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DEVELOPMENT AND EVALUATION OF TRANSDERMAL NANOEMULGEL CONTAINING TERIFLUNOMIDE FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

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ABSTRACT

The objective of this research work was development and evaluation of transdermal formulation containing teriflunomide for the treatment of rheumatoid arthritis. To bypass first pass metabolism in liver which improves patient compliance with reduced gastrointestinal side effects with transdermal formulation with improved skin permeation. Transdermal nanoemulgel containing teriflunomide were prepared by spontaneous emulsification method with oleic acid as oil and tween 80 and transcutol p as surfactant and co-surfactant. With different ratio of surfactant and co-surfactant ternery phase diagram was obtained. Using 3^2 design nanoemulsion were optimized and evaluated by zeta potential for stability, and incorporated with hydrogel matrix prepared by xanthan gum as gelling agent. The final emulgel formulation was prepared and evaluated for parameters like viscosity, pH, spreadability, drug content, in vitro diffusion and ex-vivo permeation study. The particle size of all nanoemulsion formulation were observed in nanometer range (150-250nm), PDI (0.1-0.3). Response surface methodology was helped to optimize nanoemulsion formulation, the optimized batch evaluated for zeta potential (-18.2) analysis and selected for nanoemulsion based hydrogel formulation. Nanoemulgel (NEG 1, NEG 2 and NEG 3) were evaluated for pH (5.3±0.2, 5.4±0.2, 5.4±0.3), viscosity (10,321±174.4, 14,475±176.6, 16393±148.3mpa·s), spreadability (43.24±2.18, 36.11±3.40, 22.66±1.87 g.cm/s) and drug content (98.80±0.62, 97.38±1.04, 96.24±0.74 %) accordingly. In-vitro drug diffusion of formulation was done based on release and optimum viscosity NEG 2 evaluated for ex-vivo permeability flux obtained 0.232 mg/cm2/h. and cumulative amount of drug permeated 3.41 mg/cm² (in 24 h).

KEYWORDS: Teriflunomide, Rheumatoid Arthritis, Nanoemulsion, Nanoemulgel, 3^2 full factorial design, Optimization.

INTRODUCTION

Rheumatoid arthritis is defined as chronic inflammatory disorder that primary affects the synovial joints but can also involve other systems in the body. It is classified as an autoimmune disease because the immune system of body attacks its own tissue particularly the synovium (the lining of the joints). This converts in inflammation that cause joint damage and disability. The condition leads to significant illness due to pain, potential joint destruction and swelling. RA can also have systemic effects, affecting various organs and leading to reduce quality of life. Understanding RA is required for early diagnosis and effective management.[1] Since the patients with rheumatoid arthritis are mainly middle-aged and elderly people, especially those who have difficulty in oral administration. Oral delivery of disease modifying anti-rheumatic drugs (DMARDs) approved for arthritis is related to its side effects of hepatotoxicity, carcinogenicity and hematologic toxicity.[2] In this problem associated with toxicity, use of topical drug delivery as alternative that can lower adverse effects, which is less invasive, reduce gastrointestinal problems, with avoid first-pass metabolism, leads to increase safety and efficacy.[3] Teriflunomide, the active metabolite of leflunomide, is FDA-approved for rheumatoid arthritis (RA). A BCS class II drug with low solubility and high permeability, it works as a disease-modifying antirheumatic drug (DMARD) by inhibiting dihydroorotate dehydrogenase (DHODH) to block pyrimidine synthesis.[4] The oral administration of teriflunomide is associated with serious side effects like hepatotoxicity due to first pass metabolism in liver, leading to higher exposure of hepatocytes to the drug, and severe gastrointestinal side effects.[5] So, it is better

to consider a new drug delivery system for teriflunomide. As, a result the research aims to develop teriflunomide nanoemulgel for transdermal drug delivery system which Avoids first pass metabolism that may reduce direct liver exposure may help with drug related hepatotoxicity and gastro-intestinal irritation. In transdermal drug delivery system (TDDS), use of nanoemulgel was observed as effective strategy for crossing subcutaneous barrier without affecting skin damage and achieving effective drug permeation because of nano size. These systems offer high solubilizing and drug-loading capacities, along with ease of manufacturing. They also enhance stability, safety, and retention time due to their gel-like consistency, which improves spreadability and reduces irritation. Hence, improving patient compliance, therapeutic outcome and also improving drug safety and efficacy.[3,6]

MATERIALS AND METHODS

Teriflunomide free gift sample was procured from Emcure pharmaceuticals, Gujarat. Oleic acid, olive oil, arachis oil, PEG 400, propylene glycol, and Span 80 was procured from Oxford Fine Chem. Tween 80, Tween 20 and IPM were procured from chemdyes corporation, Rajkot. Coconut oil from parachute, sunflower oil from Tirupati and transcutol P was procured from purenso globel. All the components were used were analytical grade for the formulation.

SELECTION OF EXCIPIENTS

Solubility of Teriflunomide in different oils

The solubility of teriflunomide in oils (oleic acid, olive oil, sunflower oil, coconut oil, IPM, arachis oil) was estimated by dissolving excess amount of teriflunomide in each of selected 2ml of oils in stoppered vials.

