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Formulation and Evaluation of Hydroxyzine Loaded Nanoemulsion

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ABSTRACT

The present study was focused on the formulation and estimation of hydroxyzine dihydrochloride NE for topical use. Hydroxyzine dihydrochloride (API) was obtained from the Sigma Aldrich Pvt Ltd. The nanoemulsion was made by Spontaneous emulsification method and evaluated for parameters i.e., physical appearance, droplet size & polydispersity index (PDI), In-vitro drug release, % drug content, viscosity, pH & stability. The drug- hydroxyzine was tested for solubility in different solvents as enumerated below. Hydroxyzine was found poor soluble in solvents i.e., distilled water and peppermint oil. Particles size and particle size index was observed efficient for better drug release and bioavailability of incorporated drug that confirms for its uniqueness in the formulation. *In-vitro* drug release and viscosity are important factor behind the quality of formulated nanoemulsion. In the same context, these two factors showed optimistic behaviour of NE 0-NE 6. It concludes that NE 5 and NE 6 were most prominent nanoemulsion among all the NE subtypes. It also demonstrated a better stability that can be kept for a month without change in its pH, % drug release and In-vitro drug release.

INTRODUCTION

Topical routes can be used on the skin and vagina. These are applicable in a variety of circumstances. Various dermatological and cosmetic products, whether their skin is healthy or ill (Kshirsagar, 2000). Topical therapies were anointed, wrapped, rubbed or applied on to skin to treat skin conditions in ancient Egypt, according to the Ebers P., which dates to 1550BC (Ebbell, 1937).

The active components are more suited for numerous activities when they are present as nanoparticles because they have a higher surface-to-volume ratio that encourages dispersibility in the emulsion (Singh & Lillard, 2009).

Effective medication administration entails delivering medicines to the site of action in the shortest time possible. The term topical delivery refers to a module for treating local ailments that involves applying a formulation to the skin, eyes, nose, and vaginal area (Chen & Fang, 2000; Tripathi, 2013; Mycek et al. 2009). When a medicine is applied to the topical areas, it avoids pre-systemic metabolism, pH of stomach- disturbances and fluctuations in plasma conc. that occur often when a drug is delivered orally (Torin et al. 2011).

SLNs are prepared by solid lipids at room temp. & stabilized as nanodispersion by surfactant coating- surface (Muller et al. 2002) that make it easier to formulate and stabilize lipophilic chemicals like retinol, which are prone to breakdown in presence of light & O_2, promote stratum corneum deposition, and minimize flow (Zhang et al. 2014).

Previous studies suggests that nanoemulsion of hydroxyzine dihydrochloridehas not been formulated yet. So, present study was focused on the formulation and estimation of hydroxyzine dihydrochloride NE for topical use.

The diphenylmethylpiperazine class of antihistamines includes hydroxyzine. The molecular weights of hydroxyzine, hydroxyzine dihydrochloride, and hydroxyzine pamoate are, respectively, 374.9 g/mol, 447.8 g/mol, and 763.3 g/mol. As a result of their differences in molecular weight, 1 mg of hydroxyzine dihydrochloride is equivalent to roughly 1.7 mg of hydroxyzine pamoate.

Molecular formula- $C_{21}H_{29}Cl_3N_2O_2$

Molecular weight- 447.8

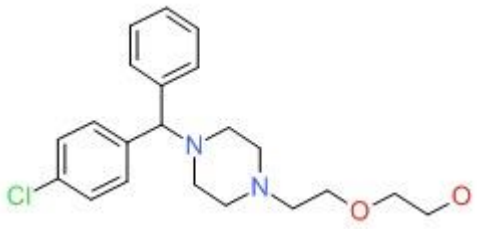

Fig. 1 Structure of hydroxyzine dihydrochloride

IUPAC name:2-(2-{4-[(4-chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethoxy)ethan-1-ol dihydrochloride

MATERIALS AND METHODS

Experimental requirements

Hydroxyzine dihydrochloride and Surfactant- PF127 (Sigma Aldrich, India), ethanol, dimethyl sulfoxide, Potassium bromide, 3-(4,5-dimethylthiazol-2-yl)- 2,5-diphenyltetrazolium bromide, phosphate buffered solution (PBS) and pH 7.2.

Preparation of formulation

The selection of the oil phase for the drug's solubilization is the initial stage. To create an oily phase, hydroxyzine solubility was initially investigated in mineral oil, fixed soybean, olive, grape, and sweet almond oils, as well as essential oils of clove, peppermint, and anise. The solubility test was predicted on the ability to see whether drug precipitates were present or absent in the oil. Until we reached a concentration of 100 mg in 1,000 litres, we added the oil to 100 mg of hydroxyzine at a rate of 100 litres.

