

Development and Characterization of Cinnamon Oil-Salicylic Acid Blended Nanoemulsion (CSN) for topical Application

Atul Pratap Singh*, TS Easwari

IIMT College of Medical Sciences, IIMT University, Meerut, Uttar Pradesh, INDIA.

ABSTRACT

Background: This study aimed to develop and describe a Cinnamon Oil-Salicylic Acid Blended Nanoemulsion (CSN) for topical use. Different ratios of oil, surfactants, and water were used to create the base for the nanoemulsions. **Methods:** To determine the nanoemulsion (NE) base regions, pseudo ternary phase diagrams were created. In addition, nine formulations containing mixes of Tween 80 and ethanol were examined for their droplet size, zeta potential, viscosity, pH, microscopy and spectroscopic technique.

Results: As a result of the experiments, it was discovered that the nanoemulsion comprising cinnamon oil and salicylic acid had an average size of 103.55 ± 1.83 and excellent rheological properties. Results revealed that the nanoemulsion bases, including ethanol as a co-surfactant, produced a larger emulsion area in the phase diagram than the other nanoemulsion bases. The formulation exhibited homogeneity, stability, and viscosity. Spherical NE was observed in transmission electron microscopy photos of CSN, and the size distribution was very narrow. The results of the in vitro release investigation showed that the medicine was released at a 95.87% effective rate in 24 hr. At a temperature of 25°C, the results of the short-term stability research, which was carried out for six months, revealed that CSN is stable. When applied to the skin of animals, CSN showed no signs of skin toxicity or irritation.

Conclusion: As a result, CSN is an excellent natural-based preparation that may be utilized topically against different kinds of skin conditions.

Keywords: Drug release, Permeation, Stability, Skin disorder.

INTRODUCTION

The largest organ in the human body is the skin, which serves as the body's outer layer. Additionally, it serves as the initial line of defence.¹ All ages, from newborns to the elderly, are affected by skin disorders, which are many and regularly occurring health problems that can be harmful in various ways.² It is critical to have healthy skin to have a healthy body. Skin disorders that affect the skin, such as cancer, herpes, and cellulitis, can impact a large proportion of the population. Wild plants, as well as their parts, are widely employed in the treatment of various disorders. Plants have been used from the beginning of time. Natural treatment is inexpensive and, according to some, safe. Aside from that, it is an excellent raw material for synthesizing novel synthetic compounds.³

The cinnamon tree (*Cinnamomum zeylanicum*), which is frequently referred to as the "eternal tree of tropical medicine," belongs to the Lauraceae family of plants.⁴ Spices such as cinnamon are a standard part of many people's diets across the globe. Cinnamaldehyde, cinnamic acid and cinnamate are cinnamon essential oils and derivatives. Cinnamon bark includes procyanidins, catechins, antioxidants.⁵ Because of the high demand for essential oils in the flavour, cosmetic, health, and phytomedicine industries, large quantities of cinnamon extracts, particularly cinnamon essential oil, are produced and traded worldwide. Cinnamon essential oil is particularly popular in the flavour and cosmetic industries.⁶ Cinnamon has been demonstrated to have anti-inflammatory, antioxidant, and anti-diabetic properties. Using

Submission Date: 13-05-2022;

Revision Date: 26-06-2022;

Accepted Date: 06-08-2022.

DOI: 10.5530/ijper.56.3s.169

Correspondence:

Mr. Atul Pratap Singh

Department of Pharmaceutics,
IIMT College of Medical Sciences,
IIMT University, Meerut-250406,
Uttar Pradesh, INDIA.

E-mail: atulsingh2206876@gmail.com



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a combination of medications to achieve better, augmented, or personalized features and functionality, which can provide considerable advantages in drug delivery applications, is becoming increasingly popular.⁷

Salicylic acid has been used for more than 2,000 years to treat many skin conditions, including acne. Salicylic acid (SA) belongs to a class of chemicals known as hydroxy acids, which are frequently utilized for various aesthetic reasons due to the numerous beneficial qualities they possess.⁸ It was used with cinnamon oil to boost its effectiveness against cutaneous illnesses. Salicylic acid acts as an excellent peeling agent due to its exfoliating properties. Salicylic acid, in particular, has comedolytic properties, which make it a beneficial peeling agent for people suffering from acne.⁹ The most common treatment for skin problems is topical therapy.¹⁰⁻¹¹ While gels and creams have little efficacy due to their lack of visual and aesthetic appeal, patients are less likely to stick to treatment regimens if they are not visually appealing.¹²