Sonicator bath was used for sonicate the solution for 10 min then after it was kept for 48 hrs at 37°C (± 0.5°C) in incubator shaker. in the next samples were centrifuged for 20 min at 3000 rpm and the supernants were collected and filtered through a membrane filter (0.45 µm). Then the samples were quantified for the drug content through UV-VIS spectrophotometer at 292nm.[7]

Selection of surfactant and co-surfactants

The selection of surfactant and cosurfactant for the nanoemulsion formulation was based on drug solubility cand percent transmittance criteria. The emulsification efficiency of the surfactant was evaluated by dissolving 200 mg of surfactant in 200 mg of the chosen oil. The mixture was homogenized with mild heating (~40°C) for 30 seconds. From this blend, 40 mg was taken and diluted to 40 mL with water to obtain a nanoemulsion. The resulting emulsion was then kept undisturbed for 2 hours and analysed visually for transparency and phase separation and transmittance was done by UV-VIS spectrophotometer at 638nm using water as blank. The cosurfactant were screened for formulation of nanoemulsions. Mixtures of cosurfactant (100mg), selected surfactant (200mg), and selected oil (300mg) were prepared and evaluated in the same manner as described in the procedure of surfactant screening.[8]

Drug excipients compatibility study

FTIR spectra of drug was obtained by FTIR spectrophotometer. The scanning range was 400-4000 cm^{-1}. The absorption band were compared with the mentioned reference standard peak with reported values. Drug-excipient compatibility is also done for the same drug spectra with observed functional groups.[9]

Construction of pseudo ternary phase diagrams

Aqueous titration method is used for the construction of the pseudoternery phase diagrams of oil, water, surfactant and co-surfactant. Chemix school version 13.5 was used to construct ternary diagrams. Oleic acid used as an oil phase. Smix was used in four different ratios (1:1, 1:2 and 2:1) for optimization and determination of best ratio based on the maxed coverage area of nanoemulsion where oil to Smix ratio taken as 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9. Water was added in dropwise manner by using micro syringe with continuous stirring using magnetic stirrer until turbidity appears in the emulsion and that point considered as end point titration. The end- point of different concentrations of oleic acid, Smix, and water were calculated and constructed as pseudo ternary phase diagrams.[10]

Formulation of nano-emulsions

Spontaneous emulsification method is used to formulate nanoemulsion containing teriflunomide in which teriflunomide was first dissolved in oil, followed by the addition of Transcutol P to the oil phase. The aqueous phase, consisting of Tween 80 and water, was separately formulated then the oil phase is gradually incorporated with aqueous phase with continuous stirring at an optimal temperature to form the nanoemulsion. All formulations were stored at room temperature for further studies.[11]

Optimization of nanoemulsion by response variables effects (3^2 factorial design)

A full 3^2 factorial design was employed to evaluate the effects of oil and Smix concentrations on various parameters, with oil and Smix serving as two independent variables at three levels as shown in table 1 (oil: 5, 10, and 15% w/w; Smix: 45 50, and 55% w/w). The formulated nanoemulsion was analysed for key responses, and experimental data were collected for comparison.[12] Based on a comparative assessment of zeta potential, droplet size, and drug release percentage, the optimal formulation was selected for hydrogel preparation.

Independent variables: X1 = Oil (%), X2 = Smix (%)

Dependent variables R1 = Particle Size (nm), R2 = PDI, R3 = Drug Release (%)

Table 1: Coded and uncoded values for factorial batches.

Factors	Coded value			Uncoded value		
	Low	Medium	High	Low	Medium	High
Independent variables						
X1 = Concentration of Oil (%)	-1	0	+1	5	10	15
X2 = Concentration of Smix (%)	-1	0	+1	45	50	55
Dependent variables						
R1 = Particle Size (nm)						
R2 = PDI						
R3 = Drug Diffusion (%) at 6h						

Table 2: Final formulation table for factorial batches (all quantities is in %w/w.)

Formulation	Teriflunomide (%w/w)	Oil (%w/w)	Smix (%w/w)	Water (%w/w)
F1	1	5	45	49
F2	1	10	45	44
F3	1	15	45	39
F4	1	5	55	39
F5	1	15	55	29
F6	1	10	55	34
F7	1	5	50	44
F8	1	10	50	39
F9	1	15	50	34

Evaluation of nanoemulsions Particle size and PDI

The droplet size and polydispersity index (PDI) of the nanoemulsion were determined using a particle size analyzer (Malvern analytical v2.2) based on the dynamic light scattering technique. Prior to measurement, the samples were sonicated and vortexed to ensure optimal results.[12]

Conductivity analysis of nanoemulsions

This test is for confirmation of formulated emulsion is o/w nanoemulsion. All the aqueous solution has conductance behaviour. A conductivity instrument measures the conductance in which electrode attached to a sensor dipped in emulsion at 25°C. The change in voltage shows conductivity of emulsion.[8]

