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Development And In Vitro Characterization of Submicron Emulsion Gel of Tretinoin

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ABSTRACT:
The present study aimed to develop and evaluate a tretinoin-loaded submicron emulsion gel for topical drug delivery. Tretinoin is a lipophilic drug used in the treatment of acne and other skin conditions. A submicron emulsion-based gel system was developed to improve drug incorporation and provide a suitable topical formulation. Preformulation studies included organoleptic evaluation, melting point determination, solubility studies, partition coefficient determination, UV spectrophotometric calibration, and Fourier-transform infrared (FTIR) analysis. Submicron emulsions were prepared using soybean oil as the oil phase, lecithin as the emulsifier, and poloxamer 188 (F68) as a co-emulsifier, followed by high-speed stirring and probe sonication. The optimized emulsion was subsequently incorporated into a Carbopol gel base at different polymer concentrations and evaluated for appearance, pH, drug content, viscosity, and in vitro drug release.
Among the prepared emulsions, formulation X6 exhibited the highest drug content of 87.10 ± 0.41%, with a mean globule size of 148.52 nm, a polydispersity index (PDI) of 0.124, and a zeta potential of −28.75 mV. The optimized gel formulation, X6G2, containing 1.5% Carbopol 980, demonstrated a drug content of 99.42 ± 0.36% and a viscosity of 2396.62 ± 1.09 cP. In the in vitro drug release study, X6G2 released 99.35 ± 0.89% of the drug within 24 hours, compared with 42.10 ± 0.56% from the control gel. These findings indicate that the developed submicron emulsion gel showed promising in vitro characteristics and enhanced drug release compared with the control formulation. Further studies are required to establish its stability, skin permeation, and clinical performance.

KEYWORDS: Tretinoin, Emulsion, Gel, Emulgel, Topical drug delivery

I. Introduction

Submicron emulsions are tiny granular systems in the atomic size range which act as a carrier for drug molecules for enhancing the bioavailability of therapeutics. The size of submicron emulsion range within 10-1000nm. They are thermodynamically unstable isotropic systems in which emulsifying agents (surfactant and cosurfactant) are mixed along with two immiscible liquids to form a single phase. Submicron emulsions consist of oil, water, surfactant and cosurfactant. They are spherical in shape. They are classified as: o/w emulsion, w/o emulsion and bi-continuous emulsion [1].

The submicron emulsions have been widely used by researchers over the past few years due to the advantages they possess. A few advantages of submicron emulsions are:

- Due to their greater surface area and free energy submicron emulsions are effective carrier system for drugs.
- They do not show the problem of creaming, flocculation and sedimentation because they are kinetically stable.
- Submicron emulsions are easily applicable to skin or mucous membranes.
- They are non-toxic and non-irritant.
- They improve the solubility of lipophillic drugs due to their small size.
- Another inherent advantage invested in submicron emulsions is their ability to easily penetrate through the “rough” skin surface/mucous membrane due to their very small size and lipophillic nature, which makes them a suitable dosage form for the topical delivery of drugs.
- They possess enhanced rate of absorption.
- They are easy to make at the lab scale [2]

Submicron size emulsions have been widely used by researchers for their antimicrobial property, as mucosal vaccines, for targeted delivery of drugs which is very important in treatment of diseases like cancer, for the protection of drugs against degradation, for the delivery of cosmetics etc [3,4]

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Topical drug delivery can be defined as application of drug via skin to directly treat or cure the skin disorders. These topical drug delivery systems are generally used for local skin infection like fungal infection or where other route of administration are no suitable.1It can penetrate deeper into skin and hence give better absorption. Topical preparation prevents the GI-irritation, prevent the metabolism of drug in the liver so as increase the bioavailability of the drug. Topical preparations give its action directly at the site of action.

A gel is a two-component, cross linked three-dimensional network consisting of structural materials. The structural materials that form the gel network can be composed of inorganic particles or organic macromolecules, primarily polymers[2,7].

