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A NOVEL APPROACH FOR TOPICAL GEL CONTAINING SMEDDS LOADED WITH HERBAL DRUG

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ABSTRACT: The present study was approached to prepare SMEDDS loaded herbal drug (THDC4-0475RD) for the arthritis through topical delivery by gel formulation(s). The efficiency of prepared SMEDDS and SMEDDS loaded gel to enhance the delivery of anti arthritic drug were also evaluated. Labrafil and Stelliester were used as oil phase. Cremophor used as surfactant and sodium caprylate, cutina HR pH, Lutrol Micro127, Sepitrap 4000, GMS 40-PW-(SG) as co-surfactant. Formulations were optimized using pseudoternary phase diagram. The finalized formulations (F21 and F24) and the optimized formulation F36 were characterized for various parameters. It is concluded that the research proves, the formulated SMEDDS loaded with drug has increased the solubility of poorly water soluble THDC4-0475RD and thereby increases therapeutic efficiency. It fulfilled all the required criteria of a stable SMEDDS such as globule size, size distribution, *in vitro* diffusion study, and *in vitro* anti-arthritic study. The SMEDDS gel loaded with THDC4-0475RD would be effective against arthritis through topical delivery.

INTRODUCTION: Arthritis is an autoimmune disease which is characterised with joint pain and inflammation. The progression of disease condition is related to both immunological activation and inflammatory pathways. Other sign and symptoms associated is fever, limited mobility, high ESR, fractures, synovial effusion and cartilage damage. A thin delicate lining is known as synovium, cartilage gets essential nutrients from synovium. Collegen, hyaluronic acid and fibronoctis is synthesized by synovium. Cartilage which is made of type 2 collagen and proteoglycans.

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Bone is composed of type 1 collagen. Synovial cavity has highly viscous fluid and few cells. Macrophages and fibroblasts are present in synovial layer. In arthritis cartilage and bone are invade and erode by pannus (hypertrophied synovium). New cartilage formation destructed by cytokines such as IL1 and TNF which in turn generate reactive oxygen and nitrogen and chordrolytic pathway also increases. Polymorph nuclear leukocytes may also cause degradation of bones [1].

Different methods of treatments are available for arthritis such as glucocorticoids, biologic DMARDS, NSAIDs. Many literatures reported that herbal medicines are very effective against rheumatoid arthritis. Drug (THDC4-0475RD) is very effective against in treatment of inflammatory conditions such as arthritis [2].

It inhibits the action of 5-lipoxygenenase and also act on immune system. The drug is available in different dosage forms but it is poorly absorbed through intestine, to achieve the maximum bioavailability and the therapeutic efficacy is very difficult. Hence the present study is focused on alternative ways to deliver the drug to achieve maximum bioavailability. To increase the bio-availability, the drug was formulated to SMEDDS gel which in turn enhance therapeutic efficacy by high permeation and SMEDDS gel avoids intestinal effect also. Hence it proves that SMEDDS gel is best way to deliver this drug for arthritis [3].

Oral drug delivery system and conventional topical drug delivery (ointment / cream / gel) are general /common approaches to treat arthritis. Oral delivery has own disadvantages like poor bioavailability, other side effects, adverse drug reactions and poor drug delivery at target site. Topical drug delivery has disadvantages like low dose drug loading, poor bioavailability and poor penetration to the target site [4]. To overcome these disadvantages research was carried out on SMEDDS. Through SMEDDS, high level drug delivery can be deliver at target site, can improve the bioavailability. SMEDDS preparation have been administered through oral is major. Thus, present investigation had developed why can't SMEEDS through topical unlike conventional topical gel, this approaches definitely overcome all the disadvantages of topical as well as oral delivery for arthritis. The main aim in treatment of arthritis is to control pain and inflammation.

SMEDDS is the mixture of oil, surfactant and co-surfactant. These combinations attributed in the solubility of poorly water soluble drugs. SMEDDS has been gained more attention due to its efficiency in solubilization and capability to enhance bioavailability [5]. SMEEDS is a transparent mixture which has oil, surfactant and co-surfactant as the ingredients. These three are the major composition of SMEDDS, apart from this permeation enhancer, co solvents, consistency builders can also use in the formulation. One of the characters of SMEDDS is that they are stable to self emulsify in aqueous solutions. It forms small oil droplets when it gets emulsify with aqueous solutions which increases the rate of diffusion and bioavailability.

Isotropic mixture which posses particle size less than 500nm are considered as SMEDDS. SMEDDS are physically stable formulation [6]. One of the important criteria in the formulation design is selection of oil. The selected oil must be capable of dissolving the required quantity of drug. It also should capable of improving the self emulsification process. Lipid phase polarity and solubility of drug is another factor to be considered in formulation. SMEDDS is not appropriate dosage form for high dose drugs unless it has good solubility because there is a chance to precipitate the drug in aqueous solution [7]. Drugs which has high melting point are also not suitable for SMEDDS. SMEDDS is a liquid formulation but it has stability issues hence alternatives have been developed as a result, liquid SMEDDS can also convert into solid dosage forms such as capsules, tablets, suppositories, microsponges *etc*. SMEDDS can be converted into solid by different methods such as Spray drying, Adsorption into carrier, Melt granulation and Melt extrusion [8].