Droplet sizes of less than 100 nm and extremely low interfacial tension make nanoemulsion (NE) transparent or translucent dispersions long-lasting and physically stable. Nanoemulsions have attracted much attention recently because of their potential as drug delivery systems.¹³ The smaller the droplet size, the better the drug distribution and penetration through the epidermal layer. The right combination of oils and surfactants.¹⁴ As a result, the study's protocol called for creating a Cinnamon Oil-Salicylic Acid Blended Nanoemulsion (CSN) for topically applying to the skin.

MATERIALS AND METHODS

Drugs and Reagents

Double-distilled water was used throughout the investigation. All additional compounds and solvents were of analytical reagent quality unless otherwise specified. All of the ingredients were obtained from Sigma-Aldrich USA.

Preparation of Nanoemulsion

Preparation of cinnamon oil/salicylic acid blend (CSB)

The mixture was made by gradually mixing cinnamon oil and salicylic acid in a 4:1 ratio until well combined.

Screening of Surfactants and Co-surfactants (S_{mix})

The solubility of surfactants such as tween-20, tween-80, span 20, span 80, and co-surfactants such as propylene glycol, isopropyl alcohol, ethanol, and polyethylene glycol 400 was examined in order to identify solvents with the acceptable solubilizing ability for the Cinnamon oil/salicylic acid blend.

Formulation of Nanoemulsion (NE)

In a standard room temperature environment, the surfactant and co-surfactant were mixed in different mass ratios of 1:1, 2:1, and 3:1. The essential oil and surfactant/co-surfactant

were mixed in different mass ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1 under the same conditions as the surfactant and co-surfactant. After that, water was added in a dropwise fashion. The water flow rate was maintained at roughly 1.0 mL/min throughout the experiment. A visual inspection of the system's clarity was performed, and water was added until the water transformed from murky to clear. The ternary phase diagram was created by connecting the oil phase, the surfactant/co-surfactant phase, and the water phase as the three vertices of the diagram. Considering the size of the emulsion area, the optimal mass ratio was determined.¹⁵

Construction of Pseudo-ternary Phase Diagram

A pseudo-ternary phase diagram was created to describe the extent and nature of the nanoemulsion zone. Based on solubility data, pseudo ternary phase diagrams of oil, surfactant (tween-80), co-surfactant (ethanol), and distilled water were created for cinnamon oil and salicylic acid. The pseudo ternary phase diagrams we see today were made using water titration. The phase diagrams were created using 1:1, 2:1, and 3:1 weight ratios of tween 80 and ethanol. The aliquots of surfactant and surfactant combination (S_{mix}) were mixed with the oil at room temperature. The phase diagrams show that the oil-to- S_{mix} ratio was changed to 1:9 (v/v). Water was added drop by drop to each oil- S_{mix} mixture while aggressively stirring on a mixing table using a magnetic stirrer (Remi Instruments Ltd. Mumbai, India). The samples were visually inspected and verified to be clear nanoemulsions by the testing team.¹⁶ After achieving equilibrium, no additional heating was required during the process. The phase diagrams were created with the help of the software CHEMIX SCHOOL 3.51. The monophasic region area was considered when selecting a suitable surfactant to surfactant ratio for the individual medications.

Optimization of Nanoemulsion

Cinnamon oil and salicylic acid blended Nanoemulsion

CSN were optimized for transparency, diluting properties, and particle size (globule size). In order to account for the volume and solubility of CSB that would be incorporated into the Nanoemulsion (NE), a specific oil- S_{mix} -water mixture within the NE was developed. It was found that by changing the speed and time of the stirring and the globule size, the optimal solution could be found for NE formulations.

