Research Article

Nanoemulsion Based Transdermal Patch of Curcumin and Curcumin Analogue

Rashmi D. Zode, Prachi D. Barsagade, Neha S. Giri, Milind J. Umekar, Neha S. Raut
Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur, Pin-441002, India.
*Corresponding author's E-mail: rautneha15@gmail.com

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 absorption[3,4]. It is insoluble in water under acidic or neutral condition (0.1 mg/ml) but dissolves in alkaline environment (3 mg/ml)[2]. Curcumin has wide medical use includes anti-septic, analgesic, anti-inflammatory, anti-oxidant, wound healing, diabetic wounds, certain tumors and psoriasis[1,2]. However, curcumin has extremely low aqueous solubility and rapid intestinal and hepatic metabolism, which result in poor systemic bioavailability, restrict its oral use[7,8]. Therefore, several approaches have been investigated to increase curcumin biological efficacy[6].

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 bioavailability[7]. 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 identified[10]. 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 curcumin [4].

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 transparent[11].

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 body[5]. 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[12]. 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[13].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[14].

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 40ºC 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[15].

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 [6.]

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 40ºC 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[16].

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 $37\pm0.5°C$ 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 λmax 271 nm against blank[13].

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[13].

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 30⁰C 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[17].

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[20].

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[18].

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 aluminium 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[19].

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[19].

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 zetasizer (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 polydispercity 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[21].

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[5].

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[22].

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 homogenicity of nanoemulsion[22].

pH Analysis

pH of nanoemulsion was determined at room temperature using digital pH meter, model NIG-333[11].

Viscosity study

The viscosity of Oil in water (O/W) liquid nanoemulsion was measured by model (DV-E) Brookfield viscometer using spindle no. 63[13].

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 [23].

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 wasdetermined[17].

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[17].

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[17].

Percentage moisture content= [initial weight – final weight / final weight] × 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[17].

Percentage moisture uptake= [Final weight – initial weight / initial weight] × 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[23].

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 174^0C - 176^0C.

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 In the 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 stretching respectively. The C=O peak observed at 1429.16cm^{-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.
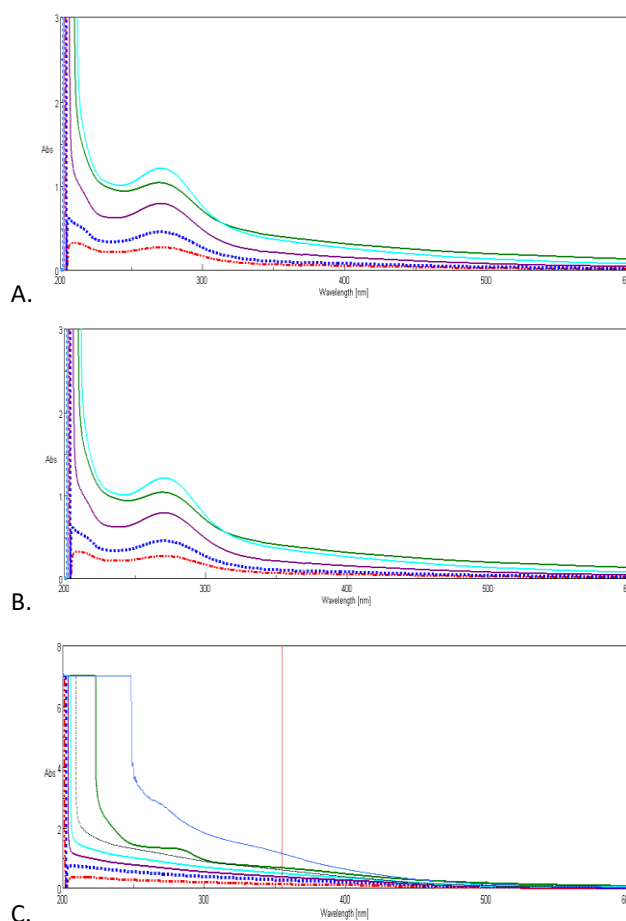

A.

B.

C.