Percent drug diffusion of nanoemulsions

Franz diffusion cell was used with cellophane membrane for in vitro drug diffusion study. The total capacity of 20ml of Franz diffusion cell was used with internal diameter of 2cm. the donor compartment was placed on the receptor compartment; the receptor compartment was filled with phosphate buffer pH 7.4 and temperature was maintained 37°C± 0.5°C with 100 RPM. a nanoemulsion containing 10mg of teriflunomide on the donor side were added. Samples withdrawn at a fix time interval through the sampling arm of the receptor compartment, at the same time the same amount of phosphate buffer saline 7.4 pH were re-filled and sample analysed by UV-VIS spectrophotometer at 292nm.[8]

Analysis of statistical data and model fit

All the responses of nanoemulsion were observed for nine formulations and fitted to various models by the application of response surface methodology (Design-Expert software version 13).

Selection of optimized batch

The final formulation was selected based on the particle size in nanometer, PDI within range of 0.1 to 0.3 and highest amount of drug diffusion. According to desirability value, the optimized levels of oil and Smix. According to the selected levels using the same methodology teriflunomide loaded nanoemulsion were prepared.

Preparation of Hydrogel

Using a high-speed mechanical stirrer the hydrogel base was prepared, Xanthan gum was used as gelling agent at different concentration (1%, 2% and 3% w/w), where xanthan gum is mixed with distilled water to make gel phase separately. Prepared gel phase was placed for 24h before mixing it with nanoemulsion.[11]

Preparation of Nanoemulgel

The optimized batch of nanoemulsion was selected to formulate nanoemulgel using hydrogel base. The optimized nanoemulsion formulation was mixed with gel base in same ratio (1:1) under gentle stirring for 15 min. three new formulation were formulated for the nanoemulgel with different concentration of gelling agent. A homogeneous nanoemulgel was formulated and the pH of formulation, drug content viscosity, spreadability, in vitro drug diffusion was evaluated.[7]

Evaluation of nanoemulgel pH

The digital pH meter was used for the determination of pH of nanoemulgel. Nanoemulgel was weighted 2g with dispersion with water 20ml. buffer capsules were used to form pH 4, 7 and 9 pH solutions to calibrate digital pH meter. Samples were evaluated in triplicate manner.[12]

Drug content

The drug content present in nanoemulgel was measured by adding 150mg prepared nanoemulgel in 15ml phosphate buffer pH7.4, then this mixture is evaluated for drug content in U.V. Visible spectrophotometer at 292nm. Phosphate buffer 7.4 were used as blank as reference.[12]

Viscosity

Viscosity of nanoemulgel were measured with Brookfield viscometer. The 63 number spindle was used in viscometer and dipped in nanoemulgel and dipped in nanoemulgel formulation then rotated with 100 RPM for 1 min at room temperature. All the samples tested in triplicate.[13]

Spreadability

The spreadability of nanoemulgel was analysed by slip and drag method. This method is made up with two glass slides, a pully was attached to the upper glass slide which one is movable and lower slide is attached to the wooden block. Nanoemulgel equivalent to 500mg were dropped on the lower slide and top slide is sandwiched on lower slide, then the weight (25g) was added on the pully with top glass slide. The time required for this slip is recorded and used to calculate spreadability, expressed in g·cm/s,[14] using the following formula:

Spreadability (S) = M x L/T Where:

- S = Spreadability (g·cm/s)
- M = Weight attached to the upper slide (in grams)
- L = Length of the slide (in cm)
- T = Time taken for the upper slide to detach (in seconds)

Ex-Vivo permeation study

For Ex-vivo permeation study Franz diffusion cell was used with diffusion area of 3.14 cm^2 with the capacity of 20ml receptor compartment. Goat skin was procured from local slaughter house and it was used to perform the study, skin hair was shaved and washed with normal saline, skin was dried using filter paper and used without storage. The skin sample was placed between donor and receptor compartment. Then equivalent to 7mg containing nanoemulgel was filled in donor compartment in Franz diffusion cell. The receptor compartment was filled with phosphate buffer solution pH 7.4 and temperature were maintained at 37 ± 0.5°C at 100 rpm. at a selected time interval, the samples were taken and the same amount of phosphate buffer solution pH 7.4 was refilled and withdrawal samples were analysed using UV Visible spectrophotometer at 292nm. The cumulative amount of drug permeation graph was plotted as %permeability vs time. The rate of permeation at steady state (*J*ss mg/cm^2/h) was calculated from the linear proportion of % permeability graph.[8]

Thermodynamic stability of nanoemulgel[8]

The selected optimized batch formulation of nanoemulgel was only selected for thermodynamic stability of the formulation was done by centrifugation and freeze thaw cycles. The nanoemulgel formulation was centrifuged at 3000 rpm for 30 min and for freeze thaw cycle, nanoemulgel was filled into the test-tube and test-tube was stoppered a stored in freezer for 16h and -21°C and then 8h at room temperature (25°C) the nanoemulgel was evaluated for any change. These cycles were repeated three times.