Unlike conventional solid dosage forms, interaction of liquid SMEDDS with soft gelatin capsules during storage which is not negligible and conversion into tablet is also not easy for SMEDDS as it is expensive. Hence the present study was focused on the SMEDDS natural drug loaded gel for arthritis. It can be used to overcome the issues related to stability of SMEDDS when it converted into gel. It has the potency to deliver natural drugs for arthritis as targeted drug delivery through skin due to enhanced solubility and permeation [9].

MATERIALS AND METHOD:

Materials: Cremphor RH 40, stelleister MCT, Labrafil M 1944CS, Sodium caprylate, Cutina HR PH, Lutrol Micro 127, Sepitrap 4000, GMS 40-PW-(SG) are the materials used for formulation of SMEDDS natural drug loaded gel. Herbal drug (spray dried powder) (THDC4-0475RD) have received from The Himalaya drug company, Bangalore. It is well known herbal medicine commonly used to relive pain by oral and topical.

Method:

Solubility of Drug: Several oils were tested to dissolve the herbal drug. In a test tube, 10ml oil was taken, into that 10mg of drug was added and sonicated for 5minutes. The solution was observed

visually for precipitation and sedimentation and then analysed the % of drug solubilised.

Screening of Surfactant: Surfactants were mixed with oil and then heated gently at 40 °C. It was stirred until it forms homogeneous mixture. This mixture was diluted with distilled water for homogeneity and transparent evaluation. It was observed periodically at different intervals such as 2hr, 8hr, 12hr, and 24hr which were kept at room temperature. Physical stability was checked visually and observed for presence of turbidity and phase separation.

Screening of Co - surfactant: Based on emulsification time co-surfactant was selected. Co-surfactants were mixed with oil phase and surfactant. Similar procedure of surfactant screening was also used for co-surfactant screening. It should able to form oil in water emulsion and the herbal drug should be chemically and physically stable in S_{mix} (Self emulsifying mixture) [10].

Mutual Miscibility of Excipients: Various proportions of drug, surfactant, Co-surfactant was taken in a test tube and shaken vigorously. To ensure the proper miscibility, the mixture was kept overnight.

Construction of Pseudoternary Phase Diagram: Water titration method was used to construct pseudoternary phase diagram. S_{mix} mixture was prepared with varying concentration of surfactant, and co-surfactant. S_{mix} were prepared in different ratios (1:1, 2:1, 3:1, 4:1). Then the prepared S_{mix} were mixed with oil in different ratios. Oil and S_{mix} mixture was stirred for 3-5 min. A transparent homogeneous mixture was formed after titrating with water which was observed for phase separation and clarity. Titration stopped once the turbidity or bluish colour appears in the solution. At this point, oil, surfactant and co-surfactant value was noted and self micro emulsifying region was noted. ProSim ternary phase diagram was used to construct phase diagram [11].

Preparation of Optimized L-SMEDDS: Labrafil and Stelliester (1:1) were taken in a beaker. 5gm quantity of drug was weighed and dissolved in oil phase. Surfactant and co- surfactant was taken in another beaker and stirred with magnetic stir at 40 °C for 100 rpm. This mixture is called as $S_{mix.}$ Oil phase was added into S_{mix} in dropwise to form O/W emulsion and stirred until it form homogeneous mixture [12].

TABLE 1: COMPOSITION OF LIQUID SMEDDS

S. no.	Ingredients	Quantity (%)
1	Drug	5
2	S_{mix}	5
3	Oil	40

Conversion of L-MSEDDS into Semisolid SMEDDS Gel: Flocculation method was followed for preparation of SMEDDS gel. Carbopol 940 was used as gelling agent. 0.05g of preservatives such as methyl paraben and propyl paraben was dissolved in 100ml of distilled water. 5g of carbopol 940 was weighed and added into the above beaker and stirred with mechanical stirrer until it forms a gel. As a rubefacient, such as menthol was dissolved in propylene glycol and was added to the above gel. To this gel, the liquid SMEDDS contain 1g of the drug was added drop wise and stirred well until the liquid SMEDDS gets homogenously mixed with the gel [13].

TABLE 2: COMPOSITION OF SMEDDS GEL

S. no.	Ingredients	Quantity (%)
1	Carbopol 940	5
2	SMEDDS	10
3	Methyl paraben	0.05
4	Propyl paraben	0.05
5	Propylene Glycol	2
6	Menthol	0.5
7	Water	Q.S.

Evaluation of L- SMEDDS:

Thermodynamic Stability Study: Six cycle freeze thaw test was carried out to confirm it's thermodynamically stability. The L-SMEDDS sample was placed in two different temperatures such as - 4 °C and 40 °C for 24 hr each. After each cycle, the sample was observed for phase separation and precipitation. Centrifugation was done at 3000rpm for 15min and visually observed for phase separation.

