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Development of ketoprofen in Transdermal Drug Delivery System

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ABSTRACT

To enhance the solubility and porosity of poorly water soluble nonsteroidal anti-inflammatory, nanoemulsion gel was developed for the treatment of rheumatoid arthritis. Among the oils,surfactants and co-surfactants elainic acid, tween80 and ethanol were chosen as they showed most solubility to drug.The pseudo ternary phase-diagrams was made to search out optimum concentration that provided the best drug loading. The ready nanoemulsions were subjected trough thermodynamical stability testing. The drop size, scanning microscopy (SEM) and zeta-potential were investigated. The optimized formulation of nanoemusion NE2 that was showing ninety five.93% drug unleash was incorporated into chemical compound gel of Carbopol 940 for convenient application and evaluated for consistency, PH, in-vitro permeations studies, skin irritation test and anti inflammatory activity. The in-vitro skin permeations profile of optimized formulation was compared with non-steroidal anti-inflammatory gel and nanoemulsion gel NG2.The significant increase in permeability quantitative relation (Kp),flux (Jss) and improvement ratio(Er) was ascertained. The anti-inflammatory impact of formulation NG2 showed vital increase 72 inhibition impact in 24hrs in comparison to nonsteroidal anti-inflammatory gel on Carrgeenan evoked paw edema in rats. The results steered that nanoemulsion gels are potential vehicles for improved transdermic delivery of non-steroidal anti-inflammatory.

Keywords: Nanoemulsion, Nanoemulsion gel,Scanning microscopy, viscosity, pH, in-vitro permeations studies

INTRODUCTION

Anti-Arrhythmic drugs are one of the numerous drugs having the limitation of poor aqueous solubility and bioavailability. Nanoemulsion is a promising tool for transdermal drug delivery and is defined as a dispersion consisting of oil, surfactant, cosurfactant, and aqueous phase, which is a single optically isotropic and thermodynamically stable liquid solution with a droplet diameter usually in range of 10–200nm [1]. The ascendancies associated with transdermal use of nanoemulsion are as enhanced drug solubility, good thermodynamic stability, and enhancing effect on transdermal ability [2]. The aptness of nanoemulsion to increase the concentration gradient and thermodynamic activity towards skin alongwith permeation enhancement activity of its components makes the system expedient for transdermal delivery. Ketoprofen, a substituted indene acetic acid chemically related to indomethacin, is a new non-steroidal anti-inflammatory, antipyretic and analgesic agent advocated for use in rheumatoid arthritis.It is known that Nanoemulsions are very good carriers for highly lipophilic drugs.

OBJECTIVE

To study the preformulation parameters solubility oils, surfactants, co-surfactants, buffers and water for selection of final formulation through Pseudo terinary phase diagrams and to determine their concentration ranges. To evaluate drug and excipient compatibility & Dispersion stability studies, droplet size, zeta potential, Refractive index, cloud point and *in-vitro* diffusion studies, *in-vitro* permeations studies, skin irritation test and anti-inflammatory activity.