Hydroxyzine was found more soluble in water, where it could be found at a concentration of 100 mg per 500ml. For the preparation, PF127 was chosen as the surfactant and peppermint essential oil as the oil phase.

Spontaneous emulsification method

The essential oil included dissolved hydroxyzine. Surfactant PF127 and preservative Novamit were dissolved in water to create the aqueous phase. In order to avoid heating the system, NEs were made by gradually integrating the oil phase into the aqueous phase using an ultrasonic processor. 15±8°C was kept as the temperature. The formulation was prepared and stored at 25°C, or room temperature. In order to assess the stability of the dispersion, we

changed the ratios of peppermint essential oil from 5% to 10% and the quantity of surfactant in the aqueous phase from 5% to 15%. We used size (mean diameter in nanometers), PDI, and appearance. Nanoemulsion was also prepared without using hydroxyzine as considered as control.

Table 1. Ingredients of Formulation (Oil phase)

Formulation	**Oil phase** ***Hydroxyzine (%)***	***Peppermint oil (%)***
NE 0	0	5
NE 1	0.5	5
NE 2	1	5
NE 3	1	5
NE 4	1	5
NE 5	1	7.5
NE 6	1	10

As table 1. Indicates that hydroxyzine was found much soluble in peppermint oil hence this essential oil used in development of nanoemulsion. NE1- NE6 were prepared in which NE 0 was kept as control that was deprived of addition of hydroxyzine (API) but other excipients were added i.e., surfactants.

Table 2. Ingredients of Formulation (Aqueous phase)

Formulation	**Aqueous phase** **PF127 (surfactant)** ***5 %***	***10 %***	***15 %***
NE 0	-	-	95
NE 1	-	-	94.5
NE 2	94	-	-
NE 3	-	94	-
NE 4	-	-	89
NE 5	-	-	91.5
NE 6	-	-	89

For formulation of nanoemulsion of hydroxyzine, aqueous phase was developed which was added into oil phase, later on. This phase was developed by addition of different proportions of surfactants- 5, 10 and 15%.

Table 3. Experimental conditions for formulation

Formulation	**Experimental conditions**		
	Amplitude (%)	***Cycle (%)***	***Time (min)***
NE 0	100	1	5
NE 1	100	1	5
NE 2	100	1	5
NE 3	100	1	5
NE 4	100	1	5
NE 5	100	1	5
NE 6	100	1	5

Table 3. Affirms about the experimental conditions required for the formulation of nanoemulsion. Experimental condition i.e., amplitude (%), cycle (%) and time (min) was kept similar in all the nanoemulsion subtypes while formulating NE 0- NE 6.

Characterization parameters

In order to characterization of nanoemulsion (NE) the following parameters were evaluated-

Physical appearance

Total 7 forms of Nanoemulsion were developed including NE0-NE6. All types were estimated for their physical appearance i.e., transparency, homogenous/heterogenous, white or turbidity.

Homogenous nanoemulsion is the sign of better formulation of nanoemulsion.

Droplet size & Polydispersity index (PDI)

Zetasizer Nano-ZS was used to measure the average globule size of the nanoemulsion (Malvern Instrument, UK). Measurements were taken at a 90-degree angle at 25ºC. To make sure the light scattering intensity was within the instrument sensitivity range, twice distilled

water was used to dilute the nanoemulsion. All measurements were made at 25c. The same instrument was used to calculate the formulation's polydispersity index. The polydispersity index revealed the width of the size distribution (Samadhan et al. 2019).

***In vitro* drug release**

When the pH of the PBS solution is 7.4, a small amount of the nanoemulsion is dissolved in it. The residual volume is then brought up to 100 ml with PBS after the solvent ethanol is added to make the polymer soluble (pH 7.4). After then, 1 ml is taken out of the solution and diluted once more up to 10 ml. At a wavelength of 270 nm, the solution's absorbance is measured, and concentration is determined.

A modified Franz diffusion cell was used to conduct in vitro diffusion. As a difusion cell, a glass cylinder of 10cm in height, 3.7 cm in outer diameter, and 3.1 cm in inner diameter was employed. To create a diffusion cell, a sheep mucosa was attached to one end of the cylinder via an. A cell was given 1 ml of the nanoemulsion, and the cell was then placed in the receptor compartment of a beaker containing 100 ml of pH 6.8 phosphate buffer. The receptor compartment was in touch with the whole surface of the cell, and a temperature of 37ºC was maintained while the receptor compartment was being churned magnetically. To keep the sink condition, 10ml of the receptor compartment samples were extracted and refilled with the same volume.

