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ORIGINAL ARTICLE

Formulation and Evaluation of Caffeine-loaded Nanoemulgel

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ABSTRACT
Caffeine, renowned for its diverse pharmacological properties, finds extensive applications in the pharmaceutical and cosmetic industries. This study presents the development and comprehensive characterization of a novel delivery system for caffeine, utilizing nanoemulgel technology. The nanoemulgel was formulated using a combination of high-energy emulsification and gelation techniques to achieve enhanced stability and sustained release properties. The physicochemical characterization of the nanoemulgel was performed using various analytical techniques including dynamic light scattering (DLS), transmission electron microscopy (TEM), and rheological analysis. Additionally, the encapsulation efficiency, drug release kinetics, and stability profile of the nanoemulgel were investigated. The results demonstrate the successful development of a caffeine-loaded nanoemulgel with uniform droplet size distribution, optimal rheological properties, and high encapsulation efficiency. Moreover, the sustained release profile of caffeine from the nanoemulgel exhibited prolonged release kinetics, indicating its potential for sustained therapeutic effects. This study elucidates the promising application of nanoemulgel technology as an efficient delivery system for caffeine, opening avenues for its utilization in pharmaceutical and cosmetic formulations.
Keywords: *Nanoemulgels, Caffeine, Gelation method, Cosmetic Application.*

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INTRODUCTION

The aging of skin is a complex and multi-faceted phenomenon influenced by both internal (chronological) and external (environmental) factors, leading to progressive changes in the structure and function of the skin. Internal aging arises from genetic factors and the natural process of cellular aging, which manifests as a gradual decline in cellular repair capacities and heightened oxidative stress from internal sources, resulting in increased levels of reactive oxygen species (ROS) that cause damage to DNA, proteins, and lipids.Extrinsic aging, mostly induced by ultraviolet (UV) light and pollution, raises ROS levels, promotes DNA damage, and causes inflammation, also known as photoaging. These mechanisms cause matrix metalloproteinases (MMPs) to degrade collagen and elastin, resulting in reduced skin elasticity, wrinkle development, and sagging [1]. Photoaged skin exhibits degeneration of oxytalan fibers and deposition of disordered elastic fibers as sun elastosis, whereas intrinsic ageing is characterized by a total depletion of these fibers. Furthermore, cellular senescence and the release of pro-inflammatory cytokines lead to extracellular matrix disintegration and slowed skin regeneration. To address these changes, an array of topical treatments and therapeutic procedures, such as peels containing chemicals, injectables, and energy-based devices, have come into existence to improve skin appearance and function by targeting specific causes of skin ageing [1,2].

Caffeine, a commonly used methylxanthine, additionally serves an important part in skin aging mechanisms due to its complex biochemical activities. It operates as an adenosine receptor antagonist and inhibits phosphodiesterase, resulting in elevated levels of cyclic adenosine monophosphate (cAMP),

which boosts cellular metabolism and may stimulate fat breakdown in skin cells. This increase in lipid metabolism can help prevent the age-related accumulation of subcutaneous fat and enhance skin tone. Furthermore, caffeine has antioxidant properties, which help to neutralize reactive oxygen species (ROS) produced by UV exposure and intrinsic aging, thus shielding skin cells from oxidative stress while decreasing the degradation of collagen and elastin fibers, which are essential for preserving skin elasticity and elasticity [3]. Caffeine's capacity to modulate enzymes like AMP-activated protein kinase (AMPK) supports its involvement in boosting lipolysis, fatty acid β-oxidation, and decreasing inflammation, all of which contribute to a young skin appearance [4]. However, caffeine's usefulness in topical formulations for anti-ageing benefits may be restricted by the ability to precipitate and produce clumps based on the vehicle used, potentially impeding skin permeability and cosmetic performance [3].

Nanoemulgel formulations, which combine the benefits of nanoemulsions with gels, provide improved topical drug delivery qualities as compared to traditional macroemulsions. Nanoemulsions' small droplet size, which usually ranges from 20 to 500 nm according to the formulation, enables uniform dispersion on the skin, a broad surface area for improved absorption, and modified active ingredient release profiles [5]. Nanoscale droplet size also leads to enhanced film formation, high stability, and a more pleasing aesthetic character and skin feel, making nanoemulgels especially ideal for cosmeceutical and medicinal uses [6],[7]. Droplet size influences the visual appearance of nanoemulgels, with formulations in the 50-200 nm range being transparent or translucent, and those nearing 500 nm appearing milky [8]. The gel matrix of nanoemulgels increases the formulation's viscosity and spreadability, increasing patient compliance and assuring controlled, targeted distribution of hydrophilic and lipophilic medicines [9]. Overall, the careful selection of technique and components is crucial to achieve these desirable nanoemulgel features, which result in a stable, effective, and user-friendly topical delivery system.

To manufacture a nanoemulgel, initially make a nanoemulsion, which is then mixed into a gel basis with a stirrer and/or homogenizer [10,11]. Methods involving high energy, like high-pressure homogenization, are frequently used to achieve the nanoemulsions small droplet size (5-500 nm)[10]. This approach includes applying high pressure (500 to 20,000 psi) to a coarse emulsion through a small aperture, which causes strong turbulence, hydraulic shear, and cavitation, all of which reduce droplet size [11,12]. The procedure can be repeated to get the appropriate droplet size and polydispersity index (PDI). High-speed stirrers and homogenizers can also be employed to prepare nanoemulsions, as reported by Haider et al., [13]. To form the nanoemulgel, the nanoemulsion is mixed with a hydrogel while being continuously stirred [14].

This research utilized the high energy emulsification method among various preparation techniques. This approach, especially high-speed homogenization, is essential for producing stable nanoemulsions, which are later integrated into gel matrices to form nanoemulgels [15]. The objective of this study was to prepare a nanoemulsion incorporating caffeine (0.5, 0.75, 1% w/v) utilizing two surfactants (Span 20 and Tween 80) through a high-energy method.

MATERIAL AND METHODS

Material

Caffeine was gifted from Evertouch Healthcare Pvt. Ltd. Kosikala, Mathura. Carbopol 934, Tween 80, Propylene glycol, Span 20, Liquid paraffin, Methyl Paraben, Triethanolamine, the material was sourced from Central Drug House (P) Ltd., located in New Delhi, India. For all experiments, distilled water was utilized. All chemicals were of pharmaceutical quality.

Solubility Determination

The solubility of caffeine within a range of solvents was determined such as water, chloroform, pyridine, pyrrole, benzene, ethanol, dichloromethane, acetone, ethyl acetate, methanol, ethanol, and carbon tetrachloride. The drug is added to the different solvents until the supersaturation is attained, kept in an orbital shaker for 24 hrs, then subjected to centrifugation for a duration of 5 minutes at a rotational speed of 6000 revolutions per minute, the resultant supernatants were subsequently gathered for the purpose of absorption assessment utilizing a UV spectrophotometer [10].

Preparation of Nanoemulsion

The aqueous phase (Tween 80 in water) and the lipid phase (Span 20 in essential oil) were heated to 60ºC and subsequently amalgamated. The emulsion was homogenized with a high-shear homogenizer (Ystral GmbH D-7801 Dottingen, X1020 homogeniser, Ballrechten-Dottingen, Germany) as well as an ultrasonic probe homogenizer (Model 3000MP Ultrasonic homogeniser, Biologics Inc., Manassas, VA, USA) for 15 minutes at 60% amplitude while cooling [16].