UV Visible Spectrophotometer

CSN was diluted in 100 ml of phosphate buffer (pH 6.8) in a volumetric flask and purified using a filter. Take 1 ml of the phosphate buffer and dilute it with 100 ml of water. A UV-visible spectrophotometer was used to determine the maximum concentration of CSN.¹⁷

Fourier Transform Infrared (FT-IR) Analysis

Using an FT-IR spectrophotometer, the drug-excipient compatibility of the pure drug and the physical mixture were determined (8400S, Shimadzu Kyoto, Japan). Separately, the CSN and the physical mixture were ground into powder and pressurized at a pressure of 5 tonnes for 5 min in a KBr press (Technosearch Instrument Mumbai, India) to form pellets or thin films, and FT-IR spectra were recorded in the wavelength range 4000-400 cm^{-1} for each.¹⁸

Characterization of prepared Nanoemulsion

Globule size and polydispersity index (PDI)

At 25°C, water was used as a dispersant in a Zetasizer HAS 3000 (Malvern Instruments, UK) to estimate CSN average globule size and polydispersity index (PDI). Every decision was made three times to assure precision.¹³

Zeta potential

With the help of a small volume disposable zeta cell and the Helmholtz-Smoluchowski equation, we detected electrophoretic mobility (lm/s), which was then transformed to zeta potential by a zeta sizer. The zeta potential charge must be either negative or neutral for the system to be stable. The zeta potential is an essential instrument for determining the flocculation rate of particles and is used in many applications.¹⁹

Viscosity and Conductivity of Nanoemulsion

A Brookfield viscometer and a Brookfield conductivity metre were used to measuring CSN viscosity and conductivity. After 5 min of equilibration, a 30 mL sample was placed in a beaker and spun at 0.5, 1, 2.5, and 5 rpm to determine viscosity. The viscometer's dial was read at each speed, and the value was recorded. It was confirmed using a conductivity metre that the Nanoemulsion was the correct type by determining its conductivity at room temperature. Every judgment was made three times.²⁰

Refractive index of Cinnamon Oil-Salicylic acid Blended Nanoemulsion

A digital Abbe refractometer (Atago Co. Ltd., Tokyo, Japan) was used to measure the system's refractive index after one drop of CSN was poured onto a slide, and the result was recorded. Using a colourimeter (Digital Colorimeter, D-801, Photocon) at wavelengths between 570 and 590 nm, the percent transmittance of the system was determined.²¹

pH determination

While at room temperature, a digital pH metre was used to determine the pH of the formulation (Rolex, India). Because of the topical administration of the CSN, pH monitoring was a critical parameter in ensuring that the CSN was nonirritating.

Morphology Investigation

A scanning electron microscope was used to examine the three-dimensional internal structures of the optimized CSN, the optimal blank Nanoemulsion, and CSN were optimized (SEM; Su8020, Hitachi, Tokyo, Japan). The samples for SEM examination were prepared by rapidly freezing them in liquid nitrogen and then freeze-drying them for 48 hr.²²

Transmission Electron Microscopy (TEM)

A Hitachi TEM could be used to examine the microstructure of CSN when it was still cold (H-7500). Drying the sample on a micro carbon-coated grid and inspecting the findings under a microscope after staining at high enough magnification were used to capture photos of CSN for this study.²³

Differential Scanning Calorimeter (DSC)

DSC is used to detect thermal transitions in samples that occur during heating. When performing this procedure, it is necessary to employ a reference with a well-defined heat capacity over the temperature range of the scanning process. This approach can be used to study phase transitions in emulsions, such as melting crystalline areas in the presence of water (the solid fat proportions and ice crystals proportion). The presence of fat crystallization in emulsions has been observed to affect their stability, linked to the surfactant utilized. Differential scanning calorimetry (DSC) was used to characterize the structural properties of NE aqueous suspensions and dried NE. The DSC was also used to determine the temperature at which the surfactants crystallized.²⁴ The Q200® instrument from TA Instruments was used to conduct the measurements (New Castle, DE, USA). A nitrogen purge of 50 mL/min was used for all measurements. It was between 80°C to 160°C. Samples (approximately 10 mg) were appropriately weighed and sealed in aluminium pans (40 mL) with either a hermetic cover or a screw-on top for storage in DSC of excipients and CSN in water that gradually released water when heated above 40°C.

Table 1: Solubility of Cinnamon oil and salicylic acid in different excipients.