Experimental methods

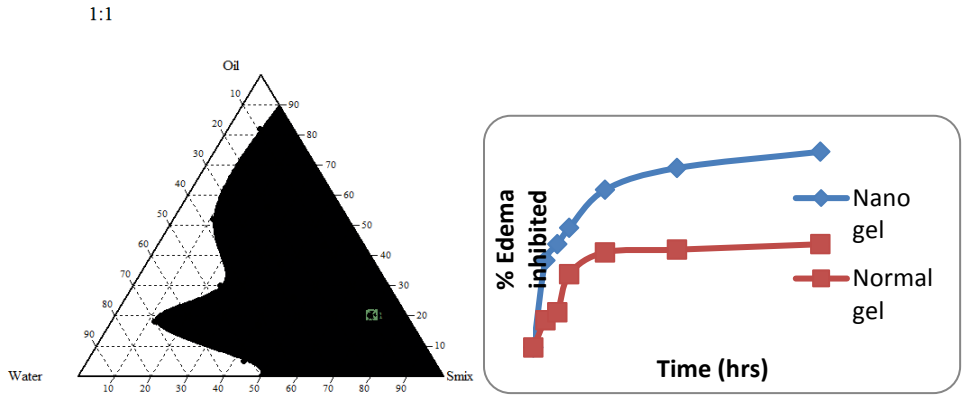
Pseudo Ternary Phase Diagram

On the basis of the solubility studies, a combination of Isopropyl Myristate was selected as the oil phase, Tween 80 and Ethanol were selected as surfactant and co-surfactant, respectively. Distilled water was used as an aqueous phase. Surfactant and Co-surfactant (Smix) were mixed at different mass ratios (1:1, 1:2, 2:1, 1:3). These ratios were chosen in increasing concentration of surfactant with respect to surfactant for a detailed study of the phase diagrams. For each phase diagram, oil and Smix at a specific ratio was mixed thoroughly at different mass ratios from 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 in different glass vials. Different combinations of oil and Smix, were made so that maximum ratios were covered for the study to delineate the boundaries of phases precisely formed in the phase diagrams. Pseudo ternary phase diagrams of Oil, Smix and aqueous phase were developed using the aqueous titration method.The final optimized formulations were evaluated for the following Parameters Thermo dynamic Stability Studies,ParticleSize**,** PolyDispersability Index**,**Viscosity Determination**,**Refractive Index**,**pH**,**Zeta Potential andScanning Electron Microscopy (SEM)

Permeation data analysis Permeability parameters like steady-state flux (J_{ss}), permeability coefficient (K_p), and enhancement ratio (E_r) were significantly increased in Nanoemulsions and the Nanogel (NG_2) formulation as compared with conventional gel

Results & Discussion The viscosity of all formulations was found to be in range limits of BP specifications. Diffusion studies i.e. % Cummulative drug release vs time (hrs) were performed and its % cummulative drug release for all formulations was in between 83.57% to 95.93%in pH 4.5buffer. Out of ten formulations NE2 showed the maximum % cumulative release of 95.93%. The mean particle size of all formulations were in the Range of 93.3nm to 197.2 nm .The Zeta Potential ofall formulations NE1 to NE10 were found to be in the range of 0.5mV and -19.7mV.

Skin irritation test was performed with optimized formulation NE_2 by applying it to left ear of mice to study irritancy by comparing with its right ear to which formulation was not applied. The study was carried out for six days and it was found that the Nanogel of NE_2 causes no irritation or erythema.



Fig,2: Percentage edema inhibition effect.

Fig 1. Psuedo Ternary phase diagram showing the o/w Nanoemulsion(Shaded Area) regions of Isopropyl Myristate (oil), Tween 80 (Surfactant), Ethanol(Cosurfactant) at Smix ratio 1:1,Table 1. Particle size analysis and Zeta potential,pH and Refractive Index

Sample Code	Mean Particle Size (nm)	Polydispersity Index	Zeta Potential	pH	Refractive Index
NE1	197.2	0.589	0.5	6.8±0.32	1.421±0.1
NE2	93.3	0.254	-19.7	6.9±0.34	1.622±0.12
NE3	96.23	0.425	-01.3	6.3±0.33	1.331±0.11
NE4	95.1	0.456	-0.6	6.2±0.36	1.439±0.16
NE5	116.2	0.310	-02.5	6.6±0.31	1.674±0.13
NE6	173.5	0.336	-04.8	6.5±0.3	1.583±0.14
NE7	94.3	0.412	-02.3	5.9±0.37	1.739±0.15
NE8	99.1	0.572	-06.1	6.1±0.32	1.734±0.11
NE9	101.2	0.513	-02.1	5.8±0.31	1.632±0.13

NE10	131.5	0.573	0.1	6.7±0.29	1.634±0.12

Conclusion

The optimized formulation contained 10 % of oil phase (Oleic acid), 50 % of surfactant mixture (Tween 80 as surfactant and Ethanol as co-surfactant) and 40 % of distilled water. From the studies, it is observed that the formulated Nanoemulsions and Nanoemulsion gel released up to 95.93% and 86 % of the drug, respectively.