Percentage Drug content

In a 10ml volumetric flask, a specific amount of the formulation was taken and diluted with ethanol. The absorbance of the resulting solution was sonicated for three minutes at room temperature, and its absorbance was measured at a maximum of 240 nm against a blank (Samadhan et al. 2019)

Viscosity

At room temperature (23±2°C), the viscosity of a nanoemulsion was determined using a Brookfield viscometer. Three separate tests were carried out using two spindle speeds to measure viscosity (Makhmalzadeh et al. 2012).

pH

Calculating pH is a crucial component of the nanoemulsion evaluation process. The pH of the finished preparation and, consequently, the route of administration are determined by the excipients employed in the formulation. A digital pH metre was used to determine the formulation's pH. To decrease mistake, the findings were taken in three copies (Derie et al. 2008).

Stability

The stability of the nanoemulsion was investigated at 37°C for a month, respectively. Transparency was assessed in the sample. Every month for three months, check the % drug content, pH, and in-vitro drug release.

RESULTS AND DISCUSSION

Preformulation studies

Solubility

The drug- hydroxyzine was tested for solubility in different solvents as enumerated below. Hydroxyzine was found poor soluble in solvents i.e., distilled water & peppermint oil. It was found soluble in 0.1N HCl, ethanol and phosphate buffer. So, it may confirm that hydroxyzine is better soluble in acidic & basic aqueous environment with better solubility in amphoteric solvent-ethanol.

Table 4. Solubility of Hydroxyzine

Solvent	**Hydroxyzine**
Distilled water	Freely Soluble
0.1N HCl	Freely Soluble
Ethanol	Soluble
Peppermint oil	Poor Soluble
Phosphate Buffer	Soluble

Drug excipients compatibility studies

Hydroxyzine (API) was also tested for drug-excipients compatibility studies using FT-IR spectrum as single once and in formulation to compare.

This compatibility was recorded and demonstrated as below-

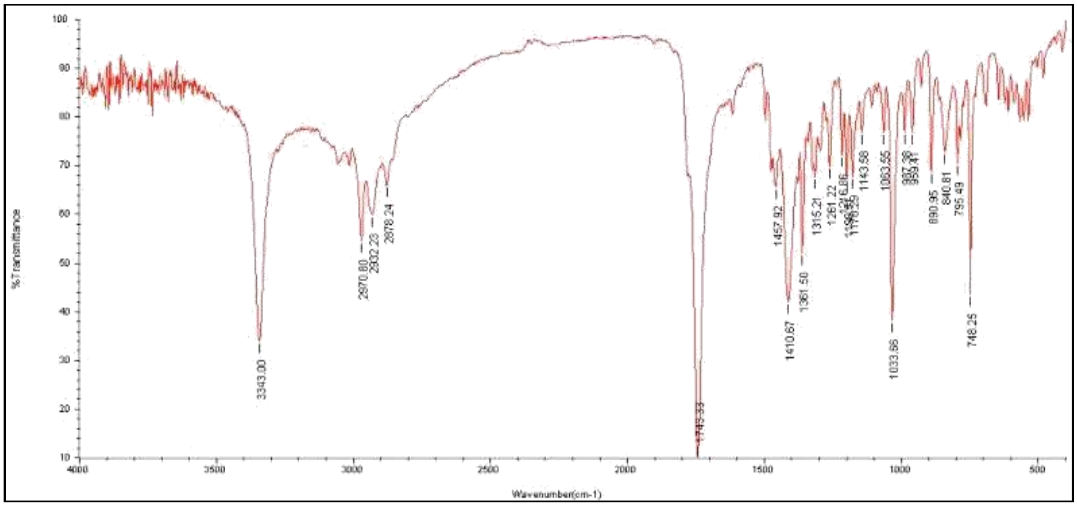

Fig 2. FT-IR representation of Hydroxyzine (API)

