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FORMULATION AND CHARATERIZATION OF NANOEMULGEL FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT

The present study focused nanoemulsion-based emulgel for transdermal delivery of Lamivudine. Pseudoternary phase diagram were constructed using titration method to get a nanoemulsion region. Soyabean were oil selected as oily phase, Tween 80 were selected as surfactant and PEG 400 were selected as co surfactant. Nanoemulsion were selected on the basis of compatability studies and emulsification ability. Nanaoemulsion were prepared by spontaneous emulsification method and characterized for percentage transmittance, pH, viscosity, particle size, zeta potential, surface morphology, *Invitro*-drug release. The optimized nnaoemulsion formulation (NS4) were converted to nanoemulgel by using 2% aloeveragel., and evaluated for pH, viscosity, drug entrapment efficiency, release kinetics and stability studies. The optimized formulation showed 95.36% for 12 hours then release kinetics were fitted with different kinetic model and found that they follow first order kinetics. After the evalution it concluded that Lamivudine nanoemulgel could increase the drug permeability across the membrane, and release of the drug will be fast and can delivered successfully.

KEYWORDS: Lamivudine, Nanoemulgel, Transdermal drug delivery, Pseudoternary phase diagram.

INTRODUCTION

Emulsion are heterogeneous having two immiscible liquids, they are thermodynamically unstable and not suitable in pharmaceutical field. Nanoemulsion can be divided to three types: water in oil (W/0), oil in water (O\W) and bi- continuous by which it will generate

variety of structures and phases through a mixture of water, oil, and surfactant. Nanoemulsion increases solubilizing capacity and intensify of the topical and transdermal distribution.[1] When compared to conventional topical formulation like emulsion and gel, nanoemulsion has been reported better permeation of many drugs.[2,3] Widely used topical agents like lotion and ointments are having certain disadvantages. They are having problems like less spreading coefficient, very sticky, causing discomfort, rubbing required for application to the skin and stability problem will appear for formulation. So due to all this problems gel will be selected for cosmetic and pharmaceutical formulation and gel also having certain problems with delivery of hydrophobic therapeutic moiety. So to get the better result emulgel based approach is used to overcome these problems.[4] By combining emulsion and gel are called as emulgel. In many aspects emulgel having advantages over conventional drug delivery and used as a novel drug delivery system. Aloevera was reported as gelling agent in many studies which will reduce inflammation and deliver drugs effectively, and also when it applied on to the skin, act as protective in nature.[5,6]

Lamivudine widely used in the treatment for HIV infected patients and it is an antiretroviral drug. They must be administered for the life span of the patients most of the anteretroviral including lamivudine are virustatic in nature. To suit various drug molecules novel drug carriers such as transdermal are versatile. Controlled dug delivery system preffered to full fill the long term treatment with anti- HIV agents.[7] Lamivudine requires frequent administration for prolonged period of time and having short biological half life. To achive constant plasm levels for prolonged period of time transdermal route is choosen, Which could be advantageous because of less dosing regimens.[8,9,10] The purpuse of this study is to formulate nanoemulsion based emulgel formulation by using gelling agent aloevera gel to overcome the problem associated with lamivudine. Hence, in the present study, nanoemulsion were prepared by spontaneous emulsification method and pseudoternary diagram were constructed to find out nanoemulsion region. Finally the nanoemulgel was obtained by incorporating nanoemulsion in Aloeveragel. nanoemulgel were obtained.

MATERIALS AND METHODS

Soyabean oil obtained from Fortune refined oil, India. Tween 80 and polyethylene glycol 400, and were purchased from SDFCL, Mumbai, Aloevera pulp obtained from cultivated Aloevera.

