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Formulation Development and Evaluation of Nanoemulsion based Gels for Nicardipine

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KEYWORDS
Nicardipine, caprylocaproyl polyoxyl-8 glycerides, S-mix heating–cooling cycles.

ABSTRACT:

Objective:
The aim of the current research was to investigate the release of Nicardipine, a poorly water-soluble drug from different formulations in vitro.

Method:
A Nano emulsion (NE) was prepared using caprylocaproyl polyoxyl-8 glycerides, diethylene glycol monoethyl ether, and propylene glycol monolaurate. For enhancing the viscosity, carbopol was used to form an NE-based gel (NEBG).

Results:
The prepared formulations were characterized for physical appearance, droplet size, zeta potential, percentage transmittance, heating–cooling cycles, phase separation, viscosity, drug content, and in vitro drug release using Franz diffusion cells. The mean droplets size for ME and ME-based gel-systems were 116.2±0.452, and 185±2.53 nm respectively, whereas the zeta potential values were −32.3±0.53 mV for the former and -34.5±0.26mV for the latter. No significant variations in the pH nor physical appearance alterations were observed while stability tests were performed. The release rate of Nicardipine formulated as NE or as NEBG had the highest release values (85.35±5.34%) and (76.25±5.26%) after 6h respectively.

Conclusion:
This was statistically significant gel had a higher viscosity suitable for topical administration without dripping. The in vitro result suggested that NE systems are powerful topical vehicles for enhanced penetration of Nicardipine.

1. Introduction

Nano Emulgel is an innovative drug delivery technique which improves the therapeutic profile of lipophilic medications (1,2). Lipophilic formulations are subject to several disadvantages, such as limited oral bioavailability, variable absorption, and poor solubility. The goal of nano-emulgel, a combined preparation of several systems, is to address these constraints (3). The new technique created by adding Nano-emulsion to gel enhances stability and permits fast and regulated release of medication. The capacity of nano-emulgel to accomplish targeted distribution, its safety profile, its ease of application, and the fact that it does not undergo first pass metabolism or gastrointestinal degradation have all contributed to its growing attention (4,5). The pharmacokinetics, safety profiles, and formulation elements of nano-emulgel for topical drug delivery are the main this research work. All the ingredients are as per the IP specifications. caprylocaproyl polyoxyl-8 glycerides, diethylene glycol monoethyl ether (6), and propylene glycol monolaurate were procured from Loba Chemicals Ltd Mumbai.

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2. Methods

NE and NEBG preparation:

Selecting components of NE and constructing a pseudo-ternary phase diagram: In order to prepare an optimized NE system, it was of great importance to select an appropriate oil, surfactant and co-surfactant combination that had a good solubilizing capacity of drug (7). For the preparation of the NE system in this study, Propylene glycol monolaurate was selected as an oil phase, caprylocaproyl polyoxyl-8 glycerides as a surfactant and diethylene glycol monoethyl ether as a co-surfactant (8). These components were chosen on the basis of a solubility study results. The pseudo ternary phase diagram was constructed to distinguish the NE domains and to detect the possibility of producing MEs with different possible concentrations of oil, surfactant, co-surfactant, and water. The phase diagram was developed at ambient temperature using an aqueous phase titration method. It was prepared at surfactant/co-surfactant ratios (S-mix) of 2:1 (9,10). The oil and Smix were combined in different weight ratios that varied from 1:9 to 9:1. The systems were stirred by a magnetic stirrer during the addition of the aqueous phase to ensure a thorough mixing. Based on visual observation, the end point of the titration was determined when the mixtures became turbid or cloudy (11). Based on the NE region that determined from the constructed pseudo ternary phase diagram, five formulations contain different proportions of oil, water, and S-mix were mixed in the ratios presented in Table 1. The drug was dissolved directly in the formulations to formulate drug loaded NEs. All NEs were then tested for in vitro drug release. Further investigations were then conducted on the formulation that provided the highest drug release profile. The areas corresponding to either micro emulsions or macro/conventional-emulsions were constructed inside the triangular phase diagram using the Microsoft Excel 2015.