Phase type	Excipient	Solubility (mg/mL)
Surfactant	Tween 80	71.39 ± 1.33
	Tween 20	60.28 ± 0.13
	Span 80	36.22 ± 1.21
	Span 20	40.09 ± 1.51
Co-surfactant	Isopropyl alcohol	35.93 ± 0.49
	Ethanol	47.20 ± 1.34
	Propylene glycol	39.64 ± 1.37
	Poly ethylene glycol 400	20.33 ± 1.54

Data are expressed mean ± SD (n = 3)

Table 2: Composition and characterization of different nanoformulations.

Batch	Oil (% wt/wt)	Smix (%wt/wt)	Water (%wt/wt)	Globule size (nm)	PDI	Zeta potential (mV)	% T
CS1	6	24	70	303.16 ± 3.93	0.320 ± 0.018	24.73 ± 1.03	96.74
CS2	6	26	68	295.11 ± 2.28	0.251 ± 0.112	32.18 ± 2.94	97.83
CS3	6	28	66	184.11 ± 2.09	0.225 ± 0.015	28.23 ± 2.84	98.44
CS4	6	30	64	181.74 ± 3.76	0.216 ± 0.017	33.12 ± 1.33	98.94
CS5	6	32	62	163.34 ± 1.61	0.197 ± 0.018	30.27 ± 2.54	99.43
CS6	6	34	60	145.27 ± 2.47	0.173 ± 0.013	29.93 ± 1.65	99.64
CS7	6	36	58	103.55 ± 1.83	0.250 ± 0.019	27.26 ± 1.37	99.88
CS8	6	38	56	134.36 ± 2.54	0.271 ± 0.001	28.23 ± 1.54	99.03
CS9	6	40	54	148.74 ± 2.98	0.296 ± 0.006	27.64 ± 1.64	99.37

Data are expressed mean ± SD (n = 3)

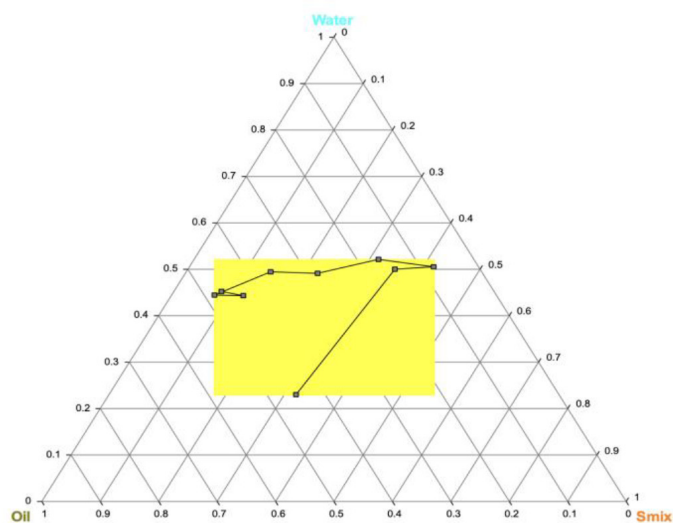


Figure 1: Pseudo-ternary phase diagram depicting Nanoemulsion region.

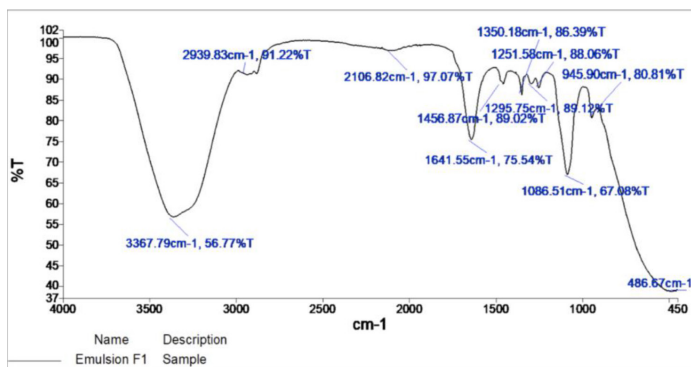


Figure 2: FTIR spectrum of CSN.