Physical evaluations such as self emulsification time, dispersibility test, % transmittance, dilution robustness, cloud point measurement, dye solubilisation test, microscopical analysis, viscosity studies and drug content characterized for prepared L-SMEDDS[14].

Evaluation of SMEDDS Loaded Gel:

Globule Shape Analysis of Gel: 1gm of sample was dissolved in purified water and agitated few minutes for homogeneous dispersion. Mean globule diameter and distribution were observed using motic microscope.

Droplet Size Analysis of Gel: 1% w/v diluted SMEDDS using distilled water was prepared for the determination of droplet size using photon correlation method [15].

Spreading Coefficient: 1cm circle was drawn on glass slide. The prepared gel was placed on that. Another glass slide was placed on the gel. 5 g weight was placed on the top of two slides for 5 min. to form a uniform film and to expel the air between the slides. The distance of the gel being spread over the slide was noted.

Extrudability Study of Gel: 5gm of gel was taken in a lacquered aluminum collapsible tube. Weight was applied on it to extrude the gel. The amount of gel extruded was noted with time taken to extrude. Extrudability can calculate by [16].

Extrudability = Applied weight to extrude gel from tube (in g) / Area (in cm^2)

Drug Content Determination: 1g of gel was taken, mixed in DMSO and filtered to obtain clear solution. Its absorbance was determined using UV spectrophotometer [17].

***In-vitro* Diffusion Study:** Drug release study was done using Franz diffusion cell. SMEDDS gel was evenly applied on the semi permeable membrane, which is clamped between receptor and donor chamber. Phosphate buffer 7.4 was used as medium. It was filled in receptor chamber and stirred using Magnetic stirrer. 1ml of sample was taken at different time intervals and the drug content was analyzed by UV spectrophotometer [18].

***In-vitro* Anti-arthritic Activity:** *In vitro* anti-arthritic activity study was carried out based on protein Denaturation method. Test solution was prepared with 0.45ml bovine serum albumin. 1N HCl was used to adjust the pH to 6.3. The samples was then incubated at 37 °C for 20minutes and heated at 57 °C for 3 minutes. 2.5ml of phosphate buffer pH 6.3 was added to the cooled sample. Test control was prepared using distilled water with bovine serum albumin and standard solution was prepared with 0.05ml of Diclofenac sodium solution in various concentrations with bovine serum albumin, rest of the procedures of test control and standard solution followed as similar as with test solution preparation[19].

The percentage inhibition of protein denaturation was calculated as follows.

Percent Inhibition = 100 – [OD of test solution – OD of test control] X100/ OD of test control

The control represents 100% protein denaturation. The result was then compared with Diclofenac sodium.

Stability Studies: The prepared SMEDDS gel were packed in Aluminium collapsible tubes (5g) and subjected for stability studies at room temperature and 40 °C / 75% RH for a month. Samples were withdrawn at 15 day time intervals and evaluated for physical appearance, pH, viscosity, drug content and drug release profile [20].

RESULT AND DISCUSSION:

Analytical Methods:

Excipient Compatability Study: Herbal drug and excipients compatibility studies were done by FTIR method. The characteristics peak was found to be identical to that of the pure drug. This is confirmed the intactness that there were no interactions between drug and excipients at different ratios.

TABLE 3: DRUG EXCIPIENT COMPATIBILITY STUDY

S. no.	Composition Details	Storage Condition 40 °C /7 5% RH	
		Initial	1 Month
1.	THDC4-0475RD alone	Buff colour powder	NCC
2.	THDC4-0475RD + Lutrol micro	Pale buff colour	NCC
3.	THDC4-0475RD + Sepitrap 4000	Pale buff colour	NCC
4.	THDC4-0475RD + Sodium caprylate	Pale buff colour	NCC
5.	THDC4-0475RD + Cutina HR pH	Pale buff colour	NCC
6.	THDC4-0475RD + GMS	Pale buff colour	NCC

NCC- No characteristic change

The above test was performed to study the compatibility of drug with excipients under accelerated condition. No characteristic changes were observed between the herbal drug and excipients. Hence, it confirms the physical compatibility of the excipients with the herbal active ingredient. Further, the compatibility studies were also analysed by FTIR. It was found the herbal drug shows band highest wave number at 3822 cm^{-1} corresponding to OH stretching, At the lower wave number region, C=O, C=N stretching at 1750 cm^{-1}. The other functional group was found to be at wave number 3741 cm^{-1} corresponding to NH stretching single bond, wave number 2359 cm^{-1} -C≡X stretching. Same functional group was found in combination of drug and excipients. Hence, the FTIR spectra of herbal drug, excipients and the formulation indicate that there are no interactions between the drug and the excipients.