Preparation of Caffeine-Loaded Nanoemulsions

It follows the same procedures described in paragraph 2.3, except that caffeine is selected according to the literature[17], dissolved in ethanol by choosing the ratio of (0.5, 0.75, 1.0%, w/w.) and then mixed with essential oils. Each formulation produces approximately 25 grams of non-ionic surfactants (Span 20 and Tween 80) using various proportions to form nanoemulsions, and the final HLB 11.1 remains the total proportion (6.2% w/w). The pH value has been adjusted to 5.7-5.9

Table: 1 Formulation Composition of Nanoemulgel

Ingredients (g)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Caffeine	0.5	0.5	0.5	0.75	0.75	0.75	1	1	1
Carbopol 934	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Liquid paraffin	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Span 20	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Tween 80	0.37	0.37	0.37	0.37	0.37	0.37	0.37	0.37	0.37
Propylene glycol	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Methyl paraben	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
Triethanolamine	pH 5.4-5.9	pH 5.4-5.9	pH 5.4-5.9	pH 5.4-5.9	pH 5.4-5.9	pH 5.4-5.9	pH 5.4-5.9	pH 5.4-5.9	pH 5.4-5.9
Distilled water (qs)	25	25	25	25	25	25	25	25	25

Preparation of Hydrogel

Carbopol 934 weighed is mixed with distilled water., and uniformity in the stirring was continued. The gel was then stored in the refrigerator for 24 hours, further adding triethanolamine to keep the gel pH at the appropriate level to eliminate any trapped air bubbles in the gel and finish the cross-linking and gelation process.

Preparation of Nanoemulgel

The formulated gel and nanoemulsion systems were combined in a ratio of 1:3 slowly with continuous homogenizing at 2500 rpm for 1 hr to integrate the nanoemulsion into the gel matrix.

Determination of FTIR Analysis of Nanoemulgel

The FTIR analysis of the nanoemulgel was conducted for qualitative identification of compounds. Using a compression machine, 3-5 mg of the sample was ground with 100-150 mg of KBr to form a KBr pellet about 1 mm in diameter. The sample pellet was analyzed using an FTIR spectrophotometer at wavelengths ranging from 4000 to 400 cm^{-1} [18].

Measurement of Size, Polydispersity Index, and Zeta Potential of Nanoemulsion

The droplet size, zeta potential, and polydispersibility index of the nanoemulsions were measured using the Malvern Zeta sizer Nano.Three separate measurements were made, and the average was calculated. Each sample zeta potential was ascertained [19].

Determination of Swelling Index

The prepared topical nanoemulgel swelling index is determined by taking 1 gram of gel on perforated foil of aluminum and placing it separately in a 50 ml beaker containing 10 ml of 0.1 N NaOH. After being reweighed, the samples were withdrawn from the beakers at different times and placed in a dry place for a while. The swelling index is determined by:

Swelling Index (SW)% = {(Wt – Wo) / Wo} x 100.

Where; (SW)% = Equilibrium percent swelling,

Wt = Weight of swollen emulgel after time t,

Wo = Original weight of nanoemulgel at zero time.

The produced nanoemulgels were packaged in aluminium collapsible tubes (5 g) and tested for stability at 5°C, 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH for three months. Samples were taken at 15-day intervals and analyzed for visual appearance, rheological characteristics, drug content,pH and drug release profiles [20].

Determination of Entrapment Efficiency (EE%)

A small drop of the formulation was put in a tube and centrifuged at 14000 RPM (4ºC) for 15 minutes. The procedure was repeated until cloudiness was removed from the supernatant using an ultracentrifuge. The cloudiness supernatant was obtained, and the amount of the drug determined with assistance of UV at a wavelength of 272 nm. Moreover, the amount of drug absorbed in the colloidal system was determined using the corresponding formula, with each reading taken in a triplet [18].

$$\textbf{D.E.E (\%)} = W_{\text{Total drug}} - W_{\text{Free drug}} / W_{\text{Total drug}} \times 100$$

where, $W_{\text{Total drug}}$ = weight of total drug

$W_{\text{Free drug}}$ = weight of free drug

Determination of viscosity

The viscosity of the developed batches has been assessed with a Brookfield Viscometer with spindle no. 5 at 10, 530, 50, 60, and 100 rpm, respectively. The formulation was added to the beaker and allowed to settle for 30 minutes at the assay temperature (25±1ºC) before [21].

Preparation of Nanoemulgel with/without Caffeine

In order to create nanoemulgels, the nanoemulsion (with or without caffeine) and hydrogel were combined in a 1:1 ratio while being continuously stirred slowly (125 rpm) at 25ºC as long as a physically homogeneous result was developed..

Evaluation of Nanoemulgel

Physical Examination

The formulated nanoemulgel organoleptic properties-color, odor, phase separation, homogeneity, and consistency were examined visually. Centrifugation was used to measure phase separation for 10 minutes at 5000 and 10,000 rpm.

Determination of Particle Size, Polydispersity, and Zeta Potential

The Malvern Zetasizer Nano was used to assess the nanoemulgel formulations zeta potential, droplet size, and polydispersity index. Three separate measurements were made, and the average has been estimated. Each sample, zeta potential was ascertained [20].

Determination of the pH of Gel and Nanoemulgel

The pH of the formulation has been measured employing a digital pH meter. The pH meter electrode was rinsed using distilled water before it was dipped into formulation to determine its pH. The entire procedure was repeated in triplet [22].

Determination of Spreadability of Nanoemulgel

Spreadability is determined by the apparatus recommended by Mutimer et al., (1956), which is appropriately modified in the laboratory & used for the study. It's made up of a block of wood with a pulley on one end. This technique assesses spreadability by examining the "slip" and "drag" qualities of nanoemulgels. On this block, a ground glass slide is installed. An additional 2 grams of the nanoemulgel undergoing assessment is placed on this ground slide. The nanoemulgel is then sandwiched between a second glass slide that is the equivalent to a placed ground slide and a hook. For five minutes, a 1 kg weight is placed on top of each of the two slides to drive air out and form a consistent layer of nanoemulgel. Scrape off any excess nanoemulgel from the edges. Following this, the topmost plate is lifted with 80 g. A string attached to the hook can be used to determine the time (in seconds) needed for the top slide to travel 7 to 5 cm. Shorter spread times signify more significant spreadability [15]. The formula for determining spreadability was as follows:

S= ML/T

Where, S = Spreadability,

M = Weight tied to upper slide,

L = Length of glass slide;

T = Time is taken to separate the slides from each other.

Determination of Stability of Nanoemulgel

Stability investigations were carried out in accordance with ICH recommendations. The formulations were kept in a hot air oven at 37 ± 2°, 45 ± 2°, and 60 ± 2° for 3 months. The samples were tested for drug content every two weeks using a UV-visible spectrophotometer. A stability analysis was carried out by evaluating variations in pH and drug content of the nanoemulgel over regularly scheduled times [21].