Pseudoternary phase diagram

Pseudoternary phase diagram were constructed to get a nanoemulsion region. Soyabean was oil selected as oily phase, Tween 80 was selected as surfactant and PEG 400 was selected as co surfactant. To prepare Smix, the surfactant, and co-surfatant was mixed with different ratio 2:1(85%), 2:1(90%), 3:1(85%), and 3:1 (90%). For each phase diagram, then Smix and oil were loded with Lamivudine in different weight ratio. Then record the all the parts of pseudoternary phase diagram. To the mixture of oil and Smix add aqueous phase by slow titration method until clear liquid formed after the addition of aqueous phase to find the region for nanoemulsion.[11]

Formulation of nanoemulsion

From the phase diagram variying ratios were taken to that Lamivudine added to the mixture of oil, Smix and Surfactant. In dropwise manner aqueous phase addede to the above mixture then the mixture were stirred at ambient temperature, then stored the nanoemulsion for further studies.[12]

Formulation of nanoemulgel

The oil phase were prepared my mixing with soyabean oil, tween 80, PEG 400 and lamivudine. The Aloevera gel was choosed as gel matrix base. Aloevera gel were swelled in a little water for 24hr and high viscous solution obtained under vertexing, oil phase was added slowly to the viscous solution of aloevera gel. Nanoemulgel were obtained.[13]

Table 1: Formulation of Lamivudine Nanoemulgel with the selected percentages of Oil, Smix and water from the pseudo ternary phase.

Formulation code	Smix ratio	Surfactant	oil	Oil %	Smix %	Water %	Drug (gm)	Aloevera gel(ml)
SN1	2:1 (85)%	Tween-80	Soyabean oil	15	75	10	0.5	1
SN2	2:1 (90%)			10	80	10	0.5	1
SN3	3:1 85%			12	82	6	0.5	1
SN4	3:1 (90%)			9	84	7	0.5	1

Charaterization of nanoemulsion

Evaluation of Nanoemulsion

A. Determination of pH

pH values were determined at ambient temperature using caliberated potentiometer, measurement were done by triplicate.[14]

B. Viscosity determination

Using a Brookfield DV III ultra V 6.0 cone and plate rheometer, viscosity of the formulation were determined. Using spinle # CPE at 25^0 C ± 0.5^0C, The one drop of formulation added to the slide in triplicate at 25^0C.

C. Percentage transmittance

Using shimadzu UV-VIS spectrophotometer percentage transmittance of the nanoemulsion were determined. Then dilute the 1 ml of the formulation 100 times,and analyze at 247nm.[15]

D. Drug entrapment efficiency

Entrapment efficiency (EE%) was done inaqueous medium by measuring the concentration of free drug. Then it will influences the release of characteristics of drug molecule, this is first important. From the nanoemulsion formulation after the separation of entrapped drug determined by the amount of drug encapsulated per unit weight of nanoparticles.[16]

$$EE = \frac{\text{Weight of total drug in formulation} - \text{weight of drug in aqueous phase} \times 100}{\text{Weight of drug in formulation}}$$

E. Particle size analysis

Based on laser light scattering phenomenon, particle size of nanoemulsion were determined using photon correlation spectrometer. Then purified water samples were diluted 200 times, after 2min stirring diluted samples placed into the module and measurement made in triplicate. From the volume size distribution droplet size were determined.[17]

F. Zeta potential

The zeta potential were measured by zetasizer using double distilled water. The formulation (0.1ml) diluted 100times, then it creates surface charges and emulsifier act as a mechanical barrier. The stable nanoemulsion will be formed when their more negative zeta potential and net charge of the droplets.[18]

G. Surface Morphology

Using the instrument scanning electron microscopy (SEM, JSM 6100 JEOL, Tokyo, Japan) the morphology of the transdermal were analyzed at an acceleration voltage of 10Kv with suitable magnification.[19]

H. *In-vitro* drug releases

Dialysis bag method used to determine *in-vitro* drug release, the conditioning of the dialysis membrane was done by soaking it in a phosphate buffer 7.4 for about 8 hours.In the previously soaked dialysis membrane about 3ml of Lamivudine nanoemulgel formulation was taken then this membranes were dipped in the 200 ml of the phosphate buffer solution pH 7.4. From the above dissolution set up the sample of about 5ml was withdrawn at interval of 1 hours after withdrawal of the sample the sink condition should be maintained by replacing the same amount of phosphate buffer. Then the obtained sample were examined by uv- spectrophotometer at 270.6 nm. Then the amount of drug release were calculated.[20]

Evaluation of emulgel

A. Drug content

1 gm of emulgel was kept in sonicator for 2 hrs accurately weighed and dissolved in 100ml chloroform, filter the solutiom through filter paper. And then measure the absorbance spectrophotometrically at 273nm against corresponding emulgel. Using slope drug content were calculated using linear regression method intercept obtainded by standarad caliberation method, and they were carried out in triplicate experiments.