Tretinoin, also known as all-trans retinoic acid (ATRA), is a medication used for the treatment of acne and acute promyelocytic leukemia. For acne, it is applied to the skin as a cream, gel or ointment. For acute promyelocytic leukemia, it is effective only when the RARA-PML fusion mutation is present and is taken by mouth for up to three months. Topical tretinoin is also the most extensively investigated retinoid therapy for photoaging.[10]

Lecithin is a generic term to designate any group of yellow-brownish fatty substances occurring in animal and plant tissues which are amphiphilic – they attract both water and fatty substances (and so are both hydrophilic and lipophilic), and are used for smoothing food textures, emulsifying, homogenizing liquid mixtures, and repelling sticking materials. Lecithins are mixtures of glycerophospholipids including phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine. Lecithins have emulsification and lubricant properties, and are a surfactant. They can be completely metabolized (see inositol) by humans, so are well tolerated by humans and nontoxic when ingested; some other emulsifiers can only be excreted via the kidneys.[11]

II. Material and Methods

Tretinoin was obtained from TCI and excipients Ethanol was obtained from Chamgshu Yangyuan Chemical, China, Methanol, Tween 80, Sodium chloride, Disodium hydrogen phosphate from Finar Pvt. Ltd. Ahemadabad, Span 40 from LobaCheim Pvt. Ltd., Mumbai, Soyabean oil, Mustard oil from Avarice laboratories Pvt. Ltd, G.B Nagar, India. Coconut Oil, Potassium dihydrogen phosphate from Molychem, Mumbai.

III. Experimental work

3.1. Preformulation studies

3.1.1. Organoleptic properties (API)

The identification of Tretinoin was done by checking the physical appearance i.e. colour, odour, taste and state. It was recorded and kept as reference for comparing with the other batches during formulation.

3.1.2. Melting point

The melting point of the tretinoin was determined by using capillary method with melting point apparatus.

3.1.3. Partition coefficient

The drug compounds were dissolved in water (Milli-Q,pre-saturated with 1-octanol) to yield saturated solution. An equal volume of 1-octanol (pre-saturated with ultrapure water) was added to the aqueous solutions, and the mixtures were shaken mechanically for 60 min at room temperature. The samples were centrifuged to assist with bilayer formation. The sample was analysed using UV spectroscopy.
Partition coefficient of tretinoin was calculated by using the following formula:

$$\text{Partition coefficient} = \frac{Concentration\ of\ drug\ in\ organic\ phase}{Concentration\ of\ drug\ in\ aqueous\ phase}$$

API in both phases was determined by UV spectroscopy and partition coefficient was calculated using the equation.[18]

3.1.4. Preparation of standard calibration curve

A Stock Solution of 100 µg/mL was prepared by dissolving 10 mg tretinoin in 1ml of the DMF and further diluted using the methanol up to the mark of the volumetric flask.Various aliquots of working stock solutions were transferred to 10 mL volumetric flasks so as to prepare various alternate clear working standard dilutions of 5, 10, 15, 20, 25, 30, 35, 40, 45 µg/mL and 9µg/mL, and volume was made upto mark with methanol. The calibration curve was prepared from these dilutions against clear blank by taking the absorbance of the prepared standard dilutions at absorption maxima 357nm. [20]

3.1.5. Drug and excipients compatibility studies

Fourier transform infrared (FTIR) analysis studies of pure drug and selected formulation was conducted

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for studying the compatibility and to determine if there are any possible drug excipients interactions The prepared samples were scanned in the range from 400cm-^{1}-4000cm-^{1}

3.1.6. Solubility Studies

The solubility of tretinoin in various solvents like water, methanol, ethanol, 0.1NHcl and phosphate buffer Ph6.8 was determined by dissolving an excess amount of tretinoin in 1ml of each of selected solvents in stoppered vials. The mixtures were continuously stirred using vortex mixer for 10 min and kept at 37°C ± 0.5°C in water bath shaker for 24h to attain equilibrium. The equilibrated samples were centrifuged (3000 rpm for 15 min) and supernatant was filtered through 0.45 µm membrane filter and diluted with methanol. Drug content was quantified by using ultraviolet-visible (UV-VIS) spectrophotometer (Shimadzu-1700, Japan) at 357 nm. [20,21]

3.2. Preparation of tretinoin loaded Submicron Emulsion

The tretinoin, phospholipid and α-tocopherol (0.3%w/w) were dissolved in soybean oil at 55°C. The water, F68, and glycerol (2.5%w/w) were mixed at 55°C. The lipid phase was stirred at 55°C at 2,000 rpm by high-speed stirrer, and the water phase was slowly injected into the lipid phase to obtain coarse emulsion. A fine emulsion was prepared by passing the coarse emulsion through a probe sonication. Sonication conditions were typically 60% amplitude for 1min. at 25°C. Afterwards, the formulation was filtered through a 0.45µm by using a novel membrane filter. After filtration, the emulsion was packed in plastic bottles and sterilized by autoclaving at 121°C for 15 min [21-23].