Screening of Surfactants: Skin irritation is one of the drawbacks of surfactant. Thus, proper selection of surfactants is important criterion for the formulation. Non ionic surfactant was selected from the pool of surfactants to avoid skin irritation. Surfactants which have HLB value between 12 - 14 is considered as suitable for SMEDDS. Self emulsification time is also important parameter in selection of surfactant.

Pseudo Ternary Phase Diagram: Pseudo ternary phase diagram was constructed to identify the self micro emulsifying region. It was constructed using different ratios of surfactant and co-surfactant (1:1, 1:2, 1:3, 1:4). Then S_{mix} was mixed with oil in different ratios (4.5:0.5, 4:1, 3.5:1.5, 3:2, 2.5:2.5, 2:3, 1.5:3.5, 1:4.0, 0.5:4.5). This mixture was then titrated with water.

TABLE 4: TRIAL BATCHES OF LIQUID SMEDDS BEFORE WATER TITRATION

S_{mix}: Oil	Appearance			
	Ratio 1:1(F1-F9)	Ratio 2:1 (F10-F18)	Ratio 3:1 (F19-27)	Ratio 4:1 (F28-36)
4.5:0.5	Off white precipitate	Off white, free flowing	Immiscible	Immiscible
4:1	Milky white	White, very viscous	Immiscible Milky white, free flowing	White viscous
3.5:1.5	Viscous white milky	Milky white, viscous	Clear viscous	Milky white free flowing
3:2	Precipitate	Clear, yellow in colour, Viscous	Milky white very viscous	Milky white very viscous
2.5:2.5	Turbid viscous	Yellow clear, viscous liquid	Milky white slight viscous	Milky white slight viscous
2:3	Turbid	Milky white, free flowing	Clear free flowing	Milky white free flowing
1.5:3.5	Turbid	Off white, slight viscous	Clear	Turbid
1:4	Turbid	Turbid	Milky white slight viscous	Milky white slight viscous
0.5:4.5	Turbid	Milky white, slight viscous	Milky white slight viscous free flowing	Clear

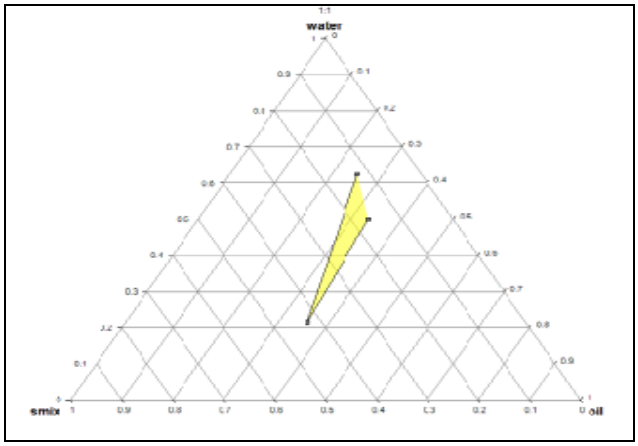

FIG. 1: RATIO 1:1

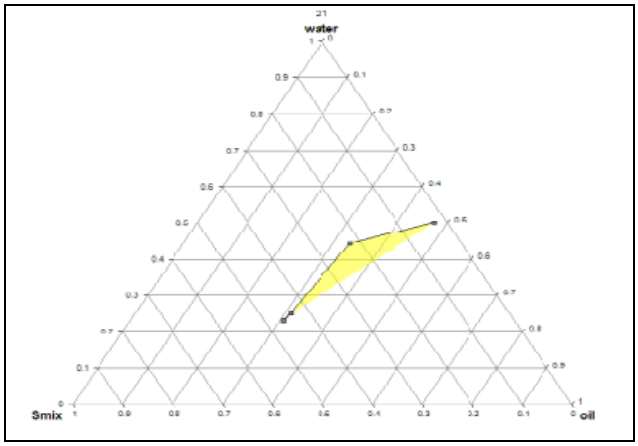

FIG. 2: RATIO 2:1

All the trial batches of the liquid SMEEDS were titrated with water to check for its miscibility with S_{mix} and oil to ensure the self emulsification which was substantiated by the formation of turbidity. Addition of water was stopped once the turbidity appeared. It was found ratio 3:1 and 4:1 formed maximum clear self microemulsion, it may be due to varying the concentration of surfactant and oil. The concentration of surfactant is more in 3:1 and 4:1 than the other two ratios.

Pseudo Ternary Phase Diagrams: The pseudoternary phase diagram for S_{mix}, oil and water was constructed using proSim software and the self emulsification region was identified.