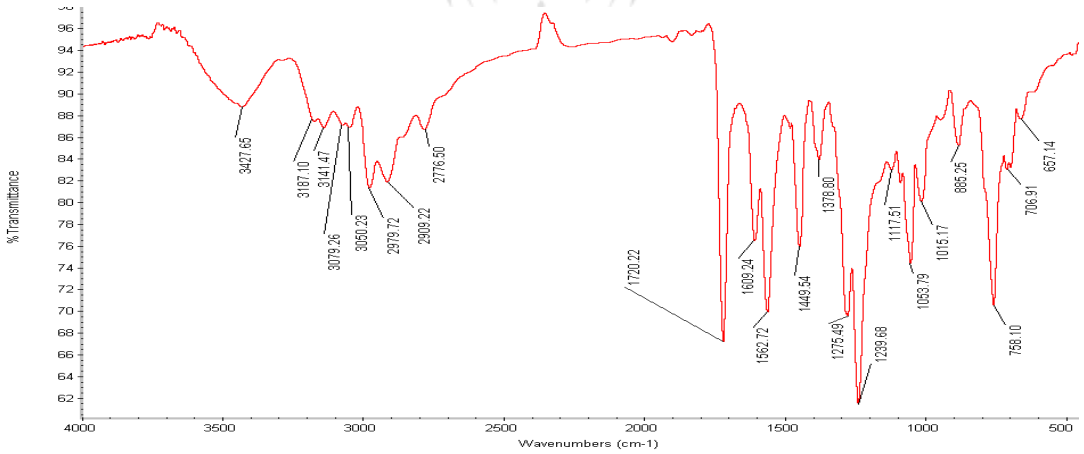

Fig 2. (a) FT-IR representation of NE 1

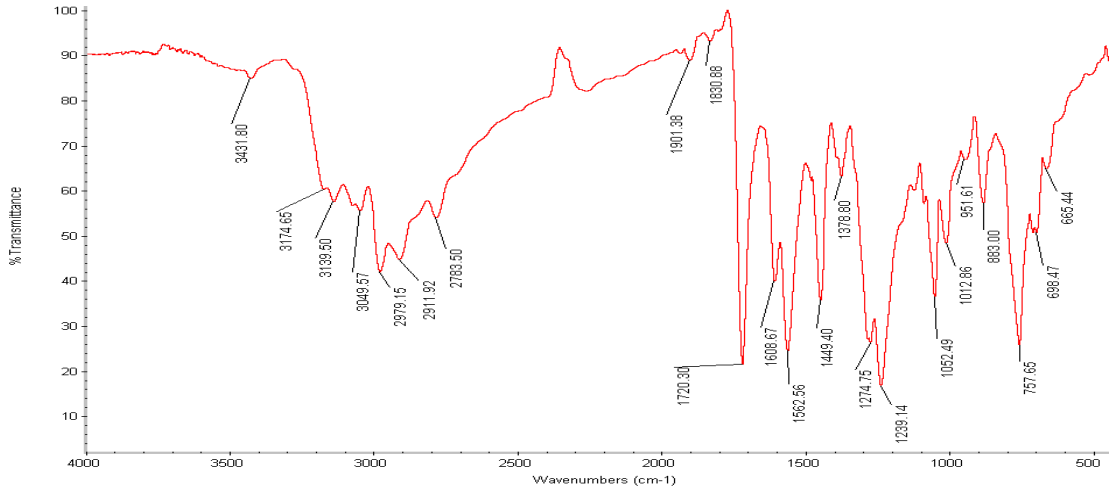

Fig 2.(b) FT-IR representation of NE 2

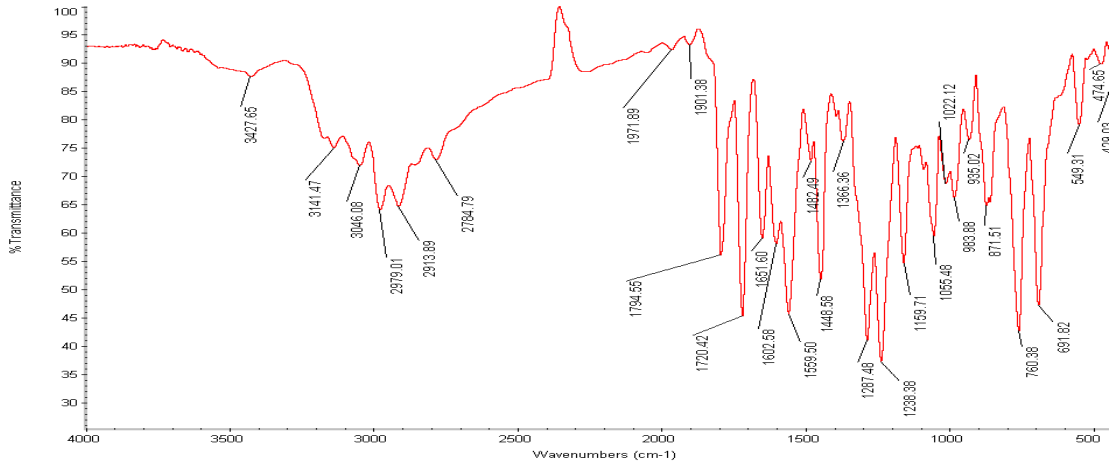

Fig 2.(c) FT-IR representation of NE 3

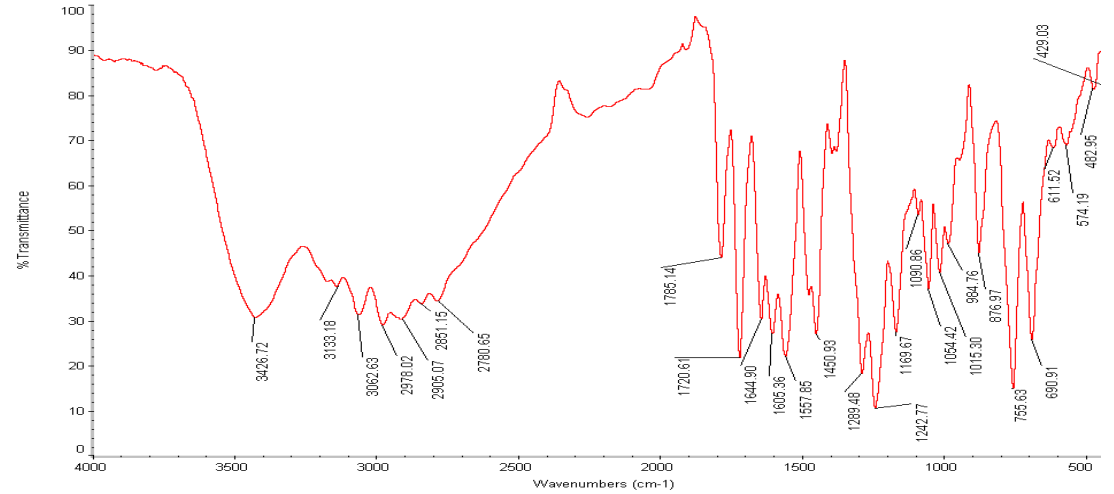

Fig 2.(d) FT-IR representation of NE 4