Accelerated stability studies

With the stressed temperature study performed by using nanoemulgel formulation at different concentration. The formulation was stored on sealed glass container in refrigerator (4°C), room temperature (25°C) and accelerated temperature (40°C) for 30 days and the formulation was evaluated for phase separation, breaking or cracking, drug content and pH.

RESULT AND DISCUSSION

Selections of excipients Solubility of teriflunomide in oils

To formulate a teriflunomide loaded nanoemulsion for transdermal formulation, it should contain good solubility in the formulation because the soluble drug can easily permeate through skin. The solubility of different oil was estimated as shown in fig 1. Teriflunomide has higher solubility in oleic acid (41.24 ± 0.53 mg/ml) than other oils. So, oleic acid was selected as oil phase based on highest solubility.

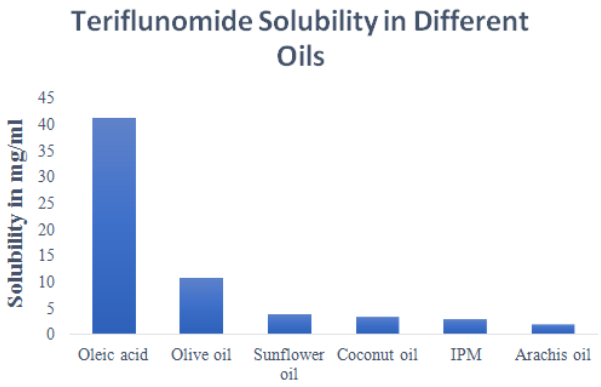

Fig. 1: Teriflunomide Solubility in Different Oils.

Selection of surfactant and co-surfactants

Surfactant and co-surfactant surfactant are based on solubility and their percent transmittance of drug with different surfactant and co-surfactants. Tween 80 shows high solubility (58 ± 1.48) with high percent transmittance as shown in table 3. Similarly in co-surfactant transcutol-p showed highest solubility with percent transmittance. Therefore tween-80 and transcutol-p is selected as surfactant and co-surfactant. However, tween- 80 is non-ionic surfactant which is proved as non-toxic compared to ionic one.and has appropriate (HLB=15) which can result stable nanoemulsion. Transcutol p has already reported as co-surfactants with efficient permeation enhancer, Co-surfactant is used to stabilize emulsion droplets. All the selected surfactant and co- surfactant were FDA (GRAS) approved.

Table 3: Solubility of teriflunomide in different surfactant and co-surfactant.

Surfactants and Co-surfactants	Solubility (mg/ml)	Percent transmittance
Tween 80	58.4 ± 0.48	96.21 ± 0.52
Tween 20	42.22 ± 0.56	92.81 ± 0.82
Span 80	34.13 ± 0.34	89.51 ± 0.69
Transcutol P	63.29 ± 0.60	97.28 ± 0.62
PEG-400	52.82 ± 1.5	96.82 ± 0.45
PG	5.8 ± 0.21	94.98 ± 0.48

Drug excipient compatibility study

The absorption peak in graph were observed of teriflunomide in the range of 450-4000 cm^{-1} the major peak for characteristics were seen at 3304.06 cm-1 (N-H stretch of amide group), 1633.71 cm-1 (C=O (amide carbonyl)), 1072.42 cm-1 (C-F stretching (aromatic fluorine)), 1521.84 cm-1 (C=C), 2220.07 cm-1 (−C ≡N of nitrile group) and 1361.74 cm-1 (-CF-bond).

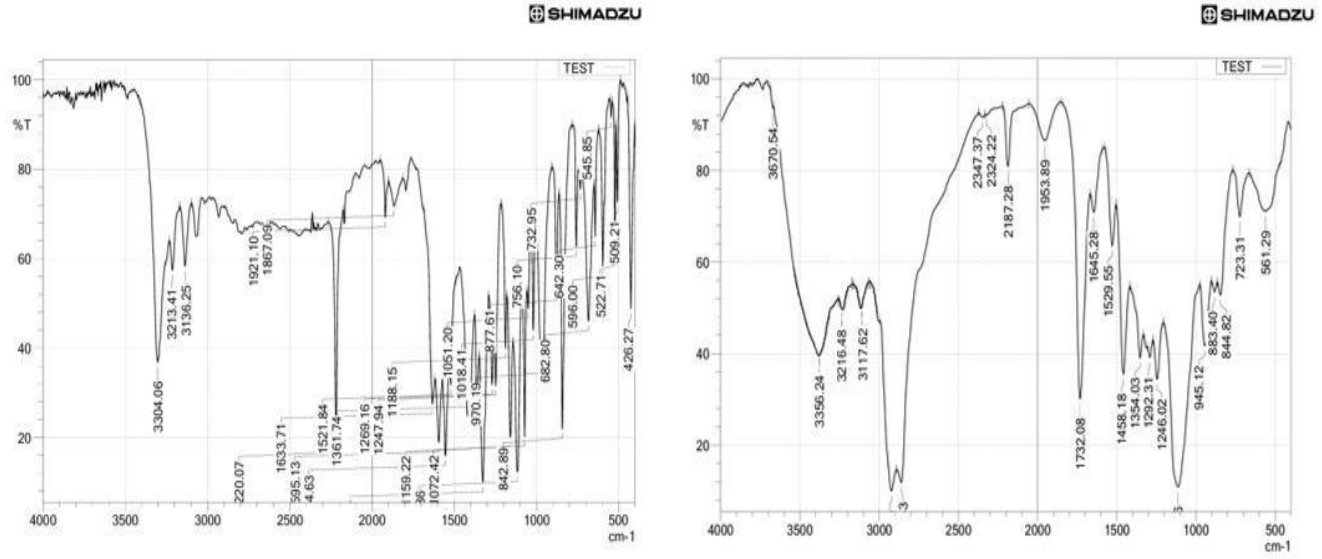

Fig. 2: Observed FTIR spectra of teriflunomide.