Figure 4: Overlain of UV spectrum of nitro derivative of Curcumin in Water, Methanol and Phosphate Buffer Ph 7.4 (10, 30, 50,70 and 90 цg/ml)
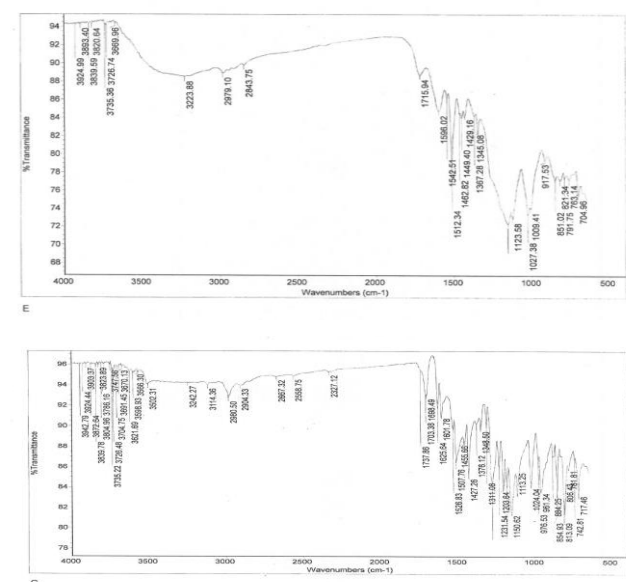

E

G

Figure 1: FTIR spectrum of Nitro derivative of Curcumin and Curcumin

Differential Scanning Calorimetry (DSC)

The DSC curve of nitro derivative of curcumin showed that indicated single sharp endothermic peak at 174.4°, 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 187.0°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 crystanillity. It also a peak at 175.1 which might be associated with the melting point of curcumin[18].
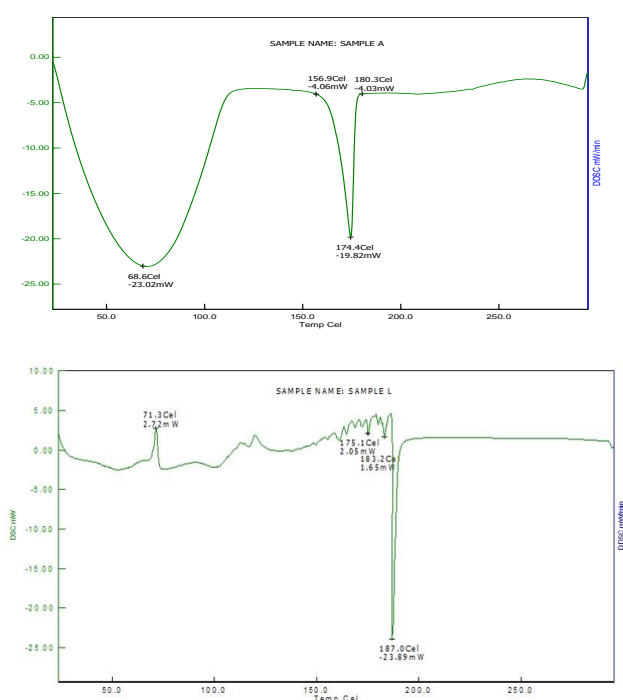

Figure 2: DSC spectrum of Curcumin and Nitro Derivative of Curcumin

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

Functional Groups	Wave number of curcumin (cm⁻¹)	Wave number of nitro derivative of curcumin (cm⁻¹)
O-H stretching	3502.31	3223.88
C=O	1625.64	1628.01
Aromatic C=O	1601.78	1596.02
Phenol, C=O	1427.26	1429.16
Enol	1231.54	1123.58
N-O	_	1542.51

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 (R^2) 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.
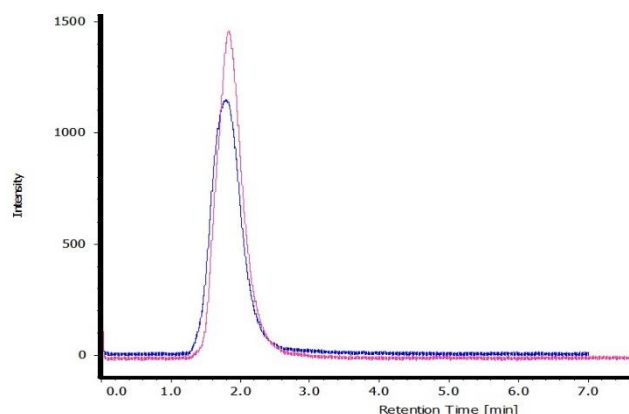

Figure 3: Chromatogram of Curcumin and Nitro derivative of Curcumin

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 lager 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.