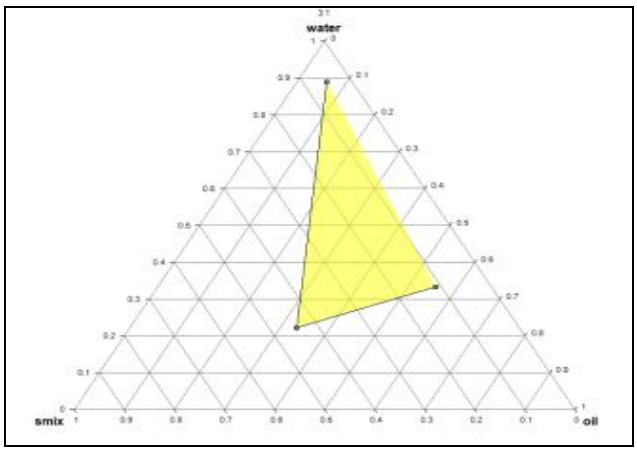

FIG. 3: RATIO 3:1

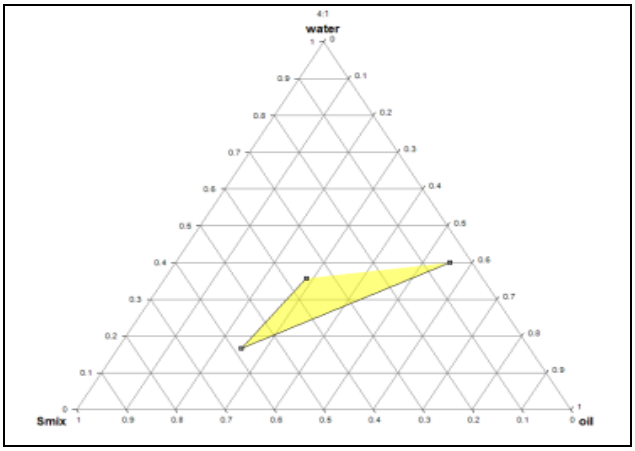

FIG. 4: RATIO 4:1

It was found that the surfactant and co-surfactant ratios of 3:1 and 4:1 showed maximum self micro emulsifying region from the pseudo ternary phase diagram. It was observed that increase in the concentration of surfactant and co-surfactant increases the self micro emulsifying region. There was no difference found in the region after incorporation of drug into it. Based on the pseudo ternary phase diagram and visual observation by water titration, formulations F36, F21, F22, F24, F25 from ratio 3:1 and 4:1 were selected for further studies.

Solubility Study:

TABLE 5: SOLUBILITY STUDY PROFILE OF DRUG AND EXCIPIENT

Materials	Water	Co-solvents	Isopropyl alcohol	Oil (castor & olive oil)	Labrafil	Stelliester	Cremophor
THDC4-0475RD	Insoluble	Partially soluble	Partially soluble	Insoluble	Soluble	Soluble	Partially soluble
Lutrol	Soluble	Soluble	Soluble	Insoluble	-	-	-
Sepitrap	Sparingly soluble	Partially soluble	Insoluble	Insoluble	-	-	-
Sodium caprylate	Soluble	Soluble	Insoluble	Insoluble	-	-	-
Cutina	Insoluble	Forming lumps	Insoluble	Insoluble	-	-	-
Gms 40-pw(SG)	Insoluble	Insoluble	Insoluble	Insoluble	-	-	-

(THDC4-0475RD) solubility in different solvents were performed using with different excipients. It was found that the (THDC4-0475RD) drug was highly soluble in Stelliester and Labrafil which were selected further as the oil phase in the preparation of SMEDDS. Cremophor was selected as the surfactant. The sodium caprylate, cutina HR PH, Lutrol Micro127, Sepitrap 4000, GMS 40-PW-(SG) were selected as co-surfactants based on their solubility.

Characterization of L-SMEDDS:

Self Emulsification Time, Dispersibility Test, % Transmittance: Self emulsification time of prepared SMEDDS was evaluated by visually. 1ml of the SMEDDS was diluted with distilled water. The results are given in (**Table 6**). The result of the self emulsification showed 4:1 is better when among other formulations. This is may be due to the increased concentration of surfactant in the formulation. Thus leading to faster emulsification.

TABLE 6: SELF EMULSIFICATION TIME, DISPERSIBILITY TEST, % TRANSMITTANCE

Batch no.	Time	Dispersibility test	%Transmittance
F36	40sec	Bluish white	82.32±0.4
F21	58sec	Bluish white	52.40±0.08
F22	98sec	Cloudy	24.33±0.95
F24	112sec	Cloudy	0.25±0.01
F25	118sec	Precipitate	0.23±0.013

Dispersability test was performed to confirm the type of formulation whether it is microemulsion, microgel, emulsion or emulgel. It is done to further substantiate the stability of the formulation. The formulation was observed by visually for clarity once diluted with distilled water. Based on their

appearance, the formulations were classified into different grades. The dispersability test showed that the formulation F36 and F21 were observed to have better results giving bluish white coloured solution compared with other ratios which precipitated or appeared cloudy.

Percentage transmittance is to find out clarity of the prepared SMEDDS. The transparency of the micro emulsion was measured in terms of % transmittance. The clarity of the formulation was compared with the value of water. The formulation which has high transparent value indicates the transparency of micro emulsion. The transparency is due to the particle size, if the particle size is high oil globules will reduce the transparency of micro emulsion. The values of % transmittance of the batches are given in (**Table 8**). The results show that % transmittance shows that the formulation F36, F21 showed better transmittance as compared with other batches.