B. pH

pH of the various formulation were determined using pH Meter, each formulation were done in triplicate. To the 100ml distilled water 1gm of emulgel were dissolved and stored for 2hrs.

C. Viscosity

Viscosity of the prepared emulgel can be measured by Brookfield viscometer**.** The corresponding dial reading was noted buy rotating the emulgel at 1rpm. By that reading viscosity of the gel obtained, viscosity were measured in poise.

D. ***In –vitro release study***

In-vitro drug release were carried out using dialysis membrane and the studies of the emulgel were carried out in modified fanz diffusion cell. Between the donar and receptor

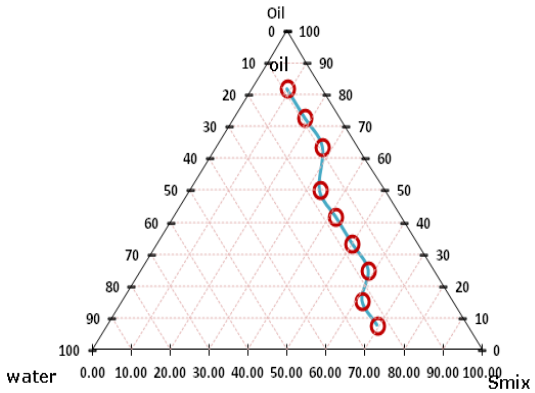
compartment membrane soaked in phosphate buffer of pH 7.4 for 12 hrs and clamped carefully. In dialysis membrane 1gm of emulgel spread uniformly. To the receptor compartment added 50 ml of phosphate buffer of pH 6.8 that will be used as dissolution medium. In contact with receptor compartment donar compartment kept as constant. The whole assemply kept on a magnetic stirrer and solution on the receptor side stirred continuously and temperature of the cell was maintained at 37 ± 0.5^0 C. Fresh dissolution medium replaced when sample (1ml) was withdrawn at suitable time interval. At 273 nm spectrophotometrically sample were analyzed. The graph were plotted of % cumulative drug releas verces time.[21]

Kinetic analysis of drug release

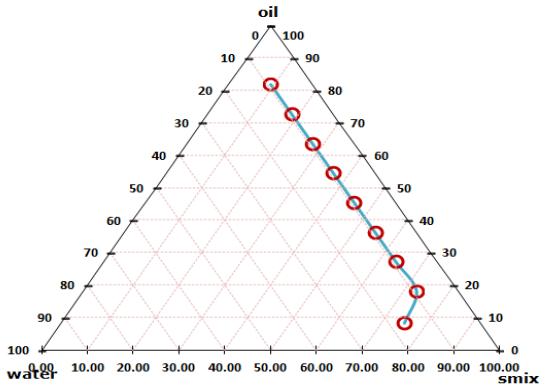
To determine the mechanism of drug releas from Lamivudine nanoemulgel the in-vitro diffusion were fitted to to first order kinetics.

Accelerated stability studies

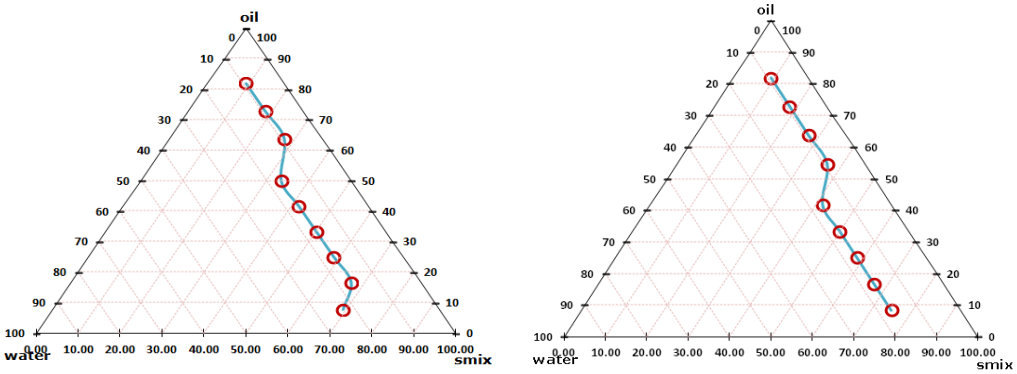
The accelerated stability test were done for optimized formulation over period of 3 months as per ICH guideline at a temperature of 30^0 C ± 2ºC, 65 ± 5% RH. The optimized nanoemulgel formulation were analyzed for changes in appearance, % CDR and drug entrapment efficiency.