Table 1: Composition of tretinoin loaded submicron emulsion

S.No.	Formulation code	Tretinoin (%w/w)	Soybean oil (%w/w)	Soybean Phospholipids (%w/w)	Poloxamer F68 (%w/w)	Sonication amplitude (%)
1	X1	0.05	5	1.0	0.1	60
2	X2	0.05	10	1.0	0.1	60
3	X3	0.05	15	1.0	0.1	60
4	X4	0.05	20	1.0	0.1	60
1	X5	0.05	15	0.8	0.1	60
2	X6	0.05	15	1.2	0.1	60
3	X7	0.05	15	1.8	0.1	60

3.3. In vitro characterization

3.3.1. Physical appearance

All of the prepared formulations underwent visual inspection to check for the presence of drug particles and the transformation of solid ingredients into liquid solutions.

3.3.2. pH analysis

The drug-loaded submicron emulsion sample weights were determined, and the corresponding volume of deionized water was added to dissolve the samples. The prepared solutions were maintained at 23±2°C. The Ph electrode was dipped into the each solution and record the pH of the each solution [21-23].

3.3.3. Percentage drug content

The test formulation were centrifuged at 18,000g for 30 minutes (4C) in order to separate the incorporated drug and the nonincorporated drug. The tretinoin was analyzed by UV for the unincorporated drug concentration to determine the entrapment percentage. EE% could be achieved by the following equation:

$$Percentage\ drug\ content = \frac{Initial\ drug - Drug\ in\ supernatent}{Initial\ drug} \times 100$$

3.3.4. Measurement of Globule size and Zeta Potential

The average hydrodynamic diameter of nanogels was determined by DLS and the nanogel surface charge was assessed by zeta potential measurements, using a Zetasizer Nanoseries instrument from Malvern Instruments. Samples were prepared in water. The DLS measurements were performed over alternating increasing and decreasing temperature cycles; at each temperature the sample

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was equilibrated for at least 3 min before performing the measurement. The average hydrodynamic diameter of nanogels under consideration corresponded to the Z-average value measured by DLS1. The zeta potential measurements were performed at 25ºC. All study was done in triplicate [24].

3.4. Method of Formulation of Submicron emulsion based Topical gel

The submicron emulsion formulation was improved, and a gel basis was added because the nano-emulsion has a very low viscosity for topical distribution. By adjusting the concentration of carbopol 980 as 1%, 1.5%, and 2%, the gel was produced. The necessary amount of carbopol was soaked in enough submicron emulsion formulation for 24hr and next triethanolamine was added to neutralizing the pH of the carbopol. For Submicron emulsion-based gel optimization, the following factors were assessed [25].

Table 2: Composition of different Submicron emulsion gel formulations

S.no.	Formulation code	Drug Concentration (%w/w)	Concentration of Carbopol 980(%w/w)
1	X6G1	0.05	1
2	X6G2	0.05	1.5
3	X6G3	0.05	2

3.5. Evaluation of tretinoin loaded submicron emulsion gel

3.5.1. Homogeneity

After being put in the container, all developed gels were visually inspected to determine their homogeneity. For appearance and the presence of any aggregates, they underwent testing [25]

3.5.2. Measurement of pH

A digital pH meter was used to measure the pH of different formulations. After being dissolved in 100 ml of distilled water, 1 g of gel was let to stand for two hours. Each formulation's pH was tested in triplicate, and the average values were computed. The topical gel formulation's pH should be between 3–9 to treat the skin infections [25]