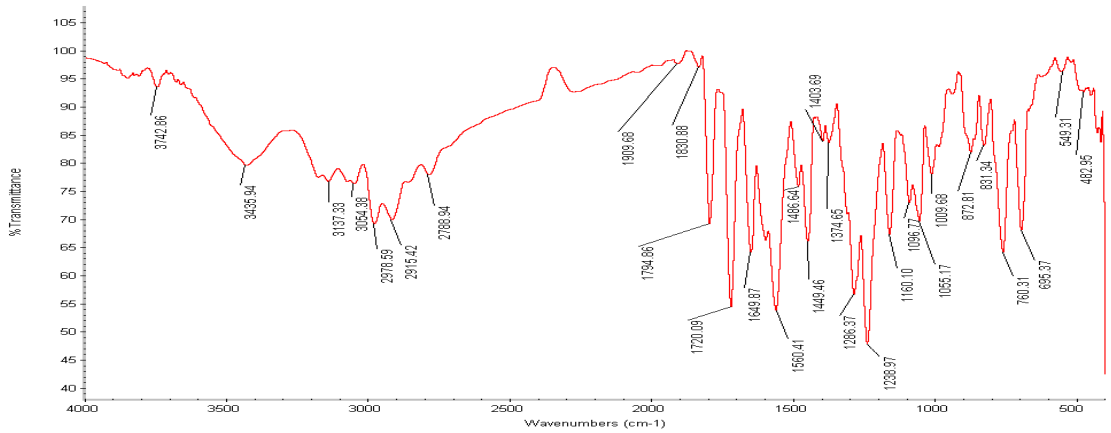

Fig 2.(e) FT-IR representation of NE 5

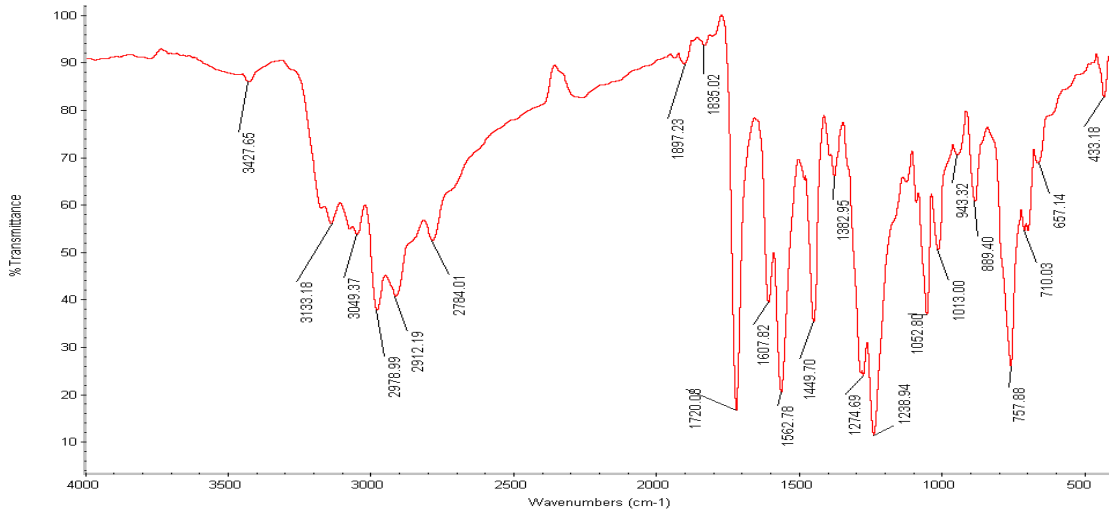

Fig 2.(f) FT-IR representation of NE 6

It has been determined that there are no significant shifts or functional peak losses between the drug and hydroxyzine nanoemulsion spectra that confirms for its better drug-excipient compatibility.