Optimization of Smix Ratio by Pseudoternary Phase Diagram

The nanoemulsion was stabilized by the optimum ratio of Smix through the construction of the pseudoternary phase diagram, the transparent region was observed in ternery phase diagram. The rest of the area in the plot was turbid when it was observed visually. The diagrams were separately done for different ratio of surfactant and co- surfactant, and based on this diagrams nanoemulsion region was identified. In Fig.3, from the pseudoternary phase diagram 1:1 smix was used and it is observed with a significant nanoemulsion region as compared to others. Hence, 1:1 ratio of Smix was selected for nanoemulsion formulation.

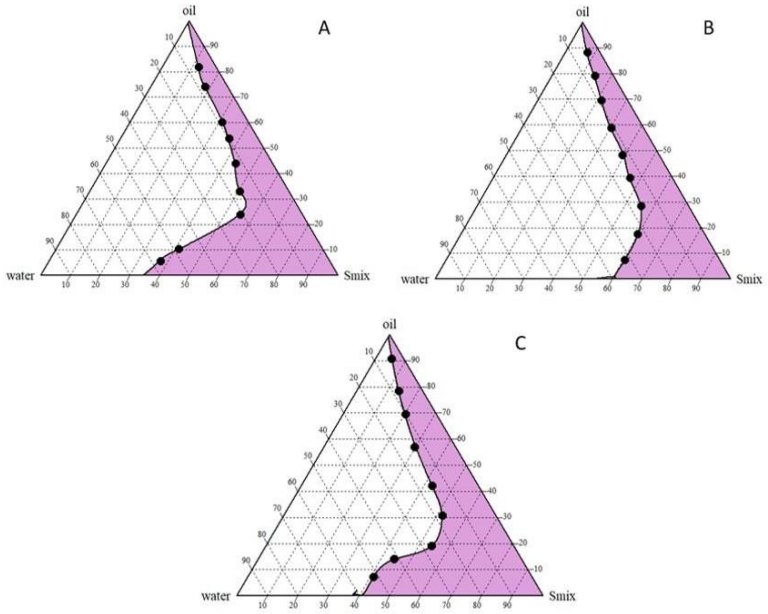

Fig. 3: Ternary diagrams of oil (oleic acid) Smix (Tween 80 and transcutol P). Smix ratio A (1:1), B(1:2), C (2:1).

Optimization of Teriflunomide loaded nanoemulsion by 3^2 factorial designs

The main purpose of 3^2 full factorial design was for selecting the stage of independent variables of oil (X1) and Smix (X2), with particle size, PDI and percent drug diffusion. Nanoemulsion formulations were optimized by 3^2 full factorial design and on the basis of response surface methodology and other evaluation parameters of nanoemulsion formulation.

Table 4: Evaluation parameters of nanoemulsions for batch F1-F9.

Formulation Code	Particle Size (nm)	PDI	Drug release (%)	Conductivity (μS/cm)
F1	176.7 ± 1.8	0.232 ± 0.008	87.19 ± 1.2	160.5 ± 0.25
F2	202.3 ± 2.2	0.24 ± 0.023	89.8 ± 1.1	130.02 ± 0.21
F3	223.6 ± 4.8	0.278 ±0.018	86.4 ± 1.3	109.7 ± 0.42
F4	168.5 ± 2.7	0.142 ± 0.029	89.01 ± 0.9	145.2 ± 0.37
F5	232.2 ± 1.3	0.289 ± 0.012	76.44 ± 1.1	99.15 ± 0.34
F6	185.6 ± 4.6	0.169 ± 0.006	87.73 ± 1.5	119.86 ± 0.24
F7	172.3 ± 3.4	0.188 ± 0.02	86.69 ± 0.9	137.1 ± 0.27
F8	195.4 ± 5.2	0.181 ± 0.02	91.80 ± 1.1	132.05 ± 0.42
F9	219.8 ± 6.6	0.272 ± 0.04	82.01 ± 1.3	109.7 ± 0.32

(n=3±sd)

Characterization of nanoemulsions Particle size and PDI

The smaller particle size of nanoemulsion droplets is good to increase the absorption of drug through skin. As the oleic acid concentration was kept 5% w/w, the droplet size observed as lowest 168.5nm at lowest shown in table 4. Increasing oil concentration to 15% w/w, the droplet size increased to 232.20nm. all the formulation batches observed in nanosized range. The PDI values were low 0.142 to 0.305 that shows narrow distribution of droplet size.