Table 1 Composition of micro emulsions containing 3% Nicardipine with various amounts of S-mix (Caprylocaproyl polyoxyl-8 glycerides/ diethylene glycol monoethyl ether), propylene glycol monolaurate and water

Formulation	% S-mix	% Water	%PG Monolaurate	Drug Solubility (µg/mL)
F1	75	0	25	99.34±2.1
F2	50	37.5	12.5	87.36±3.6
F3	60	25	15	92.26±2.4
F4	75	10	15	94.57±2.5
F5	75	12.5	12.5	89.26±2.2

Preparation of drug-loaded NE: NE formulations were formed spontaneously by mixing caprylocaproyl polyoxyl-8 glycerides as a surfactant with diethylene glycol monoethyl ether as co-surfactant at 2:1 ratio. Water and propylene glycol monolaurate were added directly and mixed gently at room temperature. An amount of 3% w/w drug was added to each NE and the formulations were stirred for 5 min at 600 rpm until a clear NE was formed (12).

Preparation of plain carbopol gel base: Carbopol 934P gel base was prepared by dispersing 1.5% (w/w) carbopol into distilled water and mixing it using a magnetic stirrer at 1200 rpm for at least 30 min. The dispersion was left for 24 h to equilibrate. After that, triethanol amine solution was added drop wise in order to get a suitable gel with appropriate viscosity and a pH between 5 and 7(13,14,15).

Preparation of drug-loaded NEBG: In order to enhance the viscosity of the formulated NE, the freshly prepared drug-loaded NE was added portion-wise onto the previously prepared plain carbopol gel in a ratio gel: NE (2:1) under continuous stirring. The final NE-based gel formulation contained 3% w/w drug (Table 2).

Table 2 Percentage composition (%w/w) of the NE and NEBG formulations

Excipients	NE	NEBG
Caprylocaproyl polyoxyl-8 glycerides	50	50
Diethylene glycol monoethyl ether	25	25

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Propylene glycol monolaurate	12.5	12.5
Drug (Nicardipine)	3	3
Carbopol 943P	--	1.5
Triethanol Amine Purified water	--	Qs
Purified Water	Qs	Qs

Physicochemical evaluation of the prepared NE and NEBG: To overcome problems related to metastable and unstable formulations during storage, the physical stability of NE formulations was assessed by the following thermodynamic stability tests.

Physical appearance: The prepared NE and NEBG loaded with drug were examined visually for their color, homogeneity, and consistency (16).

Percentage transmittance: The optical clarity of the NEs was determined by measuring the percentage transmittance of the formulations using UV–Visible spectrophotometer. The NEs were analyzed at 650 nm against distilled water as a blank solution, and three replicates were performed for each ME (17).

Centrifugation study: The NE based formulations were subjected to centrifugations by Microliter Centrifuge at 10,000 rpm with relative centrifugal force (RCF) 8960 g for 30 min at 25 °C and observed for any changes in their homogeneity (17).

Heating–cooling cycles: Heating–cooling cycles were performed to evaluate the stability of the formulations under thermal conditions. Both systems were kept at 0 °C for 48 h then at 25 °C for 4 h; each cycle was repeated five times. At the end of the experiment, both formulations were assessed for physical properties including pH, homogeneity, and consistency.

Determination of drug solubility: For determining the drug solubility in the prepared NEs, an excess amount of drug was added to 5 g of each of the previously prepared NEs and stirred at room temperature for 24 h with a magnetic stirrer. Afterward, the sample was centrifuged, and the concentration of drug in the supernatant was determined spectrophotometrically. A plain NE without drug was taken as a blank (18).

pH measurements and drug content: The apparent pH of the tested NEs formulations was determined by a digital pH meter. All measurements were performed in triplicate at 25°C. For determination of drug content, one gram of each formulation was diluted in 100 mL PBS pH 7.4. Then, the resulting solutions were filtered before subjecting it to spectrophotometric analysis. Plain formulations without drug with the same composition were taken to establish a calibration curve (20).