Determination of In Vitro Release of Nanoemulgel

The in vitro caffeine release pattern of the various formulations was examined utilizing the Electrolab Dissolution System (USP) accordingly to the procedure, 1 g of the equivalent preparations was deposited in glass tubes connected to one end by a cellophane membrane (MWCO 2000–15,000 Da). Tubes were utilized instead of baskets and revolved at 50 rpm in 750 mL of phosphate buffer (pH 5.5) at 37 ± 0.5 ◦C. To maintain the sink condition throughout the investigation, samples were taken at predetermined intervals and replenished with an equivalent volume of fresh dissolution medium. The specimens have been identified using spectrophotometry at λmax 273 nm [20].

RESULTS AND DISCUSSION

Nanoemulgel preparation and optimization.

Characterization of Nanoemulgel Formulations Physicochemically

The following investigations were used to characterize the nanoemulgel formulations for additional research.

Organoleptic Properties

Every formulation was off-white or milky. Furthermore, the formulations were uniform, as illustrated in (fig: 1&2).

Figure: 1 Physical appearance of optimized formulation.

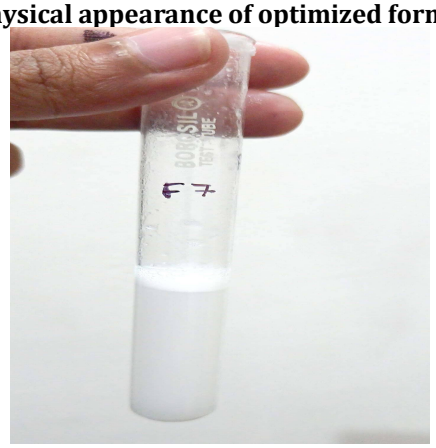

Figure: 2 Homogeneity analysis of optimized formulation.

FTIR Characterization of Optimized formulation

Table: 2 Infrared spectral assignment of Optimized formulation

GROUPS	OBSERVED VALUE cm-1
C-C	1040
C=C	1646
C=O	1653
C-H	2963
O-H	3324

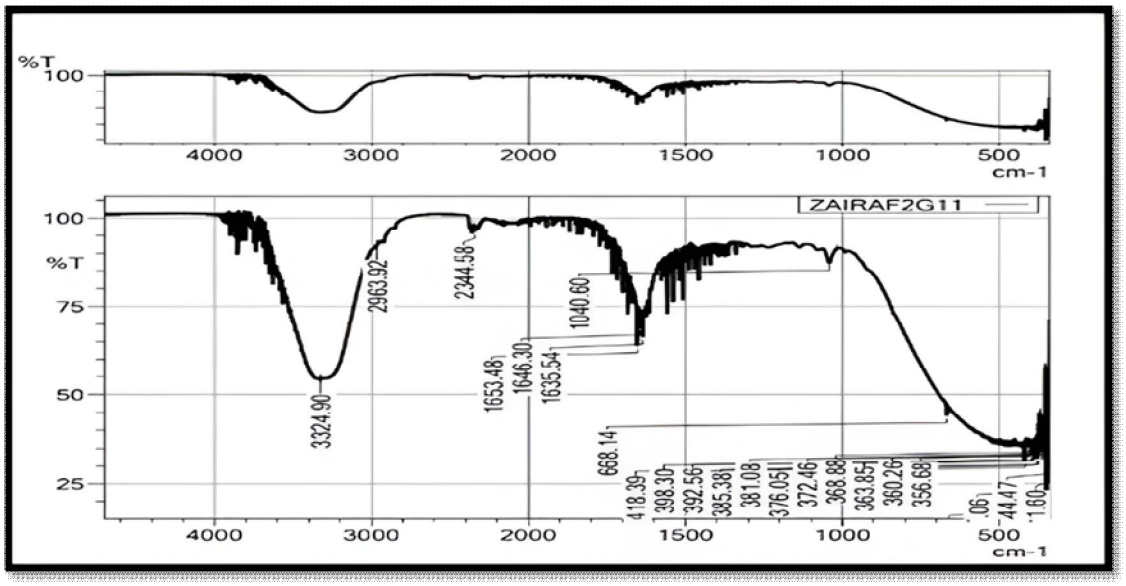

Figure: 3 FTIR Spectra of optimized formulation.

Particle size, Polydispersity Index (PDI), and Zeta potential Measurement

The optimized batch nanoemulsion particle size was determined to be 100 nm. Particle size decreases with increased homogenization speed. and the optimized nanoemulsion PDI approaches zero, i.e., 0.194, which indicates that the droplet size of the formulation is highly homogeneous and consistent, as illustrated in (fig:4). Zeta potential, in accordance with The ICH recommendations for stability studies for different drug formulations demonstrate the continued stability of the (colloidal dispersion) nanoemulsion under extreme circumstances. The smallest possible size of particle in nano size i.e., 100 has an impact on zeta potential, as illustrated in (fig: 5) displays -32 mV.

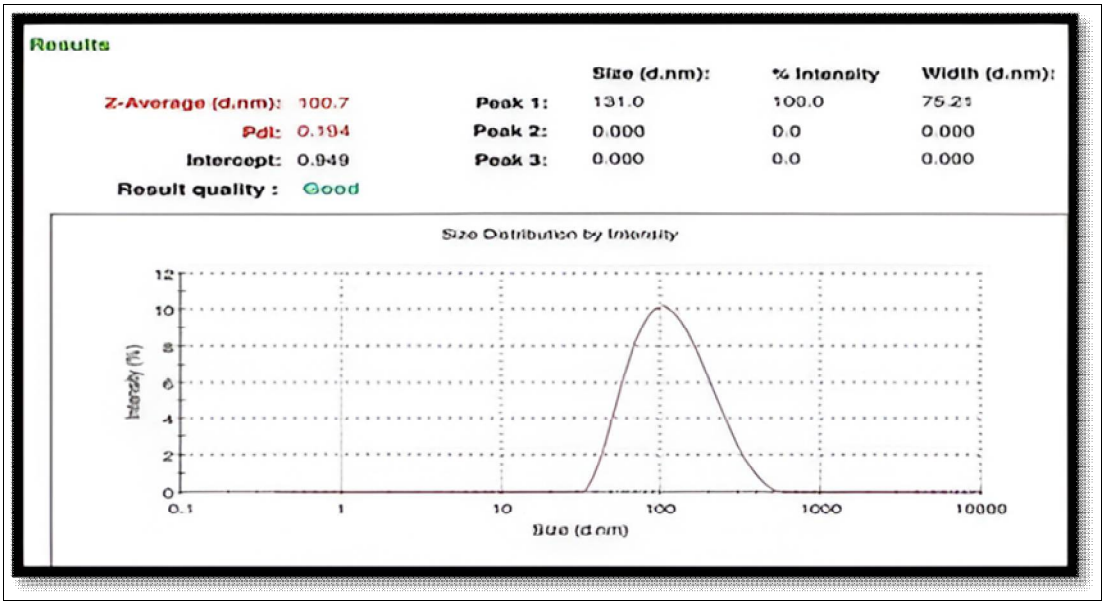

Figure: 4 Particle size and PDI of optimized Nanoemulsion.