Standard calibration curve- hydroxyzine

To examine hydroxyzine, the UV Spectrophotometric technique was employed. At a wavelength of 274nm, the drug's absorbance in phosphate buffered saline pH 7.4 with a little amount of methanol was recorded. Hydroxyzine's standard curve in PBS pH 7.4 was linear from the origin to values of 2-10g/ml. Beer Lambert's law is observed by the curve. Following figure depicts the standard calibration curve for hydroxyzine-

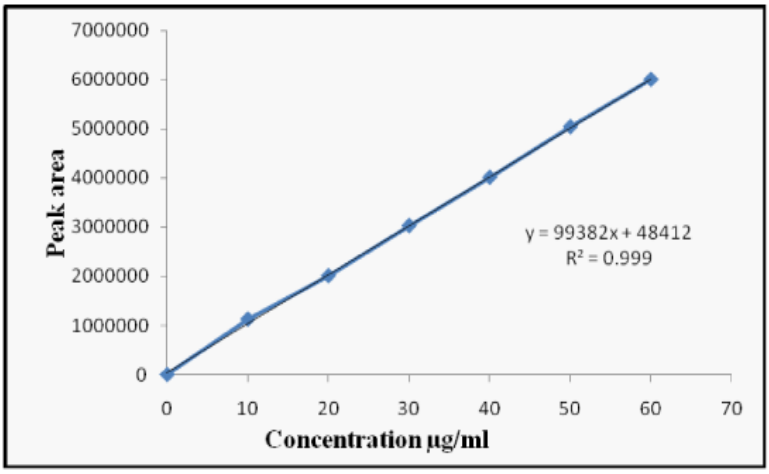

Fig 3. Std. calibration curve at pH 7.4 (PBS)

Evaluation

Physical appearance

In order to characterize total 7 forms of Nanoemulsion, NE 0- NE 6 were evaluated for their physical appearance i.e., transparency, homogenous/heterogenous, white or turbidity.

It showed that NE 0, NE 1, NE 5 & NE 6 were found as transparent & homogenous while NE 2, NE 3 & NE 4 were white & heterogenous. It represents that majority of the NE subtypes were developed in a significant manner with transparent and homogenous appearance.

Below table depicts the physical appearance of all formulated NE 0- NE 6.

Table 5. Physical appearance of formulated nanoemulsion

Formulation	Physical appearance
NE 0	Transparent & homogenous
NE 1	Transparent & homogenous
NE 2	White& homogenous
NE 3	White & heterogenous
NE 4	White & heterogenous
NE 5	Transparent & homogenous
NE 6	Transparent & homogenous

n=3, Values are expressed in Mean± SD

Determination of droplet size (nm)

Nanoemulsion's droplet size was estimated using nanodroplet analyser. Control formulation (NE 0) showed droplet size as 21.19±0.36. NE 1, NE 2, NE 3 and NE 4 showed droplet size in almost similar range as 24.20±0.27, 27.31±0.35, 28.40±0.26 and 29.40±0.26 respectively. Whereas, NE 5 & NE 6 exhibited droplet size as 263.51±1.63 and 232.43±1.27respectively, which are lowest among all.

Table 6. Determination of droplet size (nm)

Formulation	Droplet size (nm)
NE 0	21.19±0.36
NE 1	24.20±0.27
NE 2	27.31±0.35
NE 3	26.14±0.12
NE 4	28.40±0.26
NE 5	263.51±1.63
NE 6	232.43±1.27

n=3, Values are expressed in Mean± SD

Determination of Polydispersity Index

Polydispersity index (PDI) is an important factor in evaluation of topical dosage forms for their uniformity of particles. PDI was observed as 0.47±0.05 in NE 0. NE 1, NE 2, NE 3 and NE 4 demonstrated PDI in the same range as 0.49±0.07, 0.51±0.05, 0.38±0.02and 0.29±0.09 respectively.

But, PDI was estimated increased in the NE 5 & NE 6 as 0.71±0.02 & 0.85±0.05 respectively. It might be due to increased proportion of surfactants used during formulation of nanoemulsion.

Table 7. Determination of Polydispersity Index

Formulation	PDI
NE 0	0.47±0.05
NE 1	0.49±0.07
NE 2	0.51±0.05
NE 3	0.38±0.02
NE 4	0.29±0.09
NE 5	0.71±0.02
NE 6	0.85±0.05

n=3, Values are expressed in Mean± SD

***In-vitro* drug release**

Lowest *In-vitro* drug release was seen in NE 0 as 53.37±0.54. While, NE 1, NE 2, NE 3 and NE 4 showed in- vitro drug release as 83.47±0.35, 85.12±0.37, 85.39±0.58 and 84.53±0.72 respectively.