Shape Analysis: L-SMEDDS were diluted with distilled water. The diluted SMEDDS was observed under motic microscope.

Before dilution

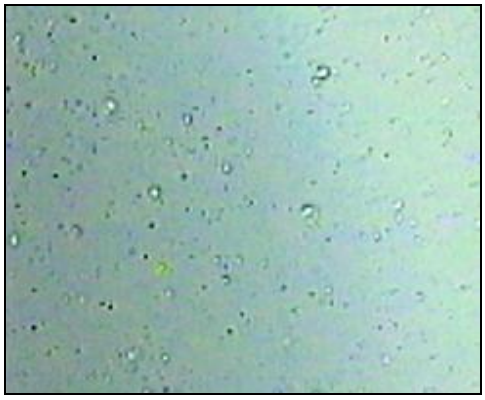

FIG. 5: [4:1(0.5:4.5)]

After dilution

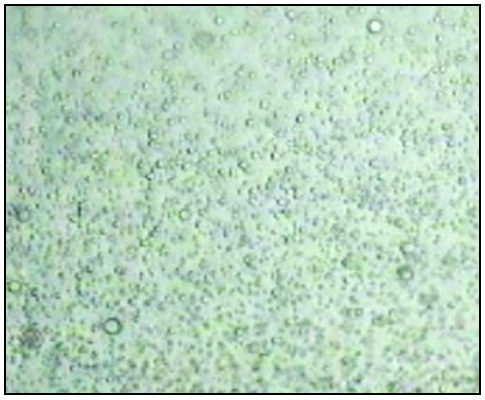

FIG. 6: [4:1(0.5:4.5)]

All the formulations were observed with spherical and uniform globules which prove that emulsion has been formed.

Dilution Robustness: 1ml of F36, F21, F22, F24 was diluted with distilled water into 50, 100, 250, 500, and 1000 times and kept at room temperature for 24hr and was observed visually for phase separation and drug precipitation. It was found the formulation were stable without no phase separation. The observations were given in (**Table 9**).

TABLE 9: DILUTION ROBUSTNESS

Batch no.	Observations
F36	No phase separation and no drug precipitation
F21	No phase separation, turbid
F22	No phase separation, turbid
F24	No phase separation, turbid
F25	No phase separation, turbid

It was found the all the formulation were stable without any phase separation and no drug precipitation which proves that all the selected formulations would not get precipitate when the SMEDDS diluted with body fluid.

Dye Solubilization Test: Rapid incorporation of 2drops of sudan red into the system was observed, indicated that the continuous phase was water, which signified the formation of o/w micro emulsion. From this test it was found all the formulations were oil in water.

Cloud Point Measurement: Cloud point of prepared liquid SMEDDS was found to be higher than 90 ^{o}C, which indicate that the prepared formulation will be stable without risk of phase separation at physiological temperature. The formulations observed visually for phase separation and drug precipitation.

TABLE 10: CLOUD POINT MEASUREMENT

Batch no.	Observation
F36	No phase separation and no drug precipitation
F21	No phase separation but drug precipitated
F22	No phase separation but drug precipitated
F24	No phase separation but drug precipitated
F25	No phase separation but drug precipitated

From the above results, it was found the formulation F36 was better when compared with other formulations since it did not show any phase separation and no drug precipitation. This may be due to high solubility of (THDC4-0475RD) in optimum oil concentration (4.5ml). It confirms that the formulation was stable till 90 °C without any phase separation and no drug precipitation.

Viscosity: When SMEDDS was diluted with 10 times and 100 times with distilled water, the viscosity of the initial formulation was decreased and became similar to the water. Viscosity of the formulations which has low viscosity indicates the formulations are oil in water emulsion.

TABLE 11: VISCOSITY OF LIQUID SMEDDS

Batch No.	Observation(cps)	Drug Content (%)
F36	24.7±0.98	88.7±0.4
F21	30.6±0.96	86.1±0.6
F22	70.4±0.94	80±0.4
F24	29.5±0.95	82.3±0.5
F25	34±0.97	80.6±0.3

The viscosity was found to be low in F36 when compare with other formulations. It may be due to the presence of optimum concentration (0.5ml) of surfactant. Drug content of the prepared formulations were evaluated to ensure that the uniform distribution of drugs in the formulations. The % drug content of F36 found to be 88.7% which was higher compared with other formulations which may be attributed to the smaller globule size in the SMEDDS.

Thermodynamic Stability Studies:

Freeze Thaw Cycle: Physical stability is one of the important characteristics for the SMEDDS appearance. The performance of the SMEDDS can be affected by the precipitation of drug. Poor physical stability of SMEDDS can even lead to phase separation. There are chances to affect the stability by different temperature conditions. Hence it is essential to check whether the formulation can withstand in different temperature conditions. Therefore thermodynamic study was conducted to confirm the physical stability.