Bibiliography

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VISCOSITY

Formulation NE2 had the least viscosity (31.21 ± 1cps) compared to other formulation. This may be due to the lower oil content. Viscosity of all nanoemulsion formulations was very low as expected. As shown in Table .

Table 2. Viscosity of Nanoemulsion Formulations

Sample Code	Viscosity (cps)
NE1	34.52 ± 1.2
NE2	31.21 ± 1
NE3	37.13 ± 1.3
NE4	45.55 ± 1.5
NE5	41.32 ± 1.8

NE6	42.40 ± 2
NE7	47.13 ± 2.2
NE8	40.21 ± 2.8
NE9	49.32 ± 3
NE10	46.33 ± 1.3

Mean ± SD, n=3

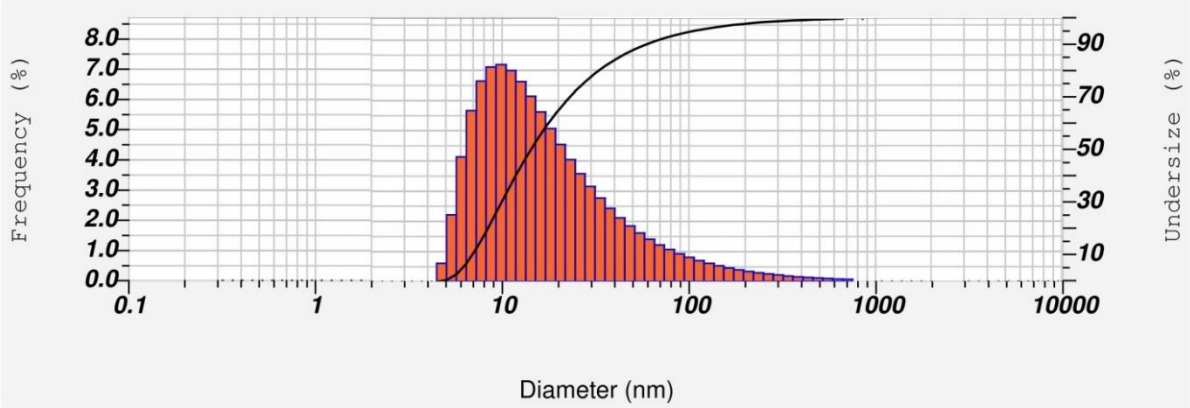
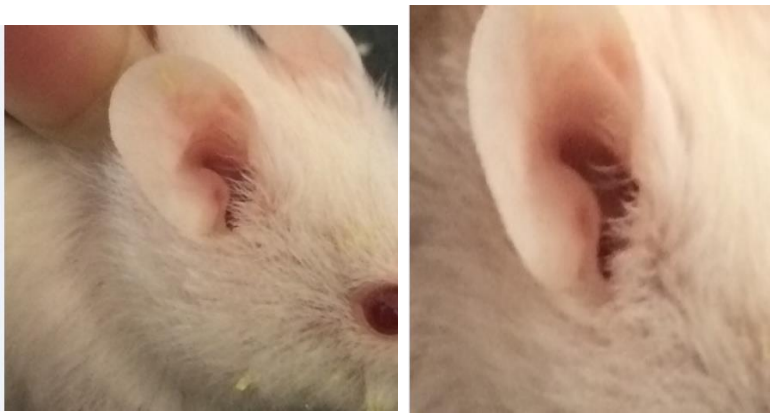


Fig 3.Graph indicating the mean particle size of Formulation NE2



Based on *in-vitro* diffusion study formulation NE_2 containing drug was optimized. Further, Skin irritation test was performed with optimized formulation NE_2 by applying it to left ear of mice to study irritancy by comparing with its right ear to which formulation was not applied. The study was carried out for six days and it was found that the Nanoemulsion NE_2 causes no irritation or erythema.