Conductivity of nanoemulsion

The conductivity of nanoemulsion was 99.15 to 160.5 μS/cm which is considered as high and it confirms all the formulations were O/W type nanoemulsion.

Percent drug diffusion

The maximum amount of drug release was observed in F8 formulation (91.89) at within 6 h the release rate of all formulation is shown in figure 4.

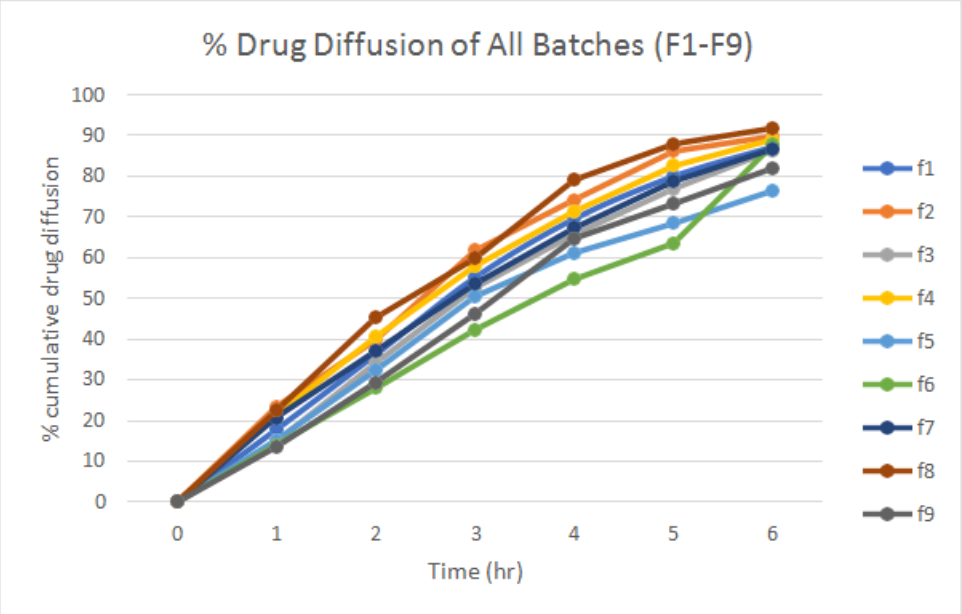

Fig. 4: % cumulative drug diffusion of all batches (F1-F9).

Optimization of nanoemulsions Analysis of statistical data and model fit

From the observed data of nanoemulsion response the nanoemulsion were optimized using different model the best fitted model was used.