2:1(85%)



2:1(90%)



3:1(85%) **3:1(90%)**

Figure (1): The pseudoternary phase diagram of double distilled water, oil and Smix ratio 2:1(85%), 2:1(90%), 3:1(85%), 3:1(90).

RESULTS

Melting point analysis

The melting point analysis of Lamivudine was found to be 175^0C which complies with melting range standard of $175\text{-}178^0$ C.

Solubility analysis

Solubility of Lamivudie was found to be in different solvents are given below-

Table 2: Solubility study.

Solvents	Solubility
Water	Very soluble
Methanol	Freely soluble
Chloroform	Freely soluble
Phosphate buffer solution pH: 7.4	Slightly soluble

Identification of drug through UV spectroscopy

Standard caliberation curve of Lamivudine as pure drug in method.

Table 3: Standard caliberation curve of Lamivudine.

Concentration in µg/ml	Absorbance
5	0.193±0.002
10	0.380 ±0.0075
15	0.575 ±0.002
20	0.75 ±0.0055
25	0.964 ±0.0206

UV shows that the Lamivudine gives maximum absorption at 270.6 nm and figure in linear standard caliberation curve shown in the figure no 2.

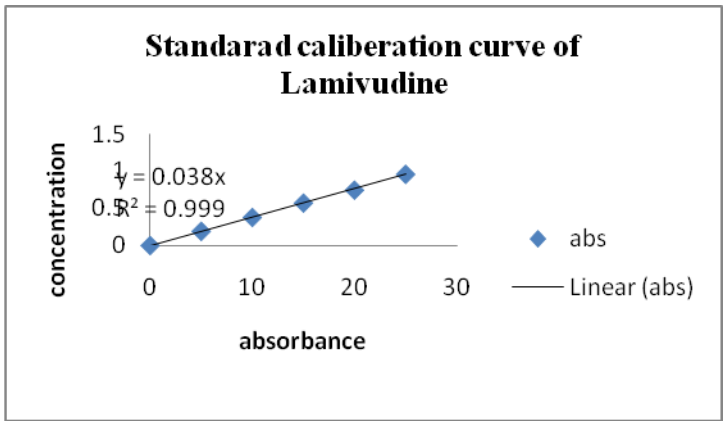


Figure 2: Standard caliberation curve of Lamivudine.

Determination of drug –excipient compatability studies

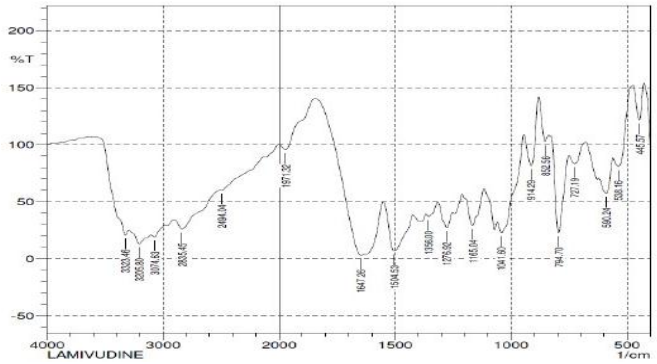


Figure 3: FTIR spectra of pure drug Lamivudine.