In vitro Release Study

Using a Franz diffusion cell (3.14 cm² diffusion area and 15.5 ml cell volume) with a cellulose acetate synthetic cell wall, researchers looked at the in vitro release profiles of CSN. The water-jacketed recipient chamber, which has a capacity of 25 mL and two arms, can be used for both sampling and temperature measurement. The Franz diffusion cell's donor

and recipient chambers were clamped together, limiting any movement. To solubilize the medicine, a 37°C±1°C phosphate buffer solution with a pH of 5.5 was added to the receptor chamber. After equilibrating the membrane, the Nanoemulsion containing 10 mg of medicine was applied to the donor site. Aliquots were taken at appropriate intervals and analyzed for drug content using UV visible spectrophotometers after being taken at appropriate intervals.²⁵

Skin Irritation Test

The CSN was subjected to a skin irritation test in order to determine the amount of irritation safety. The Institutional Animal Ethical Committee (IAEC) of the institution gave their approval to the study's procedure (Approval no. 11MT/CMS/CPCSEA 1297/IAEC/21-22/002). In a nutshell, 15 healthy male rats (weight 180-220g) were shaved on the back and then monitored for 24 hr to see if any signs of skin injury appeared. After 24 hr of observation, the shaved area on the backs of the rats was separated into two sections: one for intact tissue and the other for damaged tissue. A scalpel was used to create abrasions on the skin to develop the wounded area. The rats were then randomized into three groups at random, one for control saline, one for blank Nanoemulsion, and one for CSN. The preparations were applied to both regions in a 2cm x 2cm area on both sides. Each animal was allowed to roam freely in the same room, kept at 25°C temperature and 55% relative humidity. All of the animals were observed for erythema and oedema at intervals of 1, 24, 48, and 72 hr, and the symptoms were graded depending on the degree of visibility of the signs and symptoms. Immediately upon completion of the 72-hr research, the rats were sacrificed by cervical dislocation, and skin samples from the test region were obtained from the central section of the test area, which had an area of approximately one centimetre by one centimetre. The samples were stored in 4% polyformaldehyde at 4°C after being collected. The skins were embedded in paraffin and then sectioned into 5-micron-

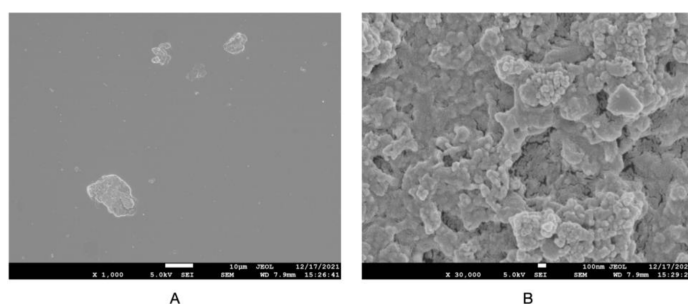


Figure 3: SEM images of the nanoemulsions.

A = Blank nanoemulsion, B = Cinnamon oil-salicylic acid blended Nanoemulsion (CSN)

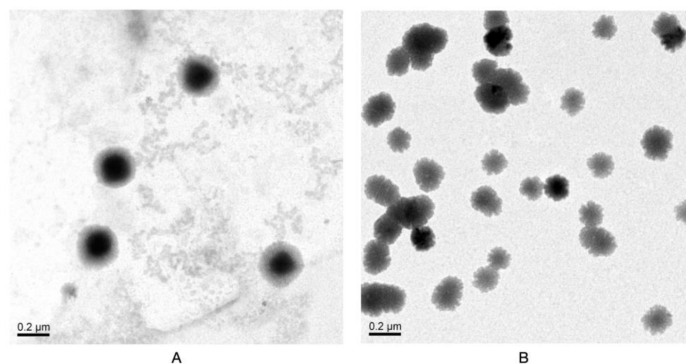


Figure 4: TEM image of nanoemulsions.

A = Blank nanoemulsion, B = Cinnamon oil-salicylic acid blended Nanoemulsion (CSN)

thick sections stained with H&E dye after being embedded in paraffin. Photographs of the histological alterations were taken under a light microscope.²⁶

Stability Studies

The CSN was subjected to six months of stability testing at room temperature to mimic patient use conditions. Creaming, phase separation or flocculation, as well as an accelerated centrifugation cycle (3000 rpm for 15 min), were used to determine physical and chemical stability after six months of storage, and the formulation was found to be chemically stable by determining the drug content, particle size, and zeta potential after six months of storage.²⁷

Statistical Analysis

Results are represented as mean \pm standard deviation (SD) ($n=3$).