NE 5 and NE 6 showed release (in-vitro) as 86.10±0.84 and 88.25±0.64 %. It has efficient in vitro drug release among all the formulations.

Table 8. *In-vitro* drug release

Formulation	*In-vitro* drug release (%)
NE 0	53.37±0.54
NE 1	83.47±0.35
NE 2	85.12±0.37
NE 3	85.39±0.58
NE 4	84.53±0.72
NE 5	86.10±0.84
NE 6	88.25±0.64

n=3, Values are expressed in Mean± SD

Determination of % Drug content

The prepared nanoemulsions showed excellent % drug content in terms of better uniformity and concentration of drug. NE 0 exhibited % drug content as Nil as it did not keep any drug amount. Whereas NE 1, NE 2, NE 3 and NE 4 showed % drug content as 97.30±0.39%, 97.50±0.25%, 96.73±0.12% and 98.91±0.34% respectively. In NE 5 and NE 6, it was much more excellent as 96.62±0.21% and 98.57±0.17%.

All the formulations demonstrated a significant % drug release that indicates for homogenous drug release.

Below table depicts the % release of the formulation NE 0- NE 6.

Table 9. Determination of % Drug content

Formulation	% Drug content
NE 0	Nil
NE 1	97.30±0.39
NE 2	97.50±0.25
NE 3	95.73±0.12
NE 4	98.91±0.34
NE 5	96.62±0.21
NE 6	98.57±0.17

n=3, Values are expressed in Mean± SD

Determination of viscosity

Minimum viscosity was estimated in formulation NE 0 as 518.42±0.13. Whereas formulation NE 1, NE 2, NE 3 and NE 4 showed increased viscosity as 527.25±0.34, 526.27±0.25, 531.31±0.15 and 534.16±0.39, respectively. Highest viscosity was estimated in NE 5 and NE 6 as 536.17±0.23 and 534.36±0.22.

High viscosity reveals better adhere and absorption property as depicted in table 10 as below-

Table 10. Determination of viscosity

Formulation	Viscosity± S.D.
NE 0	518.42±0.13
NE 1	527.25±0.34
NE 2	526.27±0.25
NE 3	531.31±0.15
NE 4	534.16±0.39
NE 5	536.17±0.23
NE 6	534.36±0.22

n=3, Values are expressed in Mean± SD

Measurements of pH

The pH was measured for better tolerability and absorption property. pH was estimated as 6.3±0.3 in NE 0. While pH was measured as 6.4±0.2, 6.5±0.2, 6.7±0.1 and 6.6±0.3 in NE 1, NE 2, NE 3 and NE 4 respectively. Whereas, high alkaline pH was estimated in formulation NE 5 and NE 6 as 6.6±0.1and 6.7±0.1.

The following table 11 demonstrates the measurement of pH of NE 0- NE 6.

Table 11. Measurements of pH

Formulation	pH± S.D.
NE 0	6.3±0.3
NE 1	6.4±0.2
NE 2	6.5±0.2
NE 3	6.7±0.1
NE 4	6.6±0.3
NE 5	6.6±0.1
NE 6	6.7±0.1

n=3, Values are expressed in Mean± SD

Estimation of % Drug release

NE 1, NE 2, NE 5 &NE 6 showed % drug release as 92.3±0.7, 86.7±0.4, 73.9±0.8&74.5±0.8, respectively at 6 hours. Whereas, F3 & F4 showed % drug release as 80.4±0.1 &75.8±0.1, respectively that was lowest among all 6 formulations.

Table 12. Estimation of % Drug release

Time (hr)	% drug release± S.D.					
	NE 1	NE 2	NE 3	NE 4	NE 5	NE 6
1	34.5±0.3	28.5±0.4	24.7±0.6	21.3±0.4	17.6±0.3	18.5±0.4
2	44.6±0.5	36.3±0.6	32.5±0.3	34.7±0.6	27.8±0.5	30.9±0.5
3	54.5±0.2	44.2±0.4	40.4±0.7	45.8±0.2	35.9±0.1	43.8±0.2
4	67.4±0.7	66.00±0.8	56.9±0.8	55.7±0.9	53.8±0.6	51.5±0.1
5	81.7±0.3	71.7±0.9	68.6±0.3	67.5±0.7	64.7±0.4	63.8±0.6
6	92.3±0.7	86.7±0.4	80.4±0.1	75.8±0.1	73.9±0.8	74.5±0.8

n=3, Values are expressed in Mean± SD

Stability data

The stability tests were performed after 30 days to confirm its actual property in terms of % drug content, pH and in-vitro drug release. NE 0 exhibited % drug content as Nil as it did not keep any drug amount. Whereas NE 1, NE 2, NE 3 and NE 4 showed % drug content as 97.30±0.39 %, 97.50±0.25 %, 95.73±0.12 % and 98.91±0.34 % respectively. In NE 5 and NE 6, it was much more excellent as 96.62±0.21 % and 98.57±0.17 % at the time of formulation.