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

Time (Day)	Room temp. (25±3°C)	Cool temp. (At 4°C)	Elevated temp. (At 45°C)	At RH of 75%, 45°C	Remark
0	No separation of phase	No separation of phase	No separation of phase	No separation of phase	Stable
2	No separation of phase	No separation of phase	No separation of phase	No separation of phase	Stable
5	No separation of phase	No separation of phase	No separation of phase	No separation of phase	Stable
7	No separation of phase	No separation of phase	No separation of phase	No separation of phase	Stable
9	No separation of phase	No separation of phase	No separation of phase	No separation of phase	Stable
12	No separation of phase	No separation of phase	No separation of phase	No separation of phase	Stable
28	No separation of phase	No separation of phase	No separation of phase	No separation of phase	Stable

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 homogenicity 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.
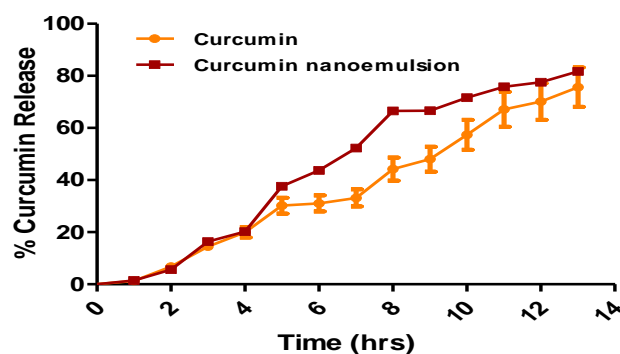

Figure 5: % Release of curcumin and curcumin nanoemulsion

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.
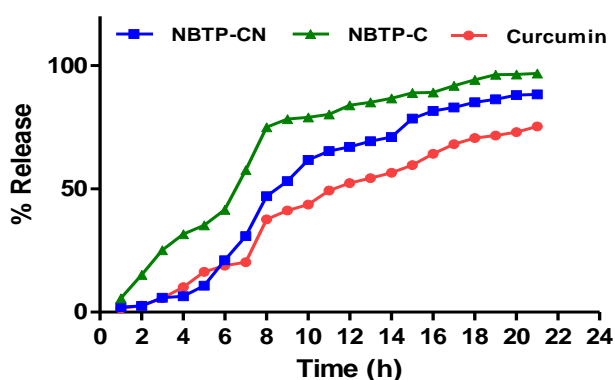

Figure 6: %Release of curcumin, Nanoemulsion based transdermal patch of curcumin (NBTP-C) and Nanoemulsion based transdermal patch of curcumin nitroderivative (NBTP-CN)

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.

REFERENCES

1. Ucisik M, Kupcu S, Schuster B, Sleytr U, Characterization of CurcuEmulsomes: nanoformulation for enhanced solubility and delivery of curcumin. Journal of nano biotechnology: 2013, 1 - 13.

2. Nardo Di V, Gianfaldoni S, Tchernev G, Wollina U, Barygina V, Lotti J, Use of Curcumin in Psoriasis, Macedonian Journal of Medical Sciences. 6(1), 2018 Jan 25, 218-220.

3. Ravichandran R, Studies on Dissolution Behaviour of Nanoparticulate Curcumin Formulation. Advances in Nanoparticles: 2013, 51-59.

4. Jantarat C, Bioavailability enhancement techniques of herbal medicine: a case example of curcumin. International Journal of Pharmacy and Pharmaceutical Sciences: Vol. 5(1), 2013, 493-500.

5. Sonkar R, Prajapati S. K., Chanchal D. K., Bijauliya K.R., Kumar S., A Review on Transdermal Patches as a Novel Drug Delivery System, International Journal of Life Sciences and Review, Vol.4(4), 2018, 52-62.

6. Rachmawati H, Budiputra D, Mauludin R, Curcumin nanoemulsion for transdermal application: formulation and evaluation. Drug Development and Industrial Pharmacy: 2014, 1 - 7.

7. Yadav V, Sarasija S, Pandit V, Puranik S, Reverse Phase High Performance Liquid Chromatography Method for the Estimation of Curcumin. Oriental Journal of Chemistry: Vol. 25(1), 2009, 105-110.