RESULTS

Preparation and Optimization of Nanoemulsion (NE)

Table 1 shows the surfactants and co-surfactants used to test the solubility of the cinnamon oil/salicylic acid combination. Nanoemulsions were formed in this study using Tween 80 and ethanol as co-surfactants to lower the oil-water interfacial tension to a level suitable for this purpose. There should be an HLB value greater than 10 when picking a surfactant, and this

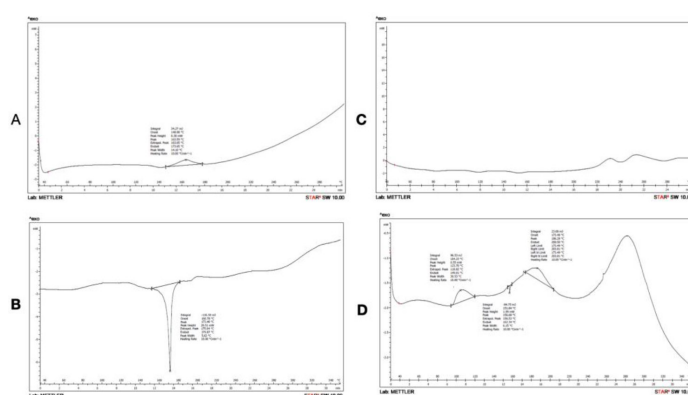


Figure 5: DSC thermograms for prepared nanoemulsions.

(A) Cinnamon oil, (B) Salicylic acid, (C) S_{mix} , (D) Cinnamon oil-salicylic acid blended Nanoemulsion (CSN)

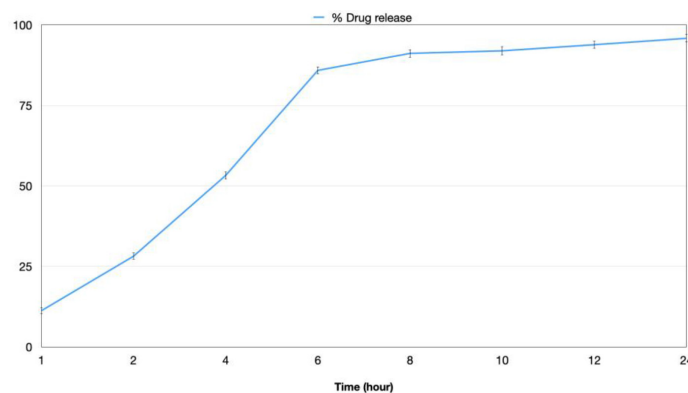


Figure 6: In vitro drug release profile of CSN in Franz diffusion cell.

is a critical consideration in the process of selection. Allowing an interfacial layer to form in a wide variety of compositions due to the reduction in bending stress, the addition of a co-surfactant reduces the bending tension.

Phase Diagram

We created ternary phase diagrams by altering the ratios of Tween 80 and ethanol, which were 1:0, 1:1, 2:1, and 3:1, respectively. The NE regions of phase diagrams are shaded areas, whereas a non-shaded area represents the turbid region. To get the best results in optimizing NE batches, the ternary phase system of S_{mix} (1:1) with the most significant area for NE production was chosen as a starting point. The experiment clearly showed that the globule size decreased as the concentration of Tween 80 was raised, as evidenced by the data. The optimization of plain NE was carried out based on percentage transmittance (percent T), globule size, and zeta potential. Table 2 reveals the results of this optimization. In order to achieve the dose requirement, the salicylic acid solubility investigation in cinnamon oil found that at least 6% of the oily phase was necessary. CSN formulations were made in nine separate batches with S_{mix} maintained at 1:1 and

water at 57.5% by weight. Figure 1 depicts the CSN phase diagram.

UV spectroscopy

In a phosphate buffer with a pH of 6.8, the absorption maxima of CSN were determined to be 304 nm.