TABLE 12: HEATING AND COOLING CYCLE

Batch no.	Cycles	Observations
F36	1	NPS, pale yellow colour
	2	NPS, pale yellow colour
	3	NPS, pale yellow colour
	4	NPS, pale yellow colour
	5	NPS, pale yellow colour
	6	NPS, pale yellow colour
F21	1	NPS, brownish colour
	2	NPS, brownish colour
	3	NPS, brownish colour
	4	NPS, light brownish colour
	5	NPS, light brownish colour
	6	NPS, light brownish colour
F22	1	NPS, light brownish colour
	2	PS, light brownish colour
	3	PS, light brownish colour
	4	PS, dark brownish colour
	5	PS, dark brownish colour
	6	PS, dark brownish colour
F24	1	NPS, light brownish colour
	2	NPS, light brownish colour
	3	NPS, light brownish colour
	4	NPS, light brownish colour
	5	NPS, light brownish colour
	6	NPS, dark brownish colour
F25	1	PS, pale yellow colour
	2	PS, pale yellow colour
	3	PS, white free flowing
	4	PS, white viscous
	5	PS, white viscous
	6	PS, white viscous

Hence the formulations were subjected to heating-cooling cycle and centrifugation while freeze thaw cycles. Heating cooling was carried out for six cycles at - 4 °C and 40 °C in alternative manner for 24 hr in each temperature; which was considered as one cycle. It was observed that the formulations did not show any phase separation. Thus they were then centrifuged for 30 minutes which resulted in phase separation of F 22 and F25 and the other 3 formulations (F36, F21, F24) remained stable.

Freeze thaw study, confirms that all formulations passed the heating and cooling cycle and F36, F21, F24 were comply in centrifugation test. Hence forth F36 was considered as best formulation, since, it did not show phase separation and there was no change found in appearance of the formulation. It remained stable in all the conditions including during centrifugation. Formulations which did not

show phase separation after centrifugation were taken for *in vitro* studies.

Droplet Size Analysis: Rate and extent of drug release is determined by the size of droplets. Smaller the droplet size will be increases the bioavailability due to its increased surface area. Drug diffusion will be faster. Droplet size can be decreased with increase in concentration of surfactants up to certain concentration. The mean droplet size of F36 from liquid SMEDDS mixture was found to be 566nm.

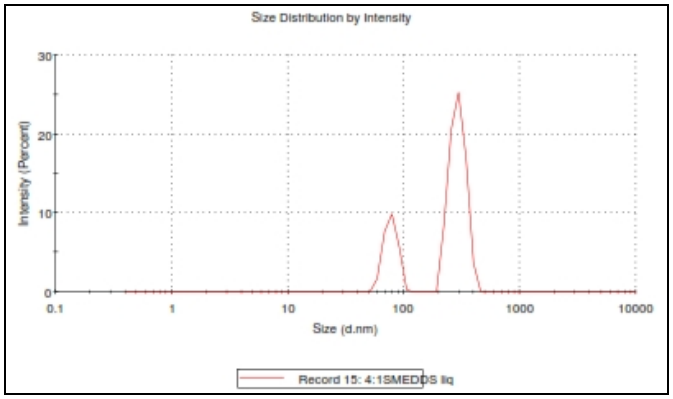

FIG. 7: DROPLET SIZE ANALYSIS

***In-vitro* Drug Diffusion Study:** The *in vitro* drug release study was carried out using Franz diffusion cell for all the prepared formulations. The study was carried out for 60 min with time interval of 15minutes. From the result it was found among all the three formulations (F21, F24, F36); F36 gave maximum release such as 103% at the end of 60 min; whereas F21 and F24, was only 52.6% and 85.6% respectively. Maximum release in F36 may be due to its small particle size.

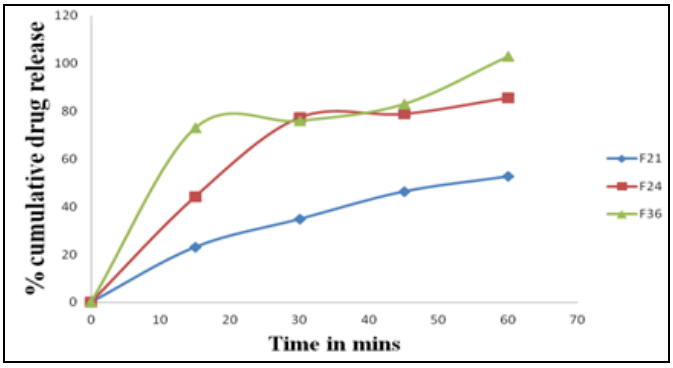

FIG. 8: *IN VITRO* DIFFUSION STUDY

***In vitro* Antiarthritic Activity of L- SMEDDS:** The prepared formulation was evaluated for its *in vitro* anti arthritic activity using BSA. The percentage inhibition of protein denaturation calculated.