Rheological studies: A Brookfield DV-III Ultra Viscometer was used to measure the viscosity of the prepared Nano emulsions. The spindle number 21 was rotated at 150 rpm using an interval of 30 s. Samples were allowed to settle at room temperature for 10 min before the measurements were conducted. The rheological measurement of the NEBG was performed using a Malvern Rheometer (Kinexus), equipped with parallel plate (22).

Particle size measurement: The particle size determination was performed by using Zetasizer Nano-DTS 1060 (Malvern Instruments Ltd, UK) at 25°C and 173° fixed angle. The samples were kept in disposable cuvettes, and observations were performed in triplicate following a proper dilution of the formulations in double distilled water. The polydispersity index (PDI) was used as a quality marker for droplet-size distribution (23).

Zeta potential determination: The surface charge of DS loaded NE, and NEBG was determined by the dynamic light scattering method employing a Zetasizer Nano-DTS 1060 (Malvern Instruments Ltd, UK). Analysis time was kept for 60 s. The zeta potential was measured using clear zeta dip cells after dilution of all samples with double distilled water. Cuvettes were washed and then rinsed with samples to be measured before each experiment. The zeta potential values were calculated according to Helmholtz-Smoluchowsky equation. All the results were the average of three measurements (24).

In vitro drug release studies: This study was carried out using six Franz diffusion cells with an effective diffusion area of 1.79 cm2 (15.1 mm diameter orifice) to determine the release rate of drug from the NEs, and the drug loaded NEBG. Synthetic 0.22 µm Polyvinylidene Fluoride (PVDF) membranes were first hydrated in phosphate buffer (pH 7.4) at 25°C for 30 min. The membranes were then clamped between the donor and receptor compartments. The receptor compartments were filled with 12 mL of phosphate buffer (pH 7.4). The receiver medium was maintained at 32.0 ± 0.5 °C using a circulating water bath, the acceptor compartment was magnetically stirred at

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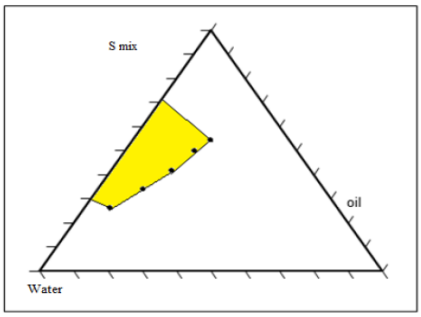
600 rpm throughout the experiment. 0.5 g of each formulation was accurately weighed and added to the donor compartment. At five time points (0.5, 1, 2, 3, 4 and 6 h), 0.1 mL aliquots were withdrawn through the sampling port and replaced immediately with an equal volume of fresh receptor solution to maintain a constant volume of the receiving solution. The samples were then analyzed spectrophotometrically against an appropriate reference. Three replicates of each experiment were conducted. The results were plotted as a cumulative percentage of drug release versus time. The release pattern of drug from NE formulations (F1–F5) was tested using hydrophilic PVDF membranes. Then, the formulation with the highest release profile was chosen to be incorporated into a carbopol gel. The release rate of drug from NE and NEBG was examined using hydrophobic PVDF membranes in order to simulate the stratum corneum, such hydrophobic synthetic membranes generally possess similar rate-limiting permeation properties as skin, thus making them as a suitable choice for predicting drug permeation (24).

3. Results

The pseudo-ternary phase diagram and NE formation: A Nano emulsion is formed when the interfacial tension between the water and oil interface is reached an extremely low level, and the interfacial layer is maintained highly flexible and fluid like. Resulting in a spontaneous dispersion of one liquid into the other. This is usually met by a careful and precise selection of surfactants and co-surfactants and their respective proportions. Moreover, the components used for developing NEs should have high drug solubilisation capacity, to ensure maximum solubility of the drug in the resultant system. According to the solubility study results, the selected oil (propylene glycol monolaurate), surfactant (caprylocaproyl polyoxyl-8 glycerides) and co-surfactant (diethylene glycol monoethyl ether) showed a high solubility profile of drug compared to other oils and among the investigated surfactants and co-surfactants. Likewise, evaluating the area of NE region in the phase diagram is essential for a successful development of an optimum NE. Hence, constructing a pseudo-phase diagram is vital to determine the concentration range of components for the existence range of NEs. It was observed that the area of NE region increased as the surfactant/co-surfactant mixture increased. This is probably due to the reduction of the interfacial tension and increased the fluidity of the system. The drug solubility was increased with the increase of the propylene glycol monolaurate as shown in Table 1. Based on the drug solubility, phase diagram and the in vitro drug release of the tested NEs, a micro emulsion containing 3% drug was prepared at surfactant to a co-surfactant ratio of 2:1 and then employed for further analysis.