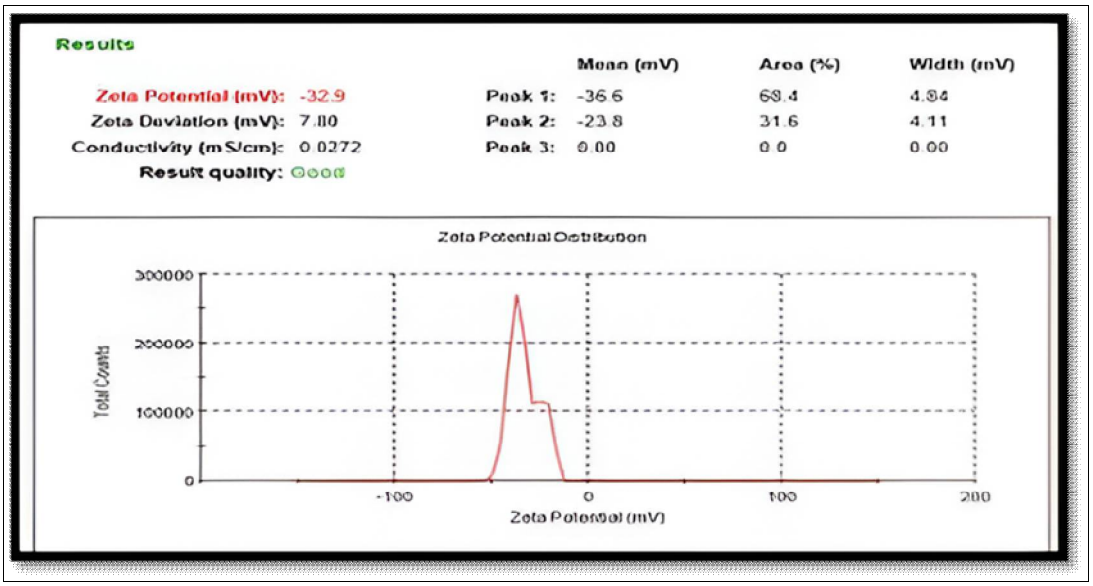

Figure: 5 Zeta potential of the optimized Nanoemulsion.

Caffeine nanoemulgel formulation were designed by combining the drug nanoemulsion into Carbopol 934 hydrogel using the self-emulsification technique.Nanoemulgel F7 presented a mean droplet diameter equal to ~ 204 nm with -44mV zeta potential as shown in (fig:6 & 7) respectively. The polydispersity index (PDI) was less than 0.5 appropriate as per the literature [19].

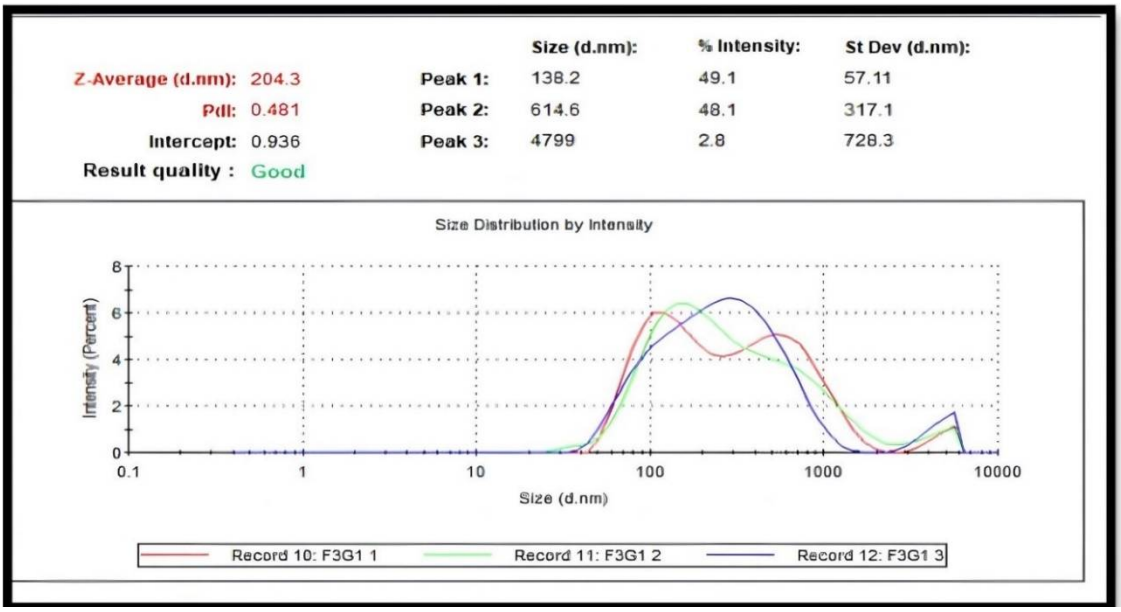

Figure: 6 Particle size and PDI of optimized Nanoemulgel.

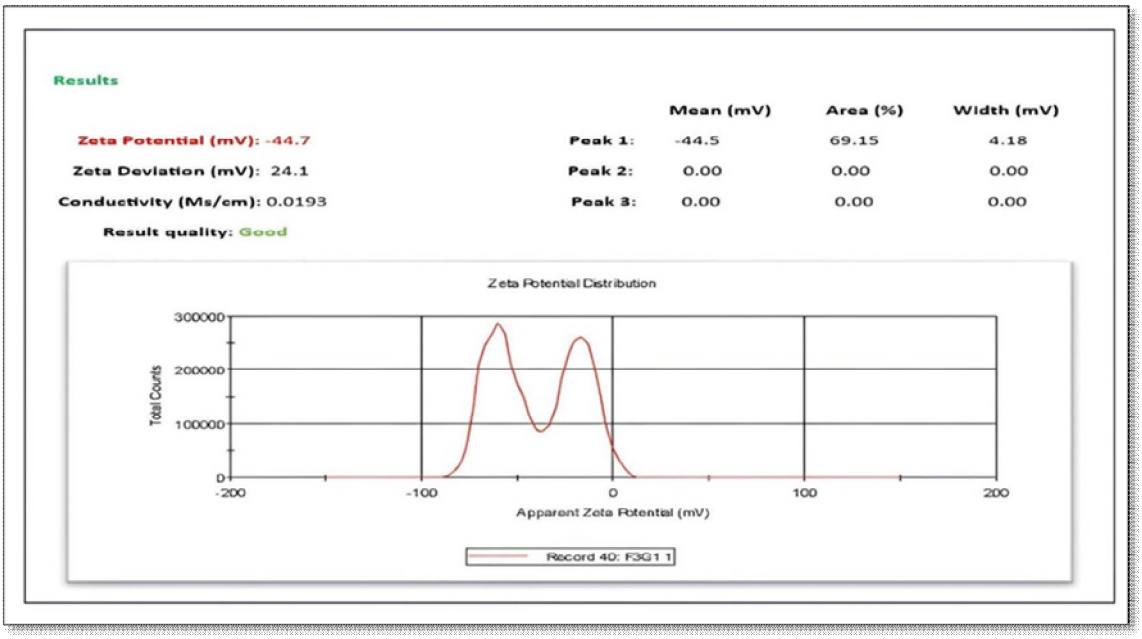

Figure: 7 Zeta potential of the optimized formulation.

pH Measurement

All nanoemulgel compositions were deemed appropriate for topical application on the skin because their pH ranged from 5.4-5.9.