3.5.3. Drug content

Each gel formulation's weighted 1 gm were added to a 250 ml volumetric flask with 20 ml of alcohol and swirled for 30 minutes. The volume was filtered and increased to 100 ml. Once more, 1 ml of the aforementioned solution was diluted to a final concentration of 10 ml with alcohol after being previously diluted to 1 ml. At 357nm, the solution's absorbance was determined spectrophotometrically [25]

3.5.4. Viscosity study

A Brookfield viscometer DVII model with a T-Bar spindle in conjunction with a helipath stand was used to measure the gel's viscosity. The viscosity of the gels was measured using the T-bar spindle (T95). Temperature, pressure, sample size, and other variables. which affected the viscosity was preserved throughout the procedure. Viscosities were provided at various locations along the path by moving the helipath T-bar spindle up and down. The torque value was consistently higher than 10%. The viscosity of gels was determined by taking an average of three readings in a minutes [25].

3.5.5. In vitro drug release study

The Franz diffusion equipment was used to measure the release of tretinoin from its submicron emulsion gel. The membrane was dipped in the medium for 24 hours before to use. The membrane was installed between the donor and receiver compartments of the Franz diffusion cell, on which the gel was evenly spread over the majority of the surface. The donor chamber of the Franz diffusion apparatus was filled with a precisely calculated amount of gel (1gm). The device's receiver chamber filled with 30 ml of phosphate buffer, pH 7.4. The experiment was conducted at a constant speed of 50 rpm at a temperature of 37 °C. At regular intervals, aliquots were taken out, filtered using a sterile Millipore filter, and the amount of medication was measured spectrophotometrically at 357 nm. The outcomes were the average values across three runs [26].

IV. Result and Discussion

4.1 Preformulation studies

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4.1.1 Organoleptic properties

The tretinoin drug appeared as yellow-to-light-orange crystalline powder. It is known for having a characteristic, sometimes unpleasant, floral.

4.1.2 Melting point

Melting point of tretinoin was determined by capillary method. It was almost same to reference value that confirms the purity of the drug.

Table 3: Value of Melting point of tretinoin

Drug	Specification	Observation
Tretinoin	180-182°C	180.33^{0}C±0.58-182±1.00

4.1.3 Standard Calibration curve of tretinoin in Methanol

Standard calibration curve was plotted in the range between 5-50µg/ml by plotting graph between absorbance and concentration. Absorbance of different concentration solutions of tretinoin as shown in table 4. The calibration curve of tretinoin as shows in graph 1 Indicated the value of regression equation y =0.016x+0.0103 with R^2 = 0.9994

Table 4: Calibration curve between absorbance and concentration of tretinoin in methanol

Concentration (µg/ml)	Absorbance
5	0.092±0.003
10	0.178±0.003
15	0.249±0.001
20	0.327±0.002
25	0.403±0.003
30	0.482±0.002
35	0.577±0.002
40	0.647±0.004
45	0.728±0.002
50	0.816±0.002