4. Figure 1: Pseudo ternary phase diagram of 2:1 Smix Ratio



Physical appearance: The prepared drug-loaded NE was clear, transparent, liquidly and with homogenous appearance. On the other hand, the NEBG was of a glossy appearance, and a smooth, homogeneous texture.

Percentage transmittance: The percentage transmittance is an essential parameter to determine the transparency of the system. If the value of the percentage transmittance (%T) is close to 100%, this indicates that the selected formulation is clear, transparent and has a micelle size in the nanometer range, which indicates that the formulations have a large surface area for drug release. It was found that the NE free drug and the NE loaded with drug have transmittance values greater than 98% (Table 3), suggesting their clarity, due to the smaller particle size, which increases the transparency of the formulated systems.

Phase separation: Emulsions are normally thermodynamically unstable system and may separate when subjected to physical stresses like centrifugation. Though NEs are visually appear homogeneous as a single-phase system, they are in reality emulsion systems, which were confirmed by laser light scattering measurements. Therefore, they were subjected to

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centrifugation to confirm the absence of phase separation. NEs did not show any sign of phase separation nor any precipitations when subjected to centrifugation, which confirms the physical stability of the NEs.

Heating–cooling cycle analysis: After five heating–cooling cycles, the physical appearances of drug loaded ME was unchanged regarding transparency and phase separation. Moreover, drug precipitation was not noticed. The drug-loaded NEBG did not show any sign of creaming, cracking or phase separation. The changes in the pH of both formulations were not significant for drug-loaded NE and drug-loaded NE gel, respectively. Therefore, the studied formulations were considered physically stable.

Particle size analysis: One of the most important characteristics to evaluate NE stability is to measure their particle size. A Zetasizer (DLS) was used to detect the particle size of the drug loaded NE and the gel-based NE. The results of particle size study are listed in Table 3. Amongst all, the drug loaded NE showed the lowest mean particle size of 108.4±0.52 nm while the highest was observed for NE gel with a particle size of 185.8±2.32 nm (Table 3). The increased size of the NE based gel might be related to the addition of carbopol 934P to the NE. Polydispersity index indicates the uniformity of droplet size within each formulation, and varies from 0 to 1. The closer to zero the polydispersity value is the more homogenous are the particles. The polydispersity values of the formulations were very low which indicated uniform droplet sizes within the formulations.

Zeta potential analysis: Zeta potential is the measurement of particle charge and/ or electrostatic repulsion. The physical stability of any disperses systems said to increase with the increase in the electrostatic repulsion energy, which is directly proportional to the particle surface charge and the thickness of the diffusion layer. The negative zeta potential of NEs usually produces steric repulsive forces of hydrocarbon chains which protrude into the oil phase and subsequently hindering aggregation with neighboring oil droplets. Hence, a negative zeta potential is imparting stability of a NEs system. The tested NEs and NE gel based formulations showed physical stability due to their zeta potential between (−24.2 and −34.5mV) as shown in Table3.These values indicated that the prepared formulations have sufficient charge and mobility to inhibit particle aggregation.