TABLE 13: *IN VITRO* ANTI-ARTHRITIC ACTIVITY OF LIQUID SMEDDS

S. no.	Concentration (µg/ml)	Percentage Inhibition (%)			
		F21	F24	F36	Diclofenac Sodium
1	50	3.3 ±0.1	10 ±0.5	58.8 ±0.4	42.116 ±0.04
2	100	4.09 ±0.16	39.02 ±0.3	52.45 ±0.4	53.886 ±1.2
3	200	51.73 ±1.3	58.50 ±0.5	58.87 ±0.6	61.276 ±1
4	400	56.6 ±1.1	46.46 ±0.1	62.43 ±0.8	67.43 ±1.1
5	800	61.58 ±1.4	61.41 ±0.5	69 ±0.4	75.905 ±1.1
6	1000	62.7 ±1.7	59.6 ±0.4	80.12 ±0.6	89.39 ±0.5

Values are reported as mean ± Standard Deviation, n = 3

It was found the formulation F36 has maximum % inhibition when compared to other two formulations and was showed a concentration dependent increase in % inhibition. F36 shows concordant results, when increasing the concentration, % of inhibition also increasing. Unlike % of inhibition of F36 is similar with Diclofenac sodium. Thus confirms that F36 would have high drug delivery capacity as that of equal to Diclofenac sodium.

Evaluation of SMEDDS Loaded Transdermal Gel: The best three batches of SMEDDS were formulated as transdermal gel and were evaluated for following parameters.

Characterization of Gel:

Physical Appearance: Physical appearance was evaluated visually.

TABLE 14: PHYSICAL APPEARANCE OF GEL

Batch no.	Colour	Homogeneity	Consistency	pH value
F36	White	No gritty particles	Gel	6.8±0.1
F21	White	No gritty particles	Gel	6.3±0.3
F24	White	No gritty particles	Gel	6.1±0.1

All the formulations showed satisfactory results in their colour, homogeneity and consistency. It was found the pH of the prepared gels were feasible for skin pH. The pH of the gel was almost neutral proving that the gel will be not irritant on skin. Normal skin pH is slightly acidic which helps to

protect the skin from bacterial infections. If the formulation is acidic it will cause redness and if alkali it cause dryness. Prepared gels show slightly acidic and almost near to neutral hence it is suitable to apply on skin without any irritation. Spreadability is one of the important criterias to achive patient compliance. It is depends on the viscosity. Of course, viscosity is also one of the important parameters to evaluate the characteristic of gel.

TABLE 15: VISCOSITY, SPREADABILITY AND EXTRUDABILITY OF SMEDDS LOADED GEL

Batch no.	Viscosity (cps)	Spreadability (cm)	Extrudability (g/cm^2)
F36	29.25±0.3	7.4±0.1	16.75±0.65
F21	79.75±0.5	5.2±0.1	14.55±0.28
F24	93.50±0.2	5.6±0.3	14.84±0.58

Values are reported as mean ± Standard Deviation, n = 3

All gels (F21, F24, F36) the formulation which showed good spreadability in less time. It was considered excellent based on viscosity, Spreadability gel extrudability and drug release. Thus, the patient should able to apply the gel uniformly on skin. Extrudability, the factor in the perspective of patient complaince. The formulation which can be easily extruded and would not be in pourable conditions will only satisfy the need of patient. F36 showed better performance among all the selected gels. Better ribbon formation and the gel strength was found high in F36 than other formulations. It may due to the optimum concentration of carbopol.

Hence F36 was considered as the best formulation. The prepared gel SMEDDS was screened and observed for its drug content using UV spectrometer. Maximum drug content was found in F36 as 78.01% than other two formulations such as F21 and F24, 65.03 and 71.5 respectively.

Droplet Size Analysis of SMEDDS Loaded Gel: Droplet size analysis of the SMEEDS loaded gel was performed and it was found the size of the droplet was reduced into smaller. It may be due to stirring during the preparation SMEDDS loaded gel. The average droplet size of the SMEDDS loaded gel is 456nm.

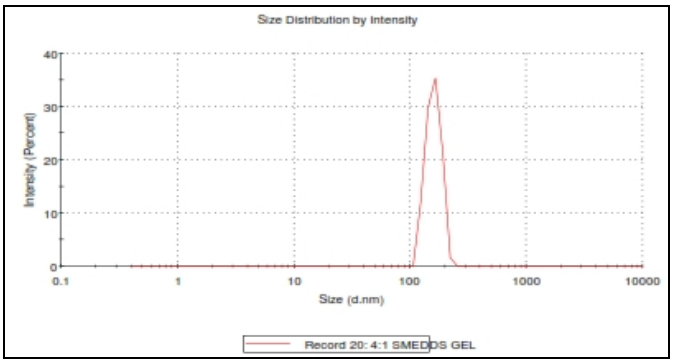

FIG. 9: DROPLET SIZE ANALYSIS OF SMEDDS LOADED GEL

***In vitro* Diffusion Study:** Further *in vitro* release study was carried out for the selected gel using Franz diffusion cell for 10 hr. It was found that the F36 achieved a maximum drug release at