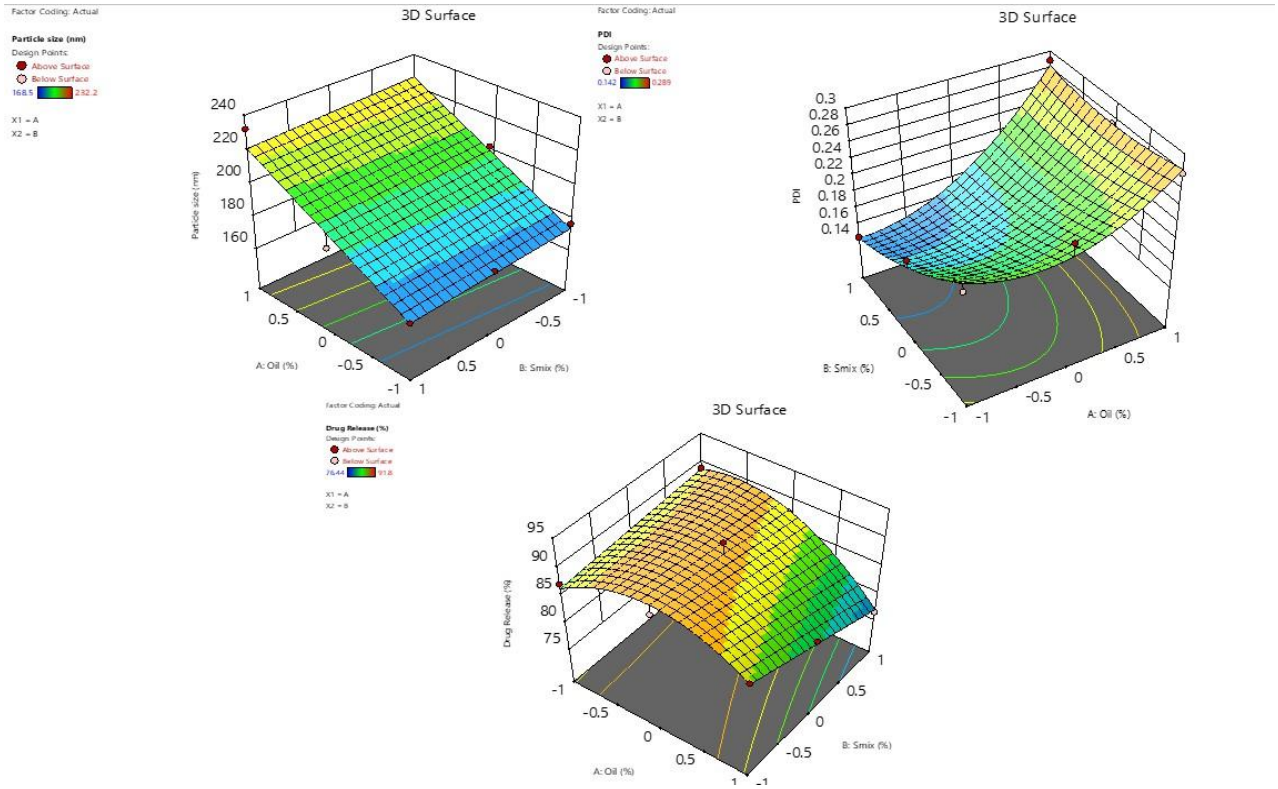

Fig. 5: Different 3d plot for Response surface.

Selection of optimized batch for nanoemulgel formulation

The final formulation was selected based on the particle size in nanometer, PDI within range of 0.1 to 0.3 and highest amount of drug diffusion. The desirability amount was found to be 0.945, the optimized levels of oil and Smix is 10% and 50% respectively. According to the selected levels using the same methodology teriflunomide loaded nanoemulsion was prepared and evaluated as per table 5.

Table 5: Selection of optimized batch.

Independent variables		Dependent variables		
Oil (%)	**Smix (%)**	**Particle size (nm)**	**PDI**	**Drug release (%)**
Predicted values				
10	50	197.378	0.189	89.77
Actual values				
		195.4	0.181	91.8
% Error		0.98	0.95	1.02

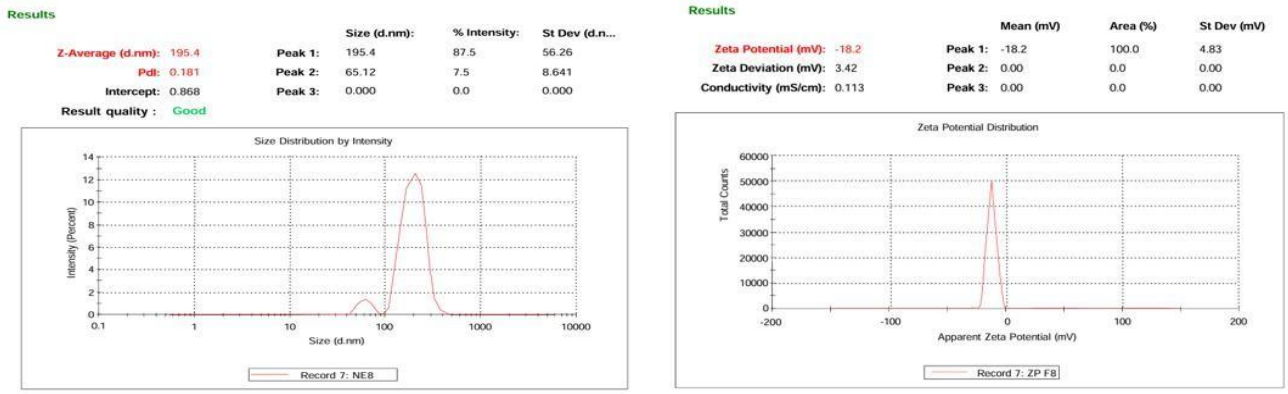

Fig. 6: Particle size and PDI and zeta potential of optimized batch.

Formulation of nanoemulgel from optimized batch

The selected batch is only incorporated in the hydrogel matrix the hydrogel is prepared separately with two different concentration and it is incorporated with the nanoemulsion in 1:1 w/w ratio to observe optimum viscosity. a total three batches were prepared and evaluated with its viscosity, spreadability, drug content, pH and in vitro diffusion study.

Evaluation of nanoemulgel

pH

The pH of all nanoemulgel were observed near to 5.5 which is near to around skin pH (4-6).

Viscosity

The viscosity of all the formulations NEG 1 NEG 2 and NEG 3 were found to be 10,321±174.4, 14,475±176.6 and 16,393±148.3 (mpa·s) accordingly. The NEG 2 contains 2% xanthan gum showed good viscosity among all of them.

Spreadability

Spreadability of nanoemulgel was found as 43.24±2.18, 36.11±3.40 and 22.66±1.87 for all the three formulations.

% Drug content

The drug content present in nanoemulgel were found in good amount 98.80±0.62, 97.38±1.04, and 96.24±0.74. the drug content data shows that equivalent amount of drug distributed in the emulgel formulations.

In-vitro diffusion of nanoemulgel formulations

The percent drug diffusion was shown in the graph where total three formulation of nanoemulgel were evaluated for the diffusion.