Viscosity Measurement

Evaluation of rheological properties is critical for semisolid forms, such as our developed drug, because it indicates the effectiveness as well as the standard of the formulation. Outcomes are presented in the (table:3).

Table: 3: Viscosity associated with various formulations at varying speeds

Speed	F1	F2	F3	F4	F5	F6	F7	F8	F9
10 RPM	40,150	40,000	40,450	40980	41,212	41,009	41,442	40,994	41,180
30 RPM	26,654	25,114	26,554	26,980	27,331	27,004	27,492	26,987	27,225
50 RPM	19,450	18,750	19,550	19,888	20,224	20,004	20,616	19,900	20,114
60 RPM	16,745	15,645	16,945	17,225	17,815	17,515	17,938	17,360	17,645
100 RPM	10,010	10,000	10,110	10,220	10,612	10,357	10,742	10,117	10,555

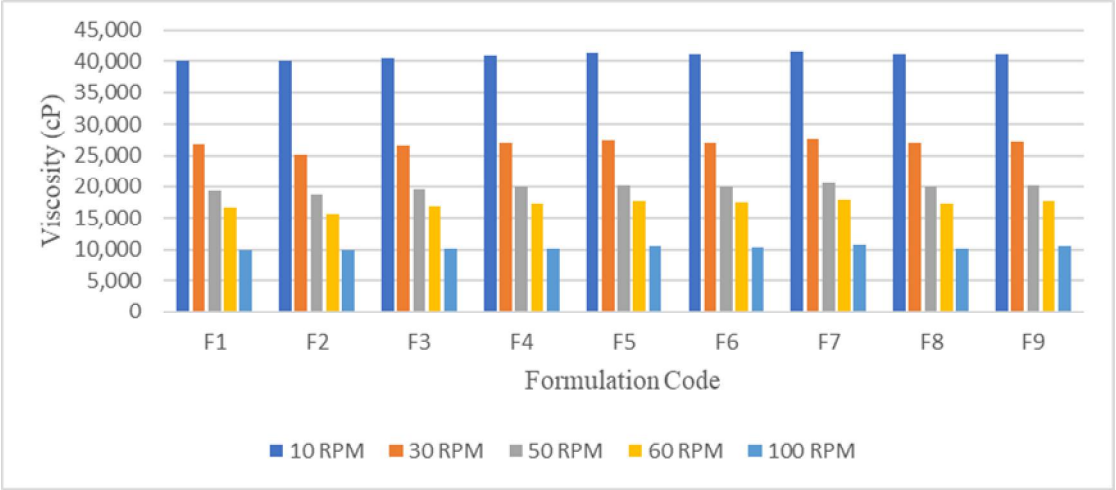

Figure: 8 Viscosity of different formulations.

Samples were permitted to rest at room temperature for 30 minutes before measurement, nanoemulgels were rotated using spindle 5 at 10, 30,50, and 100 rpm, then viscosities were measured (fig:8). In addition, the viscosities reduced with increasing shear rate, indicating that the nanoemulgel formulations exhibited pseudoplastic behavior.

Spreadability Measurement

Spreadability exhibits a reverse correlation with viscosity of the nanoemulgel as with the increase in the viscosity, spreadability decreases (table:4), Formulation F7, having optimum spreadability 18.53 g cm/sec.

Extrudability Measurement

For all formulations, extrudability was determined using the method provided (table:4) and results showed that among all formulations, F7 has good extrudability as it is easily extrudable.

Swelling index Measurement

The swelling index was calculated using the prescribed method, which focuses on the quantity of liquid content that can be absorbed. Among the nine formulations (table:4), the F7 formulation has a maximum swelling index.

Drug Entrapment Efficiency Measurement

Entrapment efficiency is referred to as the amount of medication entrapped within the polymer. Several factors influence drug entrapment efficiency in nanoemulgel. Some include the nature of the drug, polymer concentration, drug-polymer ratio, and stirring rate. All the prepared formulations complied with the pharmacopeial limits for drug content. Drug entrapment efficiency in the developed nanoemulgel formulations was found to be between 79.47- 89.81% (table:3), with optimized formulation F7 having maximum %Drug Entrapment Efficiency i.e., 98.81 (fig:9).

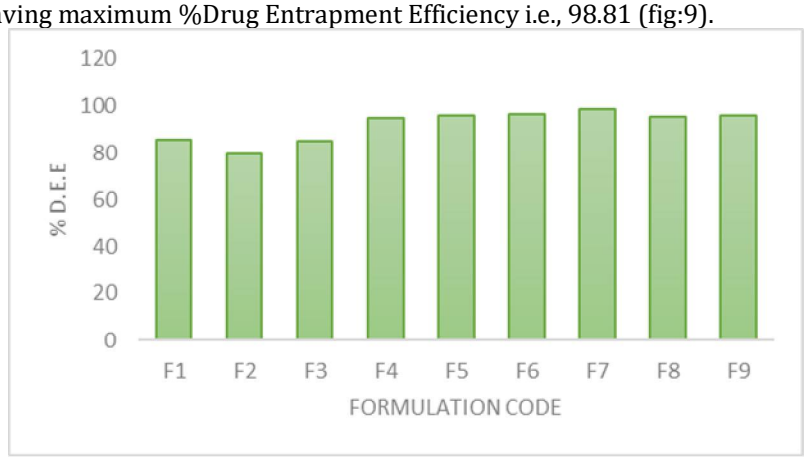

Figure:9 % Drug Entrapment Efficiency of formulations.

Table: 4 Spreadability, Extrudability, Swelling Index and Drug Entrapment Efficiency of different formulations.

S. No	Formulation code	Spreadability (g.cm/sec) ±SD	Extrudability ± SD	Swelling Index	Drug Entrapment Efficiency (%) ± SD
1.	F1	17.77 ± 0.025	10.75 ± 0.01	74	85.21 ± 0.5
2.	F2	16.00 ± 0.035	10.57 ± 0.02	72	79.47 ± 0.7
3.	F3	15.23 ±0.028	10.51 ± 0.02	70	84.89 ± 0.7
4.	F4	15.68 ±0.018	13.61 ± 0.01	85	95.09 ± 0.5
5.	F5	14.09 ±0.032	16.14 ± 0.03	87	96.09 ± 0.7
6.	F6	14.77± 0.012	16.02 ± 0.01	86	96.15 ± 0.9
7.	F7	13.53± 0.012	17.53 ± 0.04	94	98.81 ± 1.02
8.	F8	15.43 ± 0.011	15.21 ± 0.01	89	95.41 ± 0.87
9.	F9	14.04 ± 0.018	16.66 ± 0.01	90	96.10 ± 0.43

Release of Caffeine from the Formulation

Release of Caffeine from Nanoemulgel compositions were examined utilizing a release test. The Carbopol 934 method of preparation as a thickening agent was also important in selecting the best method of preparation for the preparation of the hydrogel used in the nanoemulgel formulations. The drug was dissolved in the nanoemulgel formulations and was tested for its release from the nanoemulgel formulations (table:5).