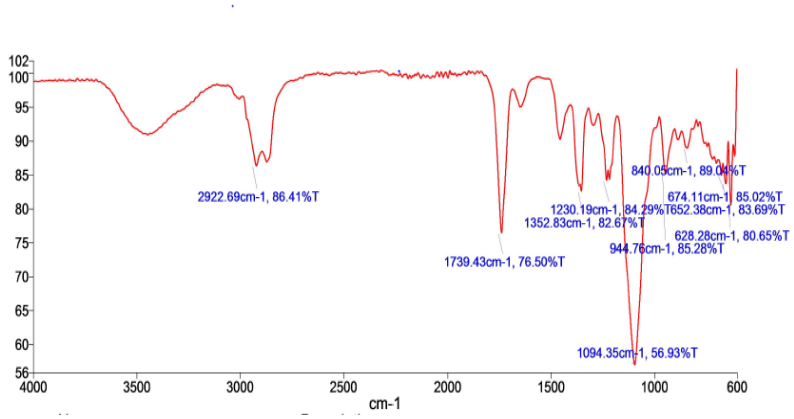


Figure 4: FTIR of Nanoemulsion formulation of SN4.

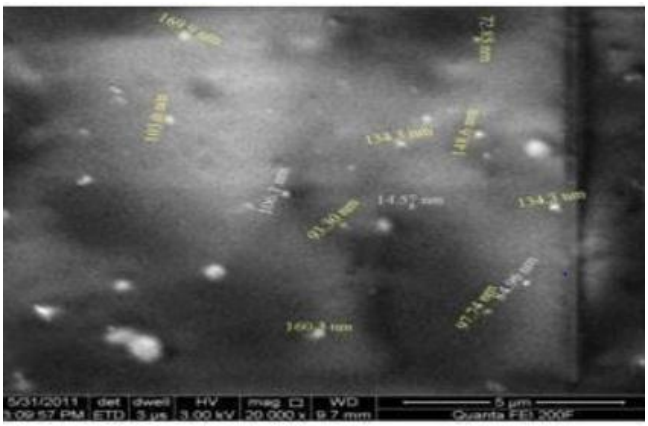


Fig 5: SEM of nanoemulsion formulation.

Table 4: Transmittance, Viscosity(ps), pH, Drug entrapment efficiency (Nanoemulsion).

Formulationcode	Transmittance	Viscosity (ps)	pH	Drug entrapment efficiency
SN1	91.53 ± 0.728	0.823±0.003	6.71± 0.01	97.17± 0.025
SN2	93.02 ± 0.021	0.854±0.004	6.72± 0.1	98.19± 0.081
SN3	97.02 ± 0.021	0.866±0.008	7.21± 0.030	98.46 ± 0.036
SN4	97.07 ± 0.378	0.872±0.005	7.40 ± 0.015	98.63± 0.040

Table 5: *Inviro* release studies of (nanoemulsion).

Time in hrs	% Cumulative drug release			
	SN1	SN2	SN3	SN4
0	0	0	0	0
1	3.15	3.08	3.19	3.84
2	5.18	5.66	5.92	6.91
4	10.35	11.33	12.23	18.88
6	38.87	44.38	47.32	42.84
8	60.46	60.96	68.70	72.96
12	80.22	86.75	89.93	95.36

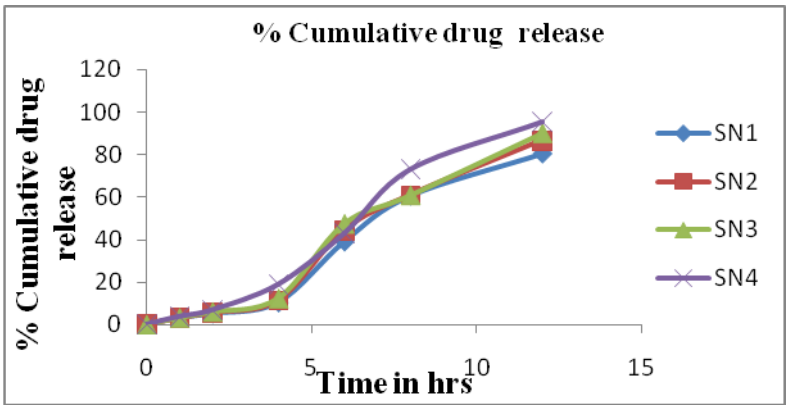


Fig 6: % cumulative drug release of formulation SNI- SN4.