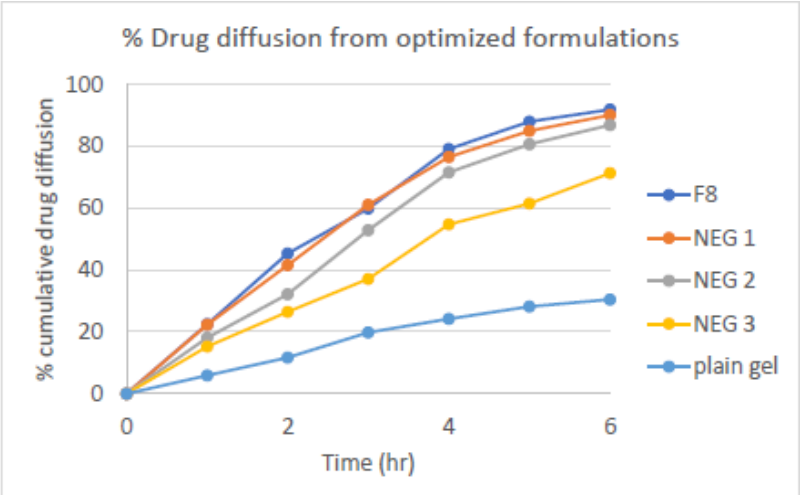

Fig. 7: % Drug diffusion from optimized formulations.

Table 6: Evaluation parameters of nanoemulgel.

Parameters	NEG 1	NEG 2	NEG 3
pH	5.3±0.2	5.4±0.2	5.4±0.3
Spreadability (g.cm/s)	43.24±2.18	36.11±3.40	22.66±1.87
Viscosity (mpa·s)	10,321±174.4	14,475±176.6	16,393±148.3
Drug content (%)	98.80±0.62	97.38±1.04	96.24±0.74

(n=3±sd)

Ex-vivo permeability study

The permeability of NEG-2 was determined for 24h of optimized formulation. Up to 74.89% drug permeation was found within 8hrs shown in fig 8. The ex-vivo flux was observed from the slope of permeability amount of drug at 3-7 hrs and transdermal flux was found to be 0.232mg/cm^2/h. the cumulative amount permeated was found **3.41 mg/cm²** (in 24 h).

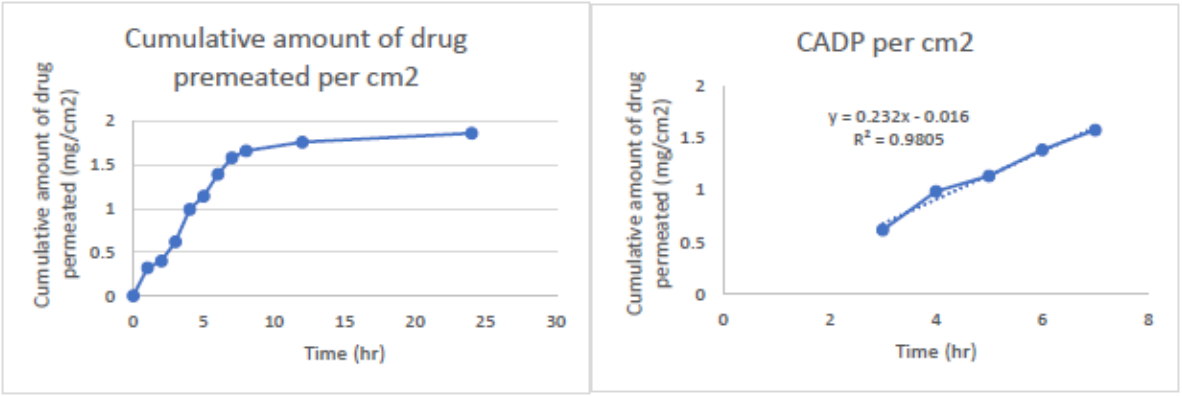

Fig. 8: Ex-vivo Permeability from optimized formulation.

Table 7: Ex-vivo parameters of optimized batch.

Parameter	Value	Unit
Cumulative Amount Permeated	Up to **3.41 mg/cm²** (in 24 h)	mg/cm²
Flux (J)	**0.232**	mg/cm²/h

Stability studies of optimized batch

Selected formulation was centrifuged and no phase separation and precipitation were observed from this it is cleared that formulated nanoemulgel was physically stable and also no phase separation and breaking were observed during freeze thaw cycles.

The results of accelerated stability studies shown in table 8, where it is indicates that nanoemulgel formulations remained stable with their parameters.

Table 8: Stability Studies.

	Temperature	Phase separation	Drug content	Ph
1 day	4℃	-	97.38±1.04	5.42±0.02
	25℃	-	97.34±0.89	5.38±0.13
	40℃	-	97.12±0.94	5.34±0.32
1 month	4℃	-	97.32±0.87	5.52±0.06
	25℃	-	97.31±0.79	5.38±0.22
	40℃	-	97.08±0.83	5.35±0.16

(n=3±sd)

CONCLUSION

The nanoemulsion based hydrogel containing teriflunomide was prepared and evaluated with optimum viscosity for transdermal formulation. Optimized nanoemulsion preparation was incorporated into hydrogel matrix which was made up of xanthan gum as gelling agent. The formulation was stable and highly permeable through skin confirming effective using oleic acid and transcutol p. the formulation confirms good permeability through skin and it can be a good alternative to oral formulation for regular arthritis therapy.

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