8. Chen y, Wu Q, Zhang Z, Yuan L, Liu X, Zhou L, Preparation of Curcumin-Loaded Liposomes and Evaluation of Their Skin Permeation and Pharmacodynamics. Molecules: 2012, 5972- 5987.

9. Bukhari S, Jantan I, Jasamai M, Ahmad W, Amjad M, Synthesis and Biological Evaluation of Curcumin Analogues. Journal of Medical Science: 2013, 501-513.

10. Ohori H, Yamakoshi H, Tomizawa M, Shibuya M, Synthesis and biological analysis of new curcumin analogues bearing an enhanced potential for the medicinal treatment of cancer. American Association for Cancer Research: 2006, 2563-2571.

11. Thakur A, Walia M, Kumar S.L., Nanoemulsion in Enhancement of Bioavailability of Poorly Soluble Drugs: A review. Pharmacophore an International Research Journal: Vol. 4(1), 2013, 15-21.

12. Gadekar R, Saurabh M,Thakur G, Saurabh A, Study of Formulation, Characterisation and Wound Healing Potential of Transdermal Patches of Curcumin. Asian Journal of Pharmaceutical and Clinical Research. Vol 5(4), 2012, 225-230.

13. Shakeel F, Baboota S, Ahuja A, Ali J, Aqil M, Shafiq S, Nanoemulsion as Vehicles for Transdermal Delivery of Aceclofenac. AAPS PharmSciTech: 2007, 1- 9.

14. Furniss B. S., Hannaford A.J., Smith P.W.G., Tatchell A.R., Vogel's Textbook of Practical Organic Chemistry Fifth Edition 1989.

15. Elosaily G, Formulation and *In-vitro* Evaluation of Nystatin Nanoemulsion-Based Gel for Topical Delivery. Journal of American Science: 2012, 8-12.

16. Tamilvanan S, Senthilkumar S, Manufacturing techniques and excipients used during the formulation of oil-in-water type nanosized emulsions for medical applications. 2012.

17. Saraswathi R, Krishnan P.N., Dilip C, Shabir Ali T.K., Formulation and evaluation of transdermal patches of curcumin. Scholars Research Library: 2010, 117-126.

18. Kumavat S, Chaudhari Y, Borole P, Shenghani K, Badhe M, Enhancement of solubility and Dissolution Rate of Curcumin by Solid Dispersion Technique. International Research Journal of Pharmacy: 2013, 226-232.

19. Li J, Jiang Y, Wen J, Fan G, Wu Y, Zhang C, A rapid and simple HPLC method for the determination of curcumin in rat plasma: assay development, validation and application to a pharmacokinetic study of curcumin liposome. Biomed. Chromatography: 2009, 1201-1207.

20. Dewani M, Borole T, Gandhi S, Determination of Voriconazole in Human Plasma by High Performance Liquid Chromatography with Ultraviolet Detection. International Journal of Research in Pharmaceutical and Biomedical Sciences: 2011, 2229-3701.

21. Affandi M, Julianto T, Majeed A, Development and Evaluation of Astaxanthin Nanoemulsion. Asian Journal of Pharmaceutical and Clinical Research, 4(1), 2011, 142-148.

22. Modi J, Patel J, Nanoemulsion –Based Gel Formulation of Aceclofenac for Topical Delivery. International Journal of Pharmacy and Pharmaceutical Science Research: 2011, 6-12.

23. Patel D, Transdermal Drug Delivery System: A Review. The Pharma Innovation: 1(4), 2006, 2277-7695.

24. Sharma K, Agrawal S, Gupta M, Development and Validation of UV spectrophotometric method for the estimation of Curcumin in bulk Drug and Pharmaceutical Dosage Forms. Int. J of Drug Development & Research: Vol. 4, 2012, 375-380.

25. Singh P, Kumar B, Jain S, Development and Characterization of a Nanoemulsion Gel Formulation for Transdermal Delivery of Carvedilol: Vol. 57, 2012, 33-45.

26. Gupta P, Pandit J, Kumar A, Swaroop P, Gupta S, Pharmaceutical Nanotechnology Novel Nanoemulsion-High Energy Emulsification Preparation, Evaluation and Application. The Pharma Research: 2010, 117-138.

27. Kharia A., Gilhotra R., Singhai A. K., Formulation and Evaluation of Transdermal patch for Treatment of Inflammation, International Journal of Pharmaceutical Sciences and Research: Vol. 10(5), 2019, 2375.

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