Table: 5 % CDR of various formulations

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	12.49 ±1.2	13.65±0.34	13.99±0.68	14.22±0.34	15.59±0.22	14.18±0.5	16.21±0.24	14.36±0.41	14.54 ±0.47
2	35.67 ±0.68	34.58±1.22	35.21±0.15	33.57±0.14	39.48±0.54	33.87±0.14	40.98±0.57	35.51±0.47	36.41 ±0.71
3	55.26 ±1.24	54.35±1.24	63.85±0.24	63.74±0.47	64.58±0.74	64.69±0.47	65.31±0.75	65.11±1.47	65.97 ±1.30
4	68.91 ±0.52	68.74±0.21	79.12±0.42	77.84±0.39	77.81±1.62	78.36±0.21	79.71±0.42	79.47±0.02	78.55 ±0.04
6	79.66 ±0.30	78.99±1.20	89.78±1.54	86.78±1.21	87.91±1.02	87.56±1.08	88.92±1.02	88.74±1.04	87.71 ±1.02
12	90.54 ±1.01	93.75±0.04	93.61±0.04	92.87±0.06	94.87±0.07	93.68±0.42	94.98±0.72	93.71±0.54	95.64 ±0.62

The release profiles for the various formulations are shown in (fig:10).

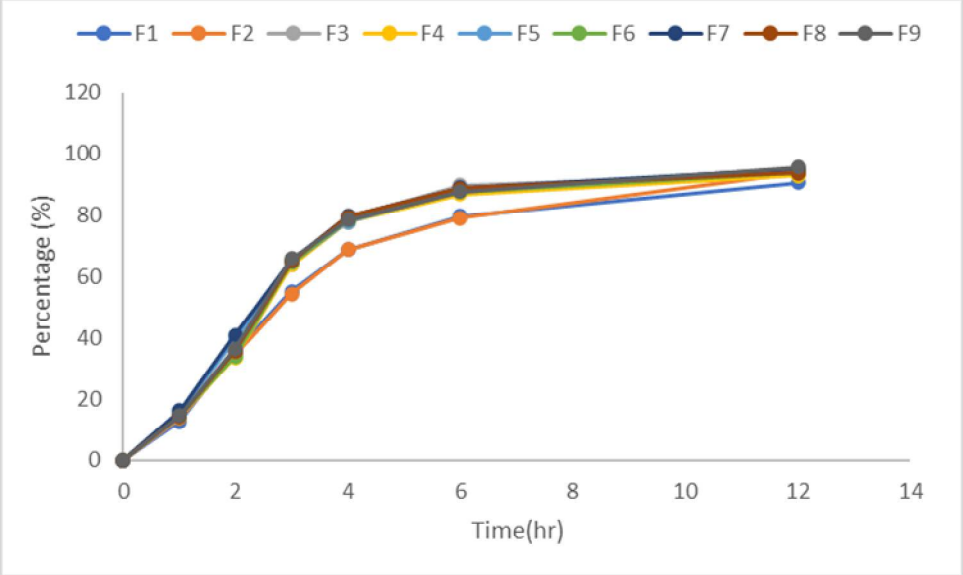

Figure: 10 % CDR of different formulations.

It was notable that the formulation with the Carbopol 934 formulating method of 24 hr gel with drug concentration. 1 % presented the highest release profile among other formulations.

Mechanism of Drug Release

For the purpose of studying the mechanism of Caffeine release from nanoemulgel, the release data were modeled by zero order, first order, Higuchi square root of time, and Korsmeyer - Peppas equations. With the drug release plot, linearity was observed by Korsmeyer Peppas model as the regression coefficient (r^2) was found to be higher, i.e., 0.9733 for formulation (F7), the other formulations (F1-F9) also followed the Korsmeyer model with increased values. This indicated that these formulations follow Fick's law of diffusion. Formulation F7 was found to have a release exponent (n) value of 0.3013, while for other eight formulations found optimum values were found, which supports the argument that all formulations follow Fickian diffusion. When the concentration of the drug was increased, having optimal gelling agent concentration with the increase of speed of rotation in the formulating method with G1(24 hr), the mechanism of drug release changed tremendously, and it was seen that these formulations exhibited first-order drug release. The data have been compiled in (table:6).

Table:6 Kinetic models of different formulations

Parameter	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero-order	0.767	0.7799	0.6891	0.7043	0.6988	0.6889	0.6908	0.6852	0.6912
First order	0.9763	0.9548	0.9418	0.9677	0.9835	0.932	0.9923	0.946	0.9532
Higuchi	0.9321	0.9288	0.9407	0.9402	0.9413	0.9413	0.9426	0.9418	0.9414
Peppas	0.9926	0.9894	0.9476	0.9479	0.9716	0.9395	0.9733	0.9448	0.9497
n value	0.3314	0.3506	0.344	0.3548	0.3114	0.3502	0.3013	0.3388	0.3345
k value	5.6971	5.6532	5.8447	5.784	5.95	5.8072	6.0093	5.8594	5.8823
Release Mechanism	Fickian	Fickian	Fickian	Fickian	Fickian	Fickian	Fickian	Fickian	Fickian

Accelerated Stability Studies

The developed nanoemulgel formulations revealed no signs of instability, such as creaming, settling, or turbidity. Furthermore, there was no significant difference in the values of pH and drug content following the stability test, exhibiting that the formulations are stable and F7 was stable for the entire period (table:7).

Table:7 Stability profile of different formulations

Time	Physical Appearance	Ph	Drug entrapment (%)
0 day	+++	6.5	98.2
30 days	+++	6.5	98.2
60 days	++	6.45	97.4
90 days	++	6.45	97.3

Box Behnken Design formulation optimization.

Three-level Box Behnken Design (BBD) (Design Expert version-13) was used to optimize the nanoemulgel formulation. Compared to a standard factorial technique, BBD may be a better choice for minimizing the number of runs and producing a higher-order response surface with fewer runs needed. Three factors were chosen as independent variables: carbopol 934 concentration (A), homogenization speed (B) and homogenization time (C). The dependent variables were chosen to be the particle size (Y1), PDI (Y2) and percent drug release (Y3). On the basis of the design, twelve formulations were produced. Formulations F1–F12 were coded. Optimization is the term used to describe how the responses alter when all three factors are altered at once, (table:8) displays the independent variables coded values. To ascertain how independent variables affected the responses, three-dimensional plots were created. It uses a 3D graphical representation to show how independent variables affect the responses. For every response variable, polynomial models were created, including interactions. Multiple regression analysis of the data and F-statistics were used to find statistically significant terms in order to evolve the models.

Table:8 Coded values for independent variables

Coded Value	Actual Value		
	Carbopol 934 (%)	Homogenization speed (rpm)	Homogenization time (min)
-1	1	1500	60
0	2	2000	90
1	3	2500	120

Nanoemulgel formulation optimization by Box Behnken Design

To investigate the impact of Carbopol 934, homogenization speed, and homogenization time on particle size, PDI, and percent drug release, a total of 12 runs were conducted using the Box-Behnken design, (table:9)reports the observed effect of the responses.