After 30 days, it was again tested for % drug content and showed very negligible change in NE 0-NE 6. A slight change was seen in NE 1 as 97.12±0.39. While NE 6 also showed % drug release as 98.54±0.17. So, it may be due to better stability of nanoemulsions.

Table 13. (i) Stability data (% drug content) after 30 days

Formulation	% Drug content	
	before	*after*
NE 0	Nil	Nil
NE 1	97.30±0.39	97.12±0.39
NE 2	97.50±0.25	96.52±0.25
NE 3	95.73±0.12	96.73±0.12
NE 4	98.91±0.34	98.91±0.34
NE 5	96.62±0.21	97.63±0.24
NE 6	98.57±0.17	98.54±0.17

n=3, Values are expressed in Mean± SD

At the time of preparation of formulation NE 0- NE 6, the pH was measured for better tolerability and absorption property. pH was estimated as 6.3±0.3 in NE 0. While pH was measured as 6.4±0.2, 6.5±0.2, 6.7±0.1 and 6.6±0.3 in NE 1, NE 2, NE 3 and NE 4 respectively. Whereas, high alkaline pH was estimated in formulation NE 5 and NE 6 as 6.6±0.1 and 6.7±0.1. After 30 days, it was again measured that was found almost same that indicates for better stability profile. The table 13 (ii) showed stability data (pH) after 30 days.

Table 13. (ii) Stability data (pH) after 30 days

Formulation	pH	
	before	**after**
NE 0	6.3±0.3	6.3±0.1
NE 1	6.4±0.2	6.4±0.3
NE 2	6.5±0.2	6.5±0.2
NE 3	6.7±0.1	6.7±0.3
NE 4	6.6±0.3	6.5±0.3
NE 5	6.6±0.1	6.6±0.2
NE 6	6.7±0.1	6.7±0.1

n=3, Values are expressed in Mean± SD

At the time of formulation of nanoemulsions, lowest *In-vitro* drug release was seen in NE 0 as 54.42±0.54. While, NE 1, NE 2, NE 3 and NE 4 showed in- vitro drug release as 83.47±0.35, 85.12±0.37, 86.39±0.58 and 84.53±0.72 respectively. NE 5 and NE 6 showed release (in-vitro) as 87.10±0.81 and 89.25±0.65%.

After 30 days, a negligible change was observed in drug release (*in-vitro*) when compared with at the time of formulation of NE 0- NE 6.

Table 13. (iii) *In-vitro* drug release (%)

Formulation	***In-vitro* drug release (%)**	
	Before	**after**
NE 0	53.37±0.54	52.38±0.52
NE 1	83.47±0.35	83.47±0.35
NE 2	85.12±0.37	85.12±0.37
NE 3	85.39±0.58	85.39±0.48
NE 4	84.53±0.72	84.53±0.72
NE 5	86.10±0.84	85.10±0.81
NE 6	88.25±0.64	88.25±0.65

n=3, Values are expressed in Mean± SD

Thus, in all the parameters chosen for stability, NE 0- NE 6 showed excellent stability strengths but much significant effect was observed in the NE 2, NE 4, NE 5 & NE 6 nanoemulsions.

In all the parameters, nanoemulsion showed an excellent formulation property when observed. Physical appearances were optimistic in terms of better clarity and transparency of the emulsions.

Particles size and particle size index was observed efficient for better drug release and bioavailability of incorporated drug that confirms for its uniqueness in the formulation. *In-vitro* drug release and viscosity are important factor behind the quality of formulated nanoemulsion. In the same context, these two factors showed optimistic behaviour of NE 0- NE 6.

After 30 days, when stability parameters performed in terms of pH, % drug content and in-vitro drug release, they all were almost like previous evaluations.

CONCLUSION

It concludes that NE 5 and NE 6 were most prominent nanoemulsion among all the NE subtypes. It also demonstrated a better stability that can be kept for a month without change in its pH, % drug release and In-vitro drug release.

Development of nanoemulsion of *S. chirata* extract might be very significant in terms of treating bacterial infections and stability parameters as well.

This formulation could be confirmed by the in-vivo clinical evaluation, after it can be employed for the treatment and drug delivery of various problems such as cancer. It can counter the skin problems specially dermatitis, pruritis and other epidermal ailments.

FUNDING

Nil.

CONFLICT OF INTEREST

None.

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