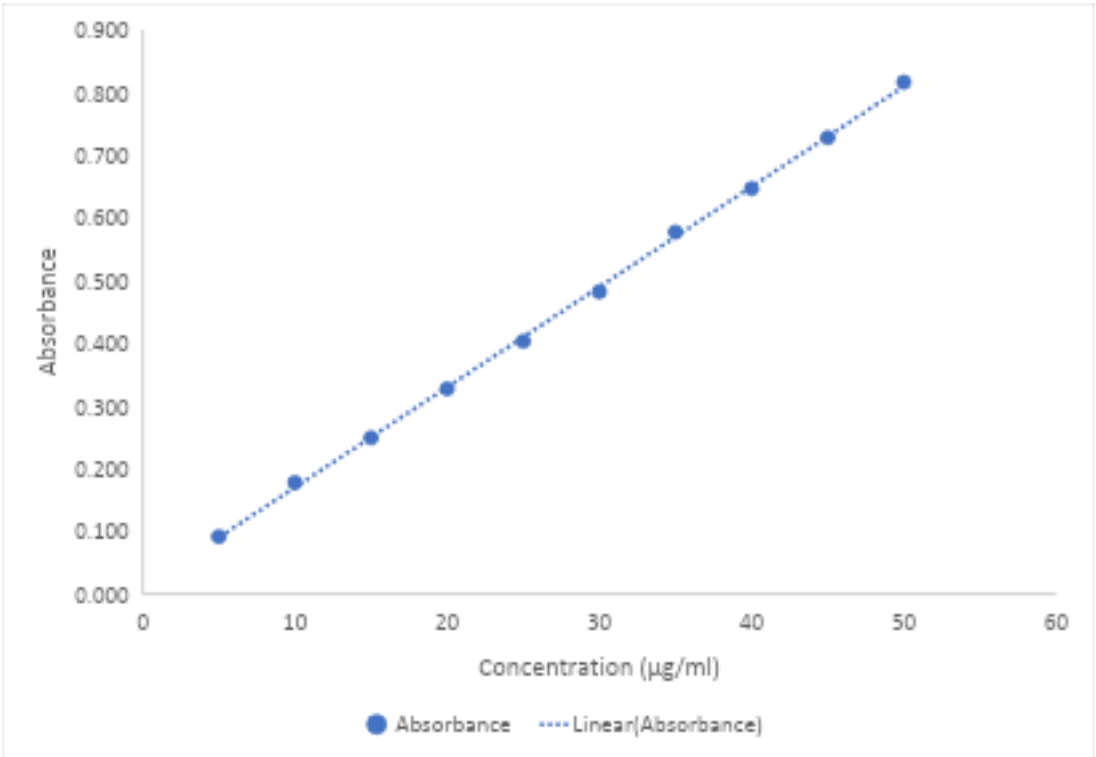

Figure 1: Graph of Standard Calibration curve between absorbance and concentration of tretinoin in methanol

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4.1.4 Solubility studies of drug

The solubility of drug was determined in water pH 6.8 and in different solvents.

Table 5: Value of Solubility (mg/ml) of tretinoin in different solvents.

Solvent	Solubility (mg/ml)
Water	0.164±0.013
Methanol	8.366±0.346
Ethanol	7.083±0.095
0.1NHcl	2.928±0.044
Phosphate Buffer 6.8pH	3.298±0.038

Table 5 displayed tretinoin showed maximum solubility in alcohol followed while in distilled water it displayed minimum solubility.

4.1.5 Partition coefficient of drug:

Partition coefficient of tretinoin in n-octanol: water mixture was shown in table 6.