Table:9 Formulation Optimization using Box Benken Design

Formulation Code	Factor A: Carbopol 934 (%)	Factor B: Homogenization speed (rpm)	Factor C: Homogenization time (min)	Particle Size (nm)	PDI	% drug release
F1	0	1	1	142	0.3	97.15
F2	0	1	-1	205	0.6	92.78
F3	0	-1	-1	114.6	0.2	93.48
F4	-1	-1	0	215	0.7	92.42
F5	0	-1	1	246	0.7	91.48
F6	1	0	1	225	0.2	95.16
F7	-1	1	0	123	0.3	95.06
F8	1	-1	0	119	0.4	88.46
F9	1	0	-1	175	0.3	90.32
F10	-1	0	-1	224	0.3	94.15
F11	1	1	0	241	0.4	95.18
F12	-1	0	1	212	0.6	95.68

Data optimization:

A second-order polynomial model was used to estimate the ideal point by correlating the relationship between the response and the independent variables.

Critical factors impact on particle size (A):

The results of the ANOVA demonstrated that the regression model used to anticipate the particle size was statistically significant. The model's F-value (5.20) was substantially higher than the P value < 0.05, as shown in (table:10). When a model exhibits a notable lack of fit, it is not well-fitting and has low prediction efficiency. Compared to the significance level (0.05), the p-value for the lack of fit test was higher (0.0455). It thus shows the non-significant lack of fit value that is preferred for a suitable model. It was discovered that the regression coefficient, $R2$ adjusted, and $R2$ predicted for the model were 0.6959 and 0.2038, respectively.

Polynomial equation:

Particle size = 186.50 – 1.75 A + 2.05 B + 13.30 C + 53.50 AB + 15.50 AC – 48.60 BC ... (1)

Table:10 Analysis of variance

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	23331.08	6	3888.51	5.20	0.0455	
A-Carbopol 934	24.50	1	24.50	0.0327	0.8635	
B-Homogenization speed	33.62	1	33.62	0.0449	0.8405	
C-Homogenization time	1415.12	1	1415.12	1.89	0.2275	significant
AB	11449.00	1	11449.00	15.30	0.0113	
AC	961.00	1	961.00	1.28	0.3085	
BC	9447.84	1	9447.84	12.62	0.0163	
Residual	3742.20	5	748.44			
Cor Total	27073.28	11				

Fit Statistics

Std. Dev.	27.36	R^2	0.8618
Mean	186.80	Adjusted R^2	0.6959
C.V. %	14.65	Predicted R^2	0.2038
		Adeq Precision	5.9249

The effect of Carbopol 934 and homogenization speed and homogenization time on particle size in the 3D response plots indicated that as the Carbopol 934 ratio rises, particle size falls because of its notable reduction in viscosity, which results in smaller droplets. Additionally, the size of the particles decreases and becomes smaller as the homogenization speed increases, and the size of the particles increases as the homogenization time increases because particles collide and grow larger if force is applied for a longer amount of time.

Critical factors impact on PDI (B):

The results of the ANOVA showed that the regression model used to predict the particle size was statistically significant, (table:11) shows that the model's F-value (5.24) was significantly higher, with a P value < 0.05. When a model exhibits a notable lack of fit, it is not well-fitting and has low prediction efficiency. Compared to the significance level (0.05), the p-value for the lack of fit test was higher (0.0447). In other words, it shows the non-significant lack of fit value that is ideal for a suitable model. It was determined that the regression coefficient, adjusted *R*2, and predicted *R*2 values for the model were 0.6982 and 0.2099, respectively.

Polynomial equation:

PDI = 0.4167 – 0.0750 A – 0.0500 B + 0.0500 C + 0.1000 AB – 0.1000 AC – 0.2000 BC ...(2)

Table: 11 Analysis of variance

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.3250	6	0.0542	5.24	0.0447	
A-Carbopol 934	0.0450	1	0.0450	4.35	0.0913	
B-Homogenization speed	0.0200	1	0.0200	1.94	0.2229	
C-Homogenization time	0.0200	1	0.0200	1.94	0.2229	
AB	0.0400	1	0.0400	3.87	0.1063	significant
AC	0.0400	1	0.0400	3.87	0.1063	
BC	0.1600	1	0.1600	15.48	0.0110	
Residual	0.0517	5	0.0103			
Cor Total	0.3767	11				

Fit Statistics

Std. Dev.	0.1017	R^2	0.8628
Mean	0.4167	Adjusted R^2	0.6982
C.V. %	24.40	Predicted R^2	0.2099
		Adeq Precision	6.4401

Based on the 3D response plots, the impact of homogenization speed and Carbopol 934 (figure-..) proposed that homogenization time and Carbopol 934 have no effect on PDI, and that PDI decreases with increasing homogenization speed because it aids in uniformly dispersing and reducing droplet size. Only the homogenization speed influences the desired PDI; the Carbopol 934 ratio and homogenization time have no discernible effects on PDI.

Critical factors impact on % drug release (C):

The results of the ANOVA showed that the regression model used to predict the particle size was statistically significant, (table: 12) shows that the model's F-value (7.11) was significantly higher, with a P value < 0.05. When a model exhibits a notable lack of fit, it is not well-fitting and has low prediction efficiency. Compared to the significance level (0.05), the p-value for the lack of fit test was higher (0.0240). In other words, it shows the non-significant lack of fit value that is ideal for a suitable model. It was discovered that the regression coefficient, adjusted *R*2, and predicted *R*2 values for the model were, 0.7693 and 0.3961, respectively.

Polynomial equation

% drug release = 93.44 – 1.02 A + 1.79 B + 1.09 C + 1.02 AB + 0.8275 AC + 1.59 BC ... (3)

Table: 12 Analysis of variance

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	60.65	6	10.11	7.11	0.0240	significant
A-Carbopol 934	8.38	1	8.38	5.90	0.0594	
B-Homogenization speed	25.67	1	25.67	18.07	0.0081	
C-Homogenization time	9.55	1	9.55	6.72	0.0487	
AB	4.16	1	4.16	2.93	0.1477	
AC	2.74	1	2.74	1.93	0.2237	
BC	10.14	1	10.14	7.14	0.0442	
Residual	7.10	5	1.42			
Cor Total	67.75	11				

Fit Statistics

Std. Dev.	1.19	R^2	0.8951
Mean	93.44	Adjusted R^2	0.7693
C.V. %	1.28	Predicted R^2	0.3961
		Adeq Precision	9.1296

The 3D response plots indicate that the percentage of drug content is positively influenced by both the amount of Carbopol 934 and the speed of homogenization (Figure ..). This is because higher concentrations of Carbopol 934 and increased homogenization speeds both contribute to the solubilization of the drug. Additionally, it was noticed that increasing the homogenization time led to a higher percentage of drug release.

CONCLUSION

Caffeine nanoemulgels have emerged as a viable strategy for combating skin aging, utilizing nanotechnology to improve stability and dermal distribution. A newly formulated caffeine nanoemulgel system employing high-energy emulsification methods attained superior physicochemical properties, characterized by droplet size of 204 and a polydispersity index (PDI) about 0.481, signifying enhanced uniformity and stability. This nanoformulation improves caffeine solubility and skin permeability by leveraging the nanoscale dimensions of the delivery vehicle, allowing for deeper epidermal penetration via various routes. The system improved UV and storage stability is due to caffeine's encapsulation within the nanoemulsion matrix, which protects it from degradation while retaining its antioxidant and anti-aging characteristics. According to studies, such formulations considerably improve caffeine's efficiency in wrinkle reduction, skin suppleness, and the reduction of oxidative stress markers linked with photoaging.

