows 0.8011±0.2632 weight uniformity, 0.6567±0.1626 thickness and 1.91% of dug content. It was observed that, the F3 had increased weight uniformity and thickness than F4.

Percentage Moisture Content

From the result, it can observed that the F4 batch (21.08%) has more moisture content than F3 (8.86%).

Percentage Moisture Uptake

The moisture uptake of the formulations was also low, which could protect the formulations from microbial contamination and reduce bulkiness. Moisture absorption study determines the affinity of film towards water. Formulated patches were subjected to room temperature and the moisture uptake noted. From the results, it was found that the F4 batch (6.25%) has more moisture uptake than F3 batch (1.36%).

Ex-vivo skin permeation study

Ex-vivo skin permeation test for all formulations were performed using a modified Franz diffusion cell and goat’s ear membrane used as a membrane for permeation. From the result of skin permeation study of nanoemulsion based transdermal patches, it was found that there was more permeation of nitro derivative of curcumin patch through skin than curcumin nanoemulsion patch in increase order at the particular time interval.

![Figure 6: %Release of curcumin, Nanoemulsion based transdermal patch of curcumin (NBTP-C) and Nanoemulsion based transdermal patch of curcumin nitroderivative (NBTP-CN)](image)

CONCLUSION

Curcumin nanoemulsion and its nitro derivative/ analogue nanoemulsion were prepared using high pressure homogenization process for improving its solubility. This study showed that nanoemulsion-based delivery systems can be efficiently used in the transdermal patch to improve their aqueous solubility and permeability through biological membrane. Screening of surfactants and co-surfactants studies helped to identify the most suitable excipients, whereas the phase diagrams gave a good idea about the concentrations of the nanoemulsion components that should be employed to achieve self-nanoemulsifying formulations. The nanoemulsion based transdermal drug delivery of curcumin and its nitro derivative of curcumin containing 45% of oil phase (castor oil), 5% of surfactant: Co surfactant mixture (Tween 80: PEG 400) and 50 % of distilled water has been optimized. From ex-vivo data it can be concluded that the developed nanoemulsion-based transdermal patch of curcumin and nitro derivative of curcumin have skin permeation for topical drug delivery. So may be useful for the treatment for skin infection and disease.

Acknowledgement: I respect and thank to our principal Dr. Milind J. Umekar for providing me an opportunity to do the project work in Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur and giving us all support and guidance which made me complete the project duly. I am extremely thankful to our guide Ms. Neha S. Raut for providing such a nice support and guidance, although she had busy schedule managing the corporate affairs.

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Source of Support: Nil, Conflict of Interest: None.