Table 6: Value of Partition coefficient of tretinoin

S. No.	Drug	Partition coefficient (Log P)	Nature of the drug
1.	Tretinoin	6.29±0.059	Lipophilic

4.1.6 FT-IR spectra

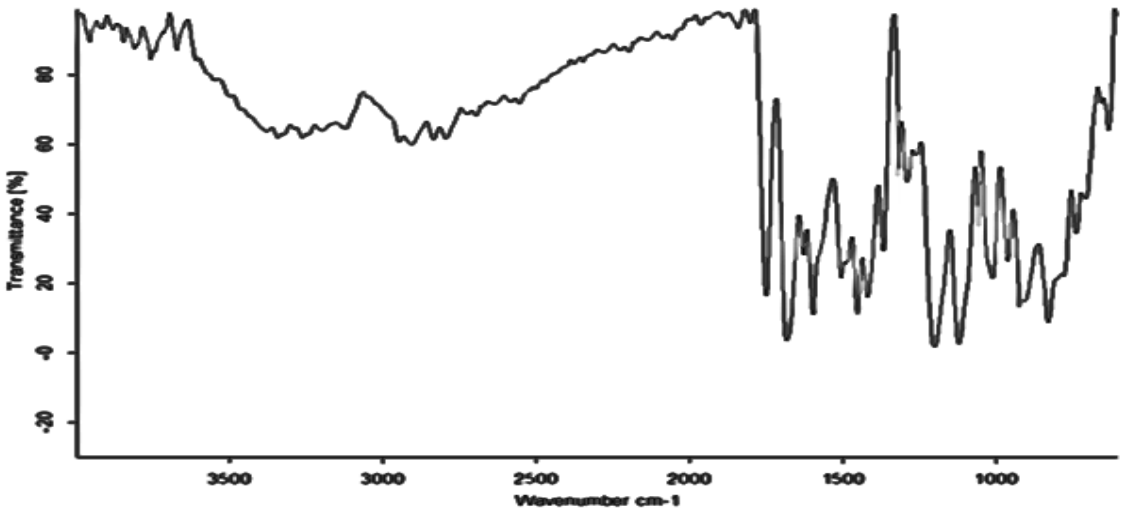

Figure 2: Graph of FTIR spectrum of tretinoin

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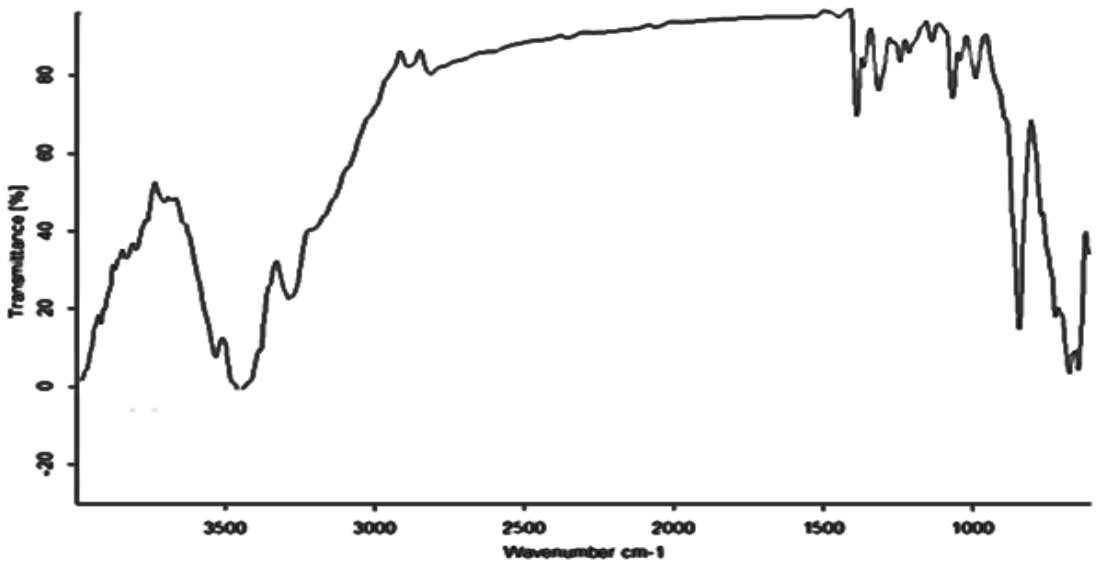

Figure 3: Graph of FT-IR Spectra of tretinoin loaded submicron gel

O-H stretching vibrations are shown by the peak at 3,489 cm−1, C = O stretching is represented by the band at 2785 cm−1, and the trans vinyl (CH = CH) groups of the molecule are shown by the peak at 923cm−1. FTIR spectrum of the optimized formulation displayed the characteristic peaks of the drug either disappeared or with reduced intensity indicated the unfirm distribution into the oil droplets.

4.2 Preparation of tretinoin loaded Submicron emulsion

Considering commercial emulsion product and characteristics of tretinoin loaded submicron emulsion, in this study, soybean oil was selected as oil phase, lecithin as the emulsifier, glycerol and poloxamer F-68 as co-emulsifier. Submicron-sized lipid emulsions were prepared using a high speed mixer followed by a ultrarsonication process. In this study, tretinoin was possess sufficient solubility in soybean oil and very less soluble in water.

4.3 In vitro characterization

4.3.1 Physical appearance

Physical appearance of the all investigated formulation were shown in table 7.

Table 7: Physical appearance of the all prepared formulation

Formulation code	Physical appearance
X1	Slight yellow, Uniform, homogenous, milky emulsion
X2	Slight yellow, Uniform, homogenous, milky emulsion
X3	Slight yellow, Uniform, homogenous, milky emulsion
X4	Slight yellow, Uniform, homogenous, milky emulsion
X5	Slight yellow, Uniform, homogenous, milky emulsion
X6	Slight yellow, Uniform, homogenous, milky emulsion
X7	Slight yellow, Uniform, homogenous, milky emulsion

4.3.2 pH

pH of the all prepared formulation were shown in table 8.