The FT-IR Spectrum of CSN

The FT-IR spectrum of CSN is shown in Figure 2. Functional groups found in CSN were as follows: 3367.79 (N-H stretching), 2939.83 (C-H stretching), 2106.82 (C=C stretching), 1641.55 (C=O stretching), 1456.87 (C-H bending), 1350.18 (O-H bending), 1295.75 (C-O stretching), 1251.58 (C-O stretching), 1086.51 (C-O stretching), 946.57 (C=C bending). The infrared spectra of the physical combination yielded all of these peaks, with only a tiny variation in location. This resulted in excellent correlations between IR spectra peaks for both the pure drug and the physical mixture, and the data showed that there was no chemical interaction between these two substances.

Characterization of CSN

Table 2 shows that when the concentration of S_{mix} in the formulations increased, the size of the globules shrank. Batch CS1 had the highest globule size (303.16 ± 3.93 nm), and batch CS7 had the smallest globule size (103.55 ± 1.83 nm), both of which contained 24 percent S_{mix} . The low PDI readings for all formulations revealed that they all had droplets in the nanoscale range. The uniformity of droplet size within a formulation is represented by the droplet distribution index (PDI), defined as the standard deviation to mean droplet size ratio. In order to determine which batch was the optimal one, we looked at the response factors. The batch CS7 (oil- S_{mix} -water, 6:36:58) was chosen because it had the best combination of 99.88 percent optical transparency, small globule size, polydispersity (0.250 ± 0.001), and zeta potential (-27.26 mV). To optimize the procedure for the creation of N, the stirring speed was varied throughout a range of time intervals (10 min; 20 min; 30 min), followed by the determination of the globule size of the resulting product. The optimal process parameters for obtaining drug-loaded NE were determined based on the minimum globule size of 95.86 ± 1.4 nm, the stirring speed of 800 rpm, and the stirring time of 30 min.

Furthermore, the conductivity, viscosity, and refractive index of CS7 were measured, and they were determined to be 0.169 mS, 386.32 cP, and 1.512 A, respectively. The high viscosity of CSN ensured that it was delivered effectively through the skin. The conductivity values of 0.169 mS suggest that the CSN is of the oil-in-water type, indicating that it transmitted electrical current. The pH of CSN was found to be between 6.5 to 6.8, which is close to the typical pH range for topical application. In terms of

formulation, this could help reduce the amount of irritation caused by CSN while applied to the skin.

Morphology Analysis through SEM

As depicted in Figure 3, the physical appearance of CSN is rather distinct. The formulation exhibited homogeneity, stability, and viscosity. The image of CSN revealed interconnected pores with a random size distribution in the same field of view. This porous structure provides sufficient area for high drug loading, drug mobility throughout the structure, and the enhancement of the drug release rate, among other things.

TEM of CSN

CSN was found to have a spherical shape and a limited size distribution, as revealed by transmission electron microscopy (TEM). The samples were tested for homogeneity and birefringence using visual inspection in a cross polarizer to determine their composition. When viewed through a cross polarizer, CSN looked dark in colour. The measurements revealed that the NE formulations were colloidal dispersions with optical isotropy of 0.5. Figure 4 depicts the TEM imaging of CSN.

DSC of prepared Nanoemulsion

CSN is shown in crystalline form in Figure 5 due to a DSC examination of its structure. During heating NE from room temperature to 160°C , the only thing that could be observed was water evaporation from the atmosphere. Having dried in the DSC pan, cooling induced crystallization, demonstrated by an exotherm that began at 30°C and persisted until the sample was dehydrated. After that, heating caused melting at 40 degrees Celsius. A similar exothermic and endothermic temperature was generated throughout the cooling and heating operations, respectively. We exposed several different types of NE components to DSC scanning to discover which materials were responsible for such thermal events on a single component and physical mixtures of components. DSC for CSN is depicted in Figure 5 for (A) cinnamon oil, (B) salicylic acid, (C) S_{mix} , and (D) a blended cinnamon oil-salicylic acid nanoemulsion (CSN).

In vitro Drug Release

It was discovered that the highest amount of medication released from CSN occurred within 8 hr. CSN had a 95.87% medication release rate after 24 hr of administration. The small size of the particles is one of the variables that contribute to the greater penetration of the particles through the skin's surface. Additionally, the inclusion of the surfactant Tween 80 helped release a higher proportion of the medication from NE. The findings revealed that the percent drug release was proportional to time passage (Figure 6).