REFERENCES

1. Shin SH, Lee YH, Rho NK, Park KY. (2023). Skin aging from mechanisms to interventions: focusing on dermal aging. Frontiers in Physiology. 10;14. DOI: 10.3389/fphys.2023.1195272L PMID: 37234413 PMCID: PMC10206231.
2. Zhang M, Lin Y, Han Z, Huang X, Zhou S, Wang S, Zhou Y, Han X, Chen H. (2024). Exploring mechanisms of skin aging: insights for clinical treatment. Frontiers in Immunology. 8;15. DOI:10.3389/fimmu.2024.1421858.
3. Herman, A.P., & Herman, A.P. (2012). Caffeine's Mechanisms of Action and Its Cosmetic Use. *Skin Pharmacology and Physiology, 26*, 8 - 14. DOI:10.1159/000343174.
4. Farias-Pereira R, Park CS, Park Y. (2019). Mechanisms of action of coffee bioactive components on lipid metabolism. Food Sci Biotechnol. 12;28(5):1287-1296. doi: 10.1007/s10068-019-00662-0. PMID: 31695927; PMCID: PMC6811484.
5. Verma, V. (2021). Nanoemulgel-A revolutionary approach for local gel-oriented formulation. *IP International Journal of Comprehensive and Advanced Pharmacology*, *6*(1), 28-30. DOI:10.18231/j.ijcaap.2021.005
6. Sayyam S. Jain, Ganesh D. Basarkar, Vishwaraj Deoda, Pragati Varpe, (2024). Advancements In Nano emulgel Formulations For Cosmeceutical Applications: A Comprehensive Review, Int. J. of Pharm. Sci., Vol 2, Issue 7, 356-369. https://doi.org/10.5281/zenodo.12670054.
7. Ansari, A., Verma, M., & Majhi, S. (2025). Nanoemulgel: A Comprehensive Review of Formulation Strategies, Characterization, Patents and Applications. *Micro and Nanosystems*, *17*(1), 12-26. DOI: 10.2174/0118764029316500240904074317
8. Chellapa P, Mohamed AT, Keleb EI, Elmahgoubi A, Eid AM, Issa YS, Elmarzugi NA. (2015). Nanoemulsion and nanoemulgel as a topical formulation. IOSR J Pharm. ;5(10):43-7.
9. Fernando, W. T., Neranja, A. G. K., & Kankanamge, S. U. (2022). A review on various plant-derived nanoemulgels and their applications. *World Journal of Advanced Research and Reviews*, *15*(3), 214-221. DOI: https://doi.org/10.30574/wjarr.2022.15.3.0916

10. Donthi MR, Munnangi SR, Krishna KV, Saha RN, Singhvi G, Dubey SK. Nanoemulgel: a novel nano carrier as a tool for topical drug delivery. Pharmaceutics. 2023 Jan 3;15(1):164. doi: 10.3390/pharmaceutics15010164
11. Mandal, S., & Vishvakarma, P. (2023). Nanoemulgel: A smarter topical lipidic emulsion-based nanocarrier. *Indian J of Pharmaceutical Education and Research*, *57*(3s), s481-s498. DOI: 10.5530/ijper.57.3s.56.
12. Kumar M, Bishnoi RS, Shukla AK, Jain CP. (2019). Techniques for Formulation of Nanoemulsion Drug Delivery System: A Review. Prev Nutr Food Sci. 24(3):225-234. doi: 10.3746/pnf.2019.24.3.225. Epub 2019 Sep 30. PMID: 31608247; PMCID: PMC6779084.
13. Haider F, Khan BA, Khan MK. Formulation and evaluation of topical linezolid nanoemulsion for open incision wound in diabetic animal model. AAPS PharmSciTech. 2022 Apr 28;23(5):129. doi: 10.1208/s12249-022-02288-8.
14. Harshitha, V., Swamy, M. V., Kumar, D. P., Rani, K. S., & Trinath, A. (2020). Nanoemulgel: A process promising in drug delivery system. *Research Journal of Pharmaceutical Dosage Forms and Technology*, *12*(2), 125-130. DOI: 10.5958/0975-4377.2020.00022.1.
15. Priyadarshini P, Karwa P, Syed A, Asha AN, (2023). Formulation and Evaluation of Nanoemulgels for the Topical Drug Delivery of Posaconazole, Journal of Drug Delivery and Therapeutics. 13(1):33-43 DOI: http://dx.doi.org /10.22270/jddt.v13i1.5896.
16. Freire TB, Dario MF, Mendes OG, Oliveira AC, Vetore A, Faria DL, Silva VR, Baby AR, Velasco MV. (2019). Nanoemulsion containing caffeine for cellulite treatment: characterization and in vitro evaluation. Brazilian Journal of Pharmaceutical Sciences. 24;55. https://doi.org/10.1590/s2175-97902019000218236.
17. Sintov, A. C., & Greenberg, I. (2014). Comparative percutaneous permeation study using caffeine-loaded microemulsion showing low reliability of the frozen/thawed skin models. *International Journal of Pharmaceutics*, *471*(1-2), 516-524. DOI: 10.1016/j.ijpharm.2014.05.040
18. Burki, I. K., Khan, M. K., Khan, B. A., Uzair, B., Braga, V. A., & Jamil, Q. A. (2020). Formulation development, characterization, and evaluation of a novel dexibuprofen- capsaicin skin emulgel with improved in vivo anti-inflammatory and analgesic effects. AAPS PharmSciTech, 21, 1-14. DOI: 10.1208/s12249-020-01760-7.
19. Khan BA, Ahmad N, Alqahtani A, Baloch R, Rehman AU, Khan MK. (2024). Formulation development of pharmaceutical nanoemulgel for transdermal delivery of feboxostat: physical characterization and in vivo evaluation. European Journal of Pharmaceutical Sciences. 1;195. DOI: 10.1016/j.ejps.2023.106665
20. Elmataeeshy, M. E., Sokar, M. S., Bahey-El-Din, M., & Shaker, D. S. (2018). Enhanced transdermal permeability of Terbinafine through novel nanoemulgel formulation; Development, in vitro and in vivo characterization. Future journal of pharmaceutical sciences, 4(1), 18-28. DOI:10.1016/j.fjps.2017.07.003.
21. Algahtani MS, Ahmad MZ, Nourein IH, Ahmad J. (2020). Co-delivery of imiquimod and curcumin by nanoemugel for improved topical delivery and reduced psoriasis-like skin lesions. Biomolecules. 27;10(7):968. doi: 10.3390/biom10070968
22. Khan, B. A., Ullah, S., Khan, M. K., Alshahrani, S. M., & Braga, V. A. (2020). Formulation and evaluation of Ocimum basilicum-based emulgel for wound healing using animal model. *Saudi pharmaceutical journal*, *28*(12), 1842-1850. https://doi.org/10.1016/j.jsps.2020.11.011