Table 8: pH of the all prepared formulations

Formulation code	pH
X1	5.860±0.015
X2	5.748±0.025
X3	5.638±0.010
X4	5.704±0.048

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X5	5.689±0.040
X6	5.879±0.087
X7	5.745±0.058

pH of the all prepared formulation were found to be in a range of the 5.648±0.010 to 5.879±0.087.

4.3.3 Percentage drug content

Percentage drug content of the all prepared formulations were shown below.

Table 9: Percentage drug content of the all prepared formulations

Formulation code	Percentage drug content (%)
X1	35.696±0.789
X2	59.236±0.845
X3	74.364±0.412
X4	72.255±0.021
X5	70.021±0.548
X6	87.102±0.410
X7	86.015±0.008

Percentage drug content of the all-prepared formulation was found to be in range of the 35.696±0.789% to 87.102±0.410%. The formulation X6 formulation possess maximum percentage of drug content 87.102±0.410%. As the amount of the oil increase the percentage drug content the tretinoin enhance because enhancement in amount of the oil will enhance the solubilization of the drug consequently the percentage drug content will enhance.

On the basis of above evaluation parameters X6 formulation was selected for further evaluation.

4.3.4 Particle size and Zeta Potential

Table 10: Average Globule size, PDI and Zeta Potential of GSME14 formulation

S.No.	Formulation code	Globule size (nm)	PDI	Zeta Potential (mv)
1	X6	148.52	0.124	-28.75

Globule size and value of PDI was found to be 148.52nm and 0.124.

4.4 Incorporation of Tretinoin loaded Submicron emulsion into carbopol gel

The optimized X6 formulation was added to a gel foundation containing various carbopol concentrations and tested for several in vitro characterization parameters, including pH, drug content, viscosity, and in vitro drug release studies.

4.5 Evaluation of tretinoin loaded Submicron emulsion into Carbopol gel

4.5.1 Visual Appearance of gel

Table 11: Appearance of all submicron emulsion gel formulation.

S. No.	Formulation code	Appearance	pH
1	X6G1	Uniform, less viscous homogenous and free from grottiness	5.468±0.145
2	X6G2	Uniform, less viscous homogenous and free from grottiness	5.581±0.231
3	X6G3	Uniform, less viscous homogenous and free from grottiness	5.640±0.843

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The gel's thickness grows as Carbopol concentration is increased. Whereas 2%w/w Carbopol gel was significantly thicker in texture, 1.5%w/w Carbopol gel was homogeneous and consistent in appearance. pH values for all gel formulations ranged from 5.468±0.145 to 5.640±0.843.

4.5.2 Percentage drug content

Table 12: Value and states of percentage drug content of all gel formulations

S.No.	Formulation code	Percentage drug content
1	X6G1	94.562±0.148
2	X6G2	99.421±0.362
3	X6G3	98.401±0.874

The range of drug content in all produced formulations was found to be between 94.562±0.148% to 99.421±0.362%. X6G2 were chosen for more investigation.

4.5.3 Viscosity of gel

Table 13: Viscosity of submicron emulsion embedded gel formulations

S.No.	Formulation code	Viscosity (Cp)
1	X6G1	1156.35±1.458
2	X6G2	2396.62±1.089
3	X6G3	3546.48±2.125

Viscosity measurements at various rpm revealed the gel's mechanical strength and flow characteristics. While the gel in a viscosity investigation remained homogeneous, there was no sign of gel disintegration. The formulation X6G2 possess adequate viscosity hence the formulation X6G2 was selected.

4.5.4 Percentage drug release study of Submicron emulsion embedded gel formulations

Table 14: Percentage drug study of submicron emulsion embedded gel formulations X6G2 and control gel

Time(Hr.)	Percentage drug release of Control gel	Percentage drug release of X6G2
0	0±0	0±0
0.25	2.56±0.26	9.56±0.41
0.5	8.569±0.19	18.41±0.62
1	14.02±0.18	28.62±0.84
2	18.52±0.56	36.56±0.42
4	25.41±0.67	51.02±0.51
6	30.45±0.85	66.84±0.54
8	36.58±0.25	79.01±0.33
10	39.41±0.34	89.51±0.28
12	42.12±0.84	99.45±0.150
24	42.1±0.56	99.35±0.89