Skin Irritation Test

The safety of the CSN was further investigated to determine that it is non-toxic to the skin and does not cause significant irritation to the skin when applied topically.

Stability Studies of CSN

After centrifugation (3000 rpm for 15 min) at room temperature, the CSN showed no evidence of drug precipitation, creaming, phase separation or flocculation when viewed visually. After six months of storage, no significant changes in the characteristics of CSN were found during the stability tests, proving that CSN is stable for at least six months. Even though the sample was diluted, the globule size, PDI zeta potential, and transmittance remained the same at 109.32 nm, 0.134 mV, and 99.78 percent, respectively.

DISCUSSION

There are several ways to treat skin conditions, but topical therapy is the most convenient and effective. Patients are less likely to use them because of the low efficacy and unappealing appearance of conventional topical therapies, such as gels and creams. Phototherapy, a systemic treatment, has substantial adverse effects, as do other forms of light therapy.¹² Lipid-based drug delivery systems are a cutting-edge technology for enhancing drug solubility in the digestive tract, which can help increase the oral bioavailability of poorly soluble medications.²⁸ Nanoemulsions provide several advantages, including enhanced medication solubilization and shelf life, ease of manufacturing, and increased bioavailability of both hydrophilic and hydrophobic drugs.

CSN, a nanoemulsion of cinnamon oil and salicylic acid, was safe and efficacious for topical skin application in this study, which comprised the formulation and characterization of the Nanoemulsion. In order to find the best surfactant and co-surfactant to aid in the optimal solubility of cinnamon oil and salicylic acid, prior research was done. It was shown that Tween 80 and ethanol could be used as surfactants and cosurfactants to deliver cinnamon oil and salicylic acid to the skin. According to the ternary phase diagram, when the ratio of surfactant to co-surfactant (S_{mix}) was 1:1, most oil was mixed into nanoemulsion systems. With just one surfactant, it may not be possible to generate a fluid film and a temporarily negative interfacial tension; therefore, the use of a co-surfactant is recommended.²⁹ While surfactant concentrations in the formulation solution can raise the interfacial film's ability to accommodate various curvatures for nanoemulsion formulation, it is the presence of co-surfactants that typically lowers the interfacial bonding stress and increases the interfacial film's pliability.³⁰ CSN globules were found to be within the nanoemulsion range of 20-200nm. A higher S_{mix} concentration in the formulation results in smaller globules. Due to low PDI values, the consistency

of droplet size was reduced across the formulation. For nanoemulsions, zeta potential ranged between 30 and 40 mV, consistent with our findings. Due to its extremely low viscosity, a characteristic of nanoemulsions, this is in line with prior nanoemulsion studies.³¹⁻³²

Spherical NE was seen in TEM photos of CSN, which had a limited size distribution compared to the surrounding area of the shot. Visual inspection of CSN during stability testing revealed that it did not cream or precipitate the medication and did not exhibit phase separation or flocculation. After centrifugation at room temperature, the emulsion formed was found to be stable. According to the results of stability investigations, there were no notable changes in CSN properties after six months of storage. Droplet size, viscosity, and RI of the optimized nanoemulsion formulation did not significantly alter throughout storage, showing that the Nanoemulsion was structurally stable. In addition, the formulation had the least depreciation of CSN following storage. The slower decomposition of CSN demonstrated the chemical stability of Nanoemulsion. These findings demonstrated both the physical and chemical stability of the formulation.

CONCLUSION

Salicylic acid was used in the current investigation in conjunction with the cinnamon oil phase, and it has excellent penetration capabilities through the skin when used as a transdermal preparation. In order to lessen or eliminate the toxicity or irritation caused by nanoemulsion formulations in the future, a low surfactant-containing nanoemulsion was selected for further exploration. The modified formulation was tested by the ICH guidelines and found stable. As a result of our findings, we can conclude that the formulation is safe for topical administration because no skin irritation was seen. It can be inferred from the study that CSN is a favorable formulation for topical application due to its small droplet size and low polydispersity, as well as its optimal surfactant and co-surfactant mix.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Cite this article: Singh AP, Easwari TS. Development and Characterization of Cinnamon Oil-Salicylic Acid Blended Nanoemulsion (CSN) for topical Application. *Indian J of Pharmaceutical Education and Research*. 2022;56(3s):s605-s612.