5. Table 3: Physicochemical characteristics of the prepared formulations (mean±SD, n=3)

Formulation	% Transmittance	Particle Size (nm)	PDI	Zeta Potential (mV)
NE	100.11±0.11	108.4±0.52	0.023±0.01	−24.2±0.53 mV
Drug Loaded NE	100.08±0.12	116.2±0.452	0.134±0.23	−32.3±0.53 mV
NEBG	99.89±0.15	185±2.53 nm	0.189±0.01	-34.5±0.26

pH measurement analysis: The NE drug-free formulation had an observed pH value of 4.83±0.012. Incorporation of drug did significantly change the observed pH value of the NE (Table 4). However, gelling the drug loaded NE with carbopol significantly increased the pH to 5.47±0.02 which is a suitable pH value for topical applications close to the pH of the skin.

Rheological studies analysis: It has been observed that the viscosity of formulations can differ (Table 4), after the addition of drug or adding carbopol gel. The NE containing drug had a higher viscosity value relative to the drug-free NE. Nevertheless, both exhibited Newtonian flow behavior. The studied NE-based gel showed a shear thinning behavior with a viscosity in the range of 108.30±24.74 cP, which is significantly higher compared to the other NEs formulations.

Table 4: pH, drug content and viscosity measurements of the prepared formulations (mean ± SD, n=3)

Formulation	pH	Viscosity
NE	4.83±0.012	36.75±2.32 CP
Drug Loaded NE	4.95±0.012	38.43±2.26 CP
NEBG	5.47±0.02	108.30±24.74 CP

In vitro drug release studies: In vitro drug release from all formulations are illustrated in Fig. 1 (F1–F5 NEs) and Fig. 2 (semisolid dosage forms). From the data obtained, it was observed that the lowest drug

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release of drug through the hydrophilic membrane was out of formulation 3. Formulation 2 and 3 exhibited similar release rates at 6 h. Both formulations differ in their Smix and water concentrations but have similar oil concentrations. The formulation with the highest diffusion rate was Formulation 5 through the hydrophilic membrane. This formulation has a 1:1 ratio of water and oil phase. The ME with the highest diffusion capability (formulation 5) was gelled with carbopol. Both un-gelled and gelled formulations were then tested against each other and commercial/compounded formulations/ preparations using a hydrophobic membrane to simulate the stratum corneum. A carbopol gel loaded with 3% drug and drug in Vaseline were used as controls. The latter showed no release while the gel-drug formulation released very less drug only. The NE showed as expected a higher drug release compared to its gel form where of drug was release from the NE versus from the gel form. This is presumably due to the increased viscosity. Other authors postulated that carbopol might hinder the drug release by entrapping the drug into its structure or by producing chemical interactions with the drug.

Figure 2: Invitro Diffusion study

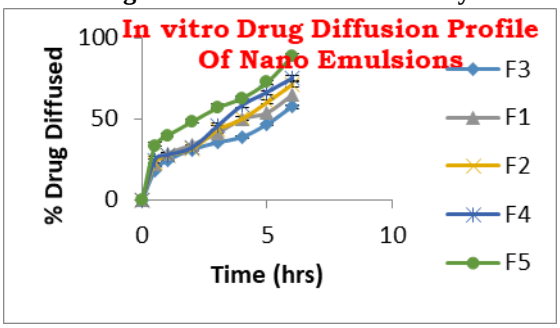
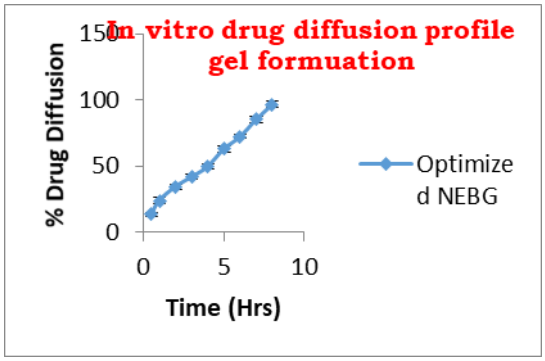


Figure 3: Invitro Diffusion study of gel



.Discussion

It was concluded that topical Nicardipine nanoemulgel has shown to be a more desirable choice in terms of a practical and efficient model of delivery. By Compared with the other formulations, gels are quite patient acceptance, and its absence of oil as a basis results in improved drug release.

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