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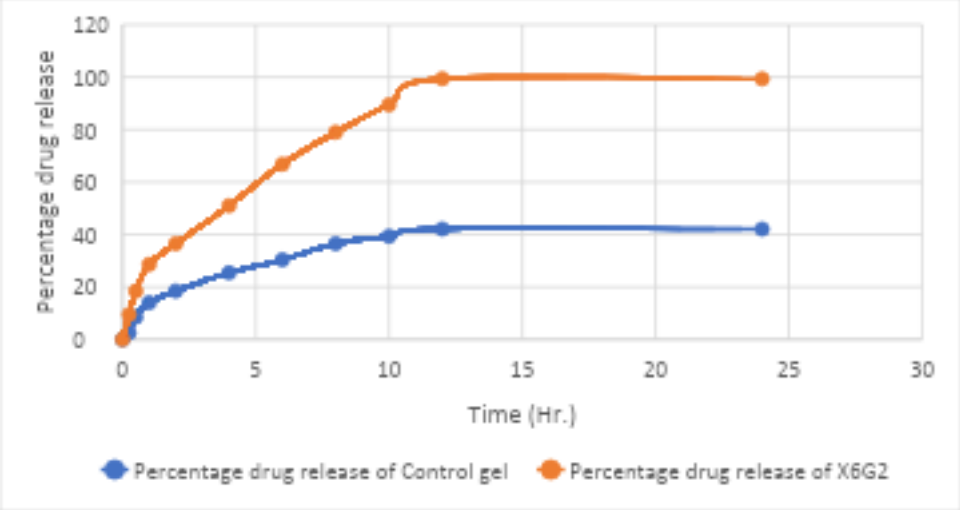

Figure 4: Comparison Graph of In-vitro drug release of control gel and X6G2 formulations

At 24 hours, it was discovered that both submicron emulsion gels had larger drug percentages than the control gel, however the release of tretinoin was discovered to be higher in the X6G2 gel than the control gel.

V. Conclusion

In current study the tretinoin was solubilized in the submicron emulsion droplet. The tretinoin drug appeared as yellow-to-light-orange crystalline powder. It is known for having a characteristic, sometimes unpleasant, floral. The melting point was found to be 180.33^{0}C±0.58-182±1.00°C. Standard calibration curve was plotted in the range between 5-50µg/ml by plotting graph between absorbance and concentration. The calibration curve of tretinoin as shows in graph 6 Indicated the value of regression equation y =0.016x+0.0103 with R^2 = 0.9994. tretinoin showed maximum solubility in alcohol followed while in distilled water it displayed minimum solubility. Considering commercial emulsion product and characteristics of tretinoin loaded submicron emulsion, in this study, soybean oil was selected as oil phase, lecithin as the emulsifier, glycerol and poloxamer F-68 as co-emulsifier. Submicron-sized lipid emulsions were prepared using a high speed mixer followed by a ultrarsonication process. In this study, tretinoin was possess sufficient solubility in soybean oil and very less soluble in water. pH of the all prepared formulation were found to be in a range of the 5.704±0.048 to 5.879±0.087. Percentage drug content of the all-prepared formulation was found to be in range of the 35.696±0.789% to 87.102±0.410%. The formulation X6 formulation possess maximum percentage of drug content 87.102±0.410%.

On the basis of above evaluation parameters X6 formulation was selected for further evaluation. Globule size and value of PDI was found to be 148.52nm and 0.124. In addition of negative zeta potential indicated is due to different polar head groups in the structure of lecithin and the arrangement of these emulsifiers at the oil–water interface, they confer negative (−28.75mV). The optimized X6 formulation was added to a gel foundation containing various carbopol concentrations and tested for several in vitro characterization parameters, including ph, drug content, viscosity, and in vitro drug release studies. Ph values for all gel formulations ranged from 5.468±0.145 to 5.640±0.843. The range of drug content in all produced formulations was found to be between 94.562±0.148% to 99.421±0.362%. X6G2 were chosen for more investigation. The formulation X6G2 possess adequate viscosity hence the formulation X6G2 was selected. At 24 hours, it was discovered that both submicron emulsion gels had larger drug percentages than the control gel, however the release of tenoxicam was discovered to be higher in the X6G2 gel than the control gel.

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