Table 6: *In-vitro* diffusion study of nanoemulgel.

Time in hrs	% Cumulative drug release
0	0
1	3.85
2	6.93
4	18.89
6	42.86
8	72.99
12	95.39

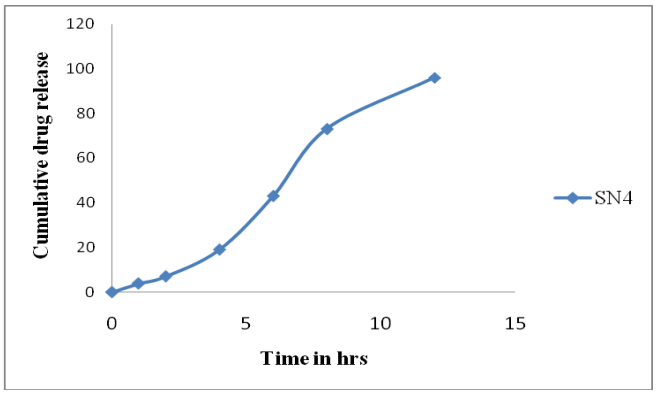


Fig 7: % cumulative drug release of nanoemulgel G-SN4.

Table 7: Release kinetics profile of nanoemulgel formulation G- SN4.

Time (hrs)	Log T	SQRT	%CDR	Log %CDR	% Drug Remaining	Log %Drug Remaining
0	0	0	0	0	100	2
1	0	1	3.85	0.58546073	96.15	1.982949289
2	0.30103	1.414214	6.94	0.84135947	93.06	1.968763048
4	0.60206	2	18.89	1.276231958	81.11	1.909074401
6	0.778151	2.44949	42.86	1.632052167	57.14	1.756940236
8	0.90309	2.828427	77.99	1.89203892	22.01	1.342620043
12	1.079181	3.464102	95.37	1.979411783	4.63	0.665580991

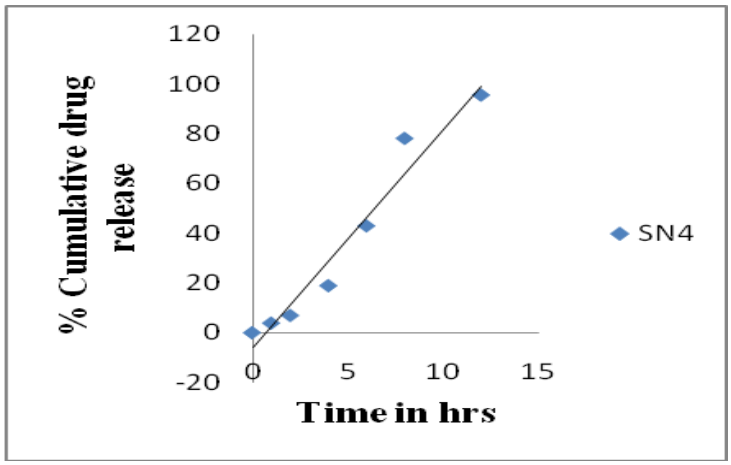


Fig 8: Zero order release kinetic profile of nanoemulgel formulation G- SN4.

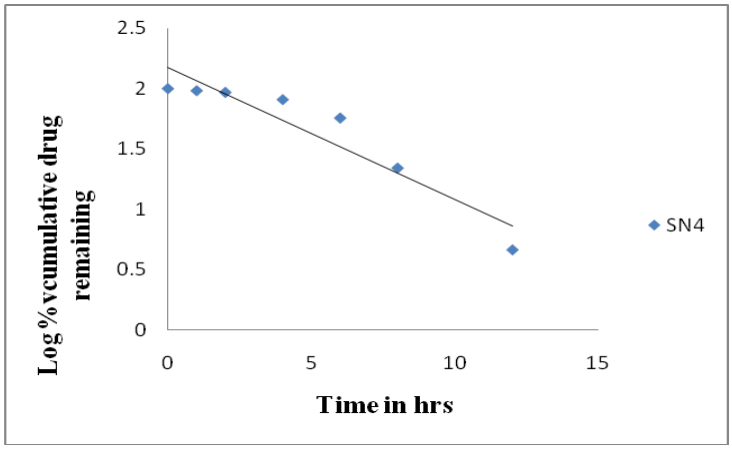


Fig 9: First order release kinetic profile of nanoemulgel formulation G-SN4.

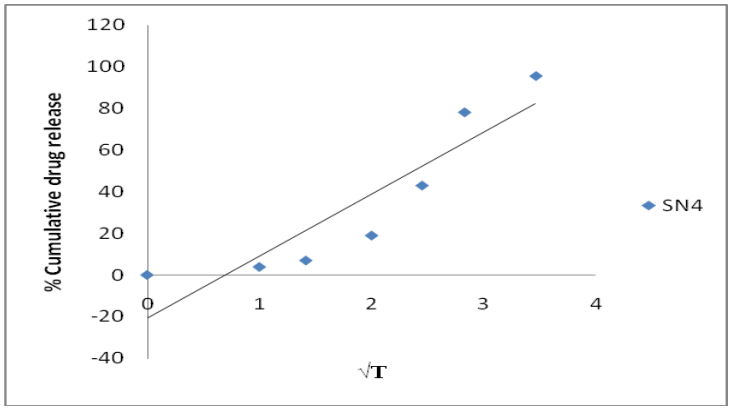


Fig 10: Higuchi release kinetic profile of nanoemulgel formulation of G-SN4.

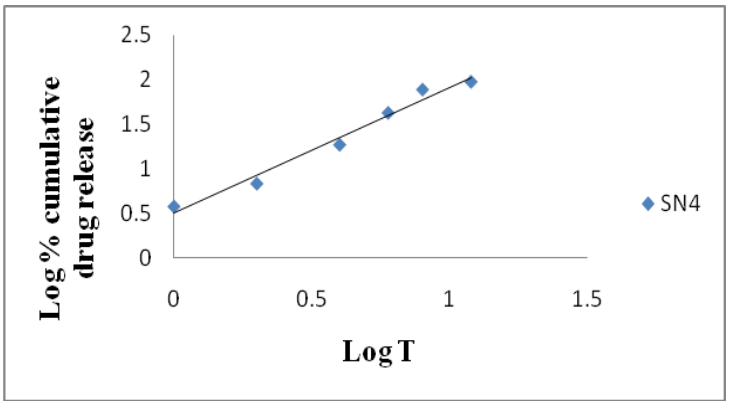


Fig 11: Peppas release kinetic profile of nanoemulgel formulation G-SN4.

Table 8: Data for different kinetic model of nanoemulgel G- SN4.

Formulation code	%Cumulative drug release	Zero order	Higuchi	Peppas	'n'value
SN4	95.37	0.9565	0.887	0.9776	1.4037

Table 9: Intermediate stability studies for optimized Nanoemulgel at 30^0 C± 2^0 C 65 ± 5% RH

Parameter	Duration in months		
	0	3	6
	G-SN4		
Drug entrapment efficieny	98.69	95.45	92.79
Cumulative drug release	95.37	92.56	87.34

DISCUSSION

The nanoemulgel were proposed as a carrier function for transdemal delivert of Lamivudine and it has dual release control system ie, nanoemulgel and gel, with the gelling agent it promoter better stability of nanoemulsion by reducing surface tension and interfacial tention thereby enhancing the viscosity of the aqueous phase for drug administration transdermally when compared to the conventional topical gels. The drug administered through nanoemulgel has better adhesion on the surface of the skin and solubilizing capacity which leads to larger concentration gradient towards the skin and influence better skin permeation. The pseudoternary phase diagram describe the selection of nanoemulsion formulation from the phase diagram to control the metastable formulation in the least possible time, phase diagram were constructed by varying the Smix ie, Tween-80 and PEG-400 ratio as 2:1(85%), 2:1(90%) and 3:1(85%), 3:1(90%). Out of four formation 3:1(90%) were taken as optimized formulation that will be formulate as nanoemulgel. From the phase diagram different ratios were taken for the mixture of soyabean oil and Tween-80 and PEG 400 Lamivudine were added. Then aqueous phase were added to the above mixture in dropwise manner and finally nanoemulsion were prepared. For the nanoemulsion preparation 2% Aloevera gel was added and vertex for few minutes nanoemulgel were obtained. From pure drug lamivudine the infraded spectruwm were recorded in the wavelength region between 4000-400, and shown in the figure 4. FTIR spectra of the pure drug and the formuation showed that there is no incompatability between the drug and excipients used. The Transmittance for the nanoemulsion formulation SN4 shows the values in the range of SN4(91.53-97.07), It proves the transperancy of the system. All the prepare nanoemulsion were analyzed for their pH. They were in the range of (6.71-7.40) so there is no need of adjusting pH. The viscosity of the selected formulations was determined by using brookfield viscometer, SN1 (0.823 ps) was lower than that of any other formulation. The viscosity of formulation SN4 was highest (0.845 ps), but it was observed that the viscosity of the nanoemulsion formulations generally low. By spectrophotometrically drug entrapment efficiency of different nanoemusion

formulation were determined were in the range of (97.17-98.63), which indicated that drug uniformly entrapped. Particle size analysis of nanoemulsion is essential for ensuring safe, efficient dosage and drug bioavailability. The particle size increases with the increase in concentration of oil in the formulations. The particle size of Optimized formulation SN4 which contains (4.14nm). A small particle size is very much important for drug delivery and the oil droplets tends to fuse with the skin and enhance the drug delivery. The SEM photomicrographs indicated that nanoemulsion were round in shape with irregular shape and mean particle size range as 5µm and shown in figure 5. The values of zeta potential of optimized nanoemulsion formulation SN4 were found to be 3.2 mv. The zeta potential has less than -10mv generally indicates high degree of stability, SN4 posses high degree of stability. *In-vitro* release study of lamivudine from various formulation were conducted for 12 hours by using franz diffusion cell. Cumulative drug release plotted against time(t). The percent drug release from SN1-SN4, was observed as follows SN1 -80.22%, SN2-86.755, SN3-89.83%, SN4-95.36%. The increase in surfactant (tween-80) ratio from SN1-SN4 cause increase in drug release. All the nanoemulsion formulation released the drug in a controlled manner. The in-vitro release data were shown in the table 4 and in the figure 6.

The physical appearace of all the Lamivudine nanoemulgel formulation was checked and showed off colourless and odourless. The prepared nanoemulgel was checked for the pH all the formulation were showing in pH:7.43. So their is no need for adjusting pH of the formulation. The viscosity of the optimized formulation were determined and formulation were having G-SN4-1.355(ps). The prepared nanoemulgel were subjected to drug entrapment efficiency the optimized nanoemulgel formulation has G-SN4-98.60 which indicates that the drug entrapped throughout the formulation. The result of *in-viro* release of lamivudine from the nanoemulgel is given in the table 7. However, the results clearly shows that the nanoemulgel have ability to retain the drug for prolonged period of time. The % CDR of nanoemulgel formulation G-SN4 was found to be G-SN4-95.36%. The best model fitted for formulas ie, G-SN4 showed 95.37% was korsmeyer peppas with slope n= 1.4037, and zero order =0.9565, higuchi = 0.887. The accelerated stability study for optimized nanoemulgel G-SN4 was performed for 3 months according to the ICH guideline % CDR, Drug entrapment efficiency were fixed as physical parameter for stability studies, that shows negligible changes in % CDR, Drug entrapment efficiency This revealed that the formulation stable on storage at 30ºC ± 2ºC and 65 ± 5%.

CONCLUSION

In this study the nanoemulgel with Lamivudien satisfies the best attributes for transdermal application. Nanoemulsion formulation were prepared by spontaneous emulsification method. Nowadays nanoemugel become acceptable carrier in drug delivery system. Soyabean oil (oil), Tween-80 (surfactant), PEG-400, co-surfactant and helps in solubilizing the drug in the formulation of nanoemulgel. The developed system could be able to release sustained pattern and it reduce the frequency of administration and improves patient compliance and can be used for transdermal and delivered successfully without use of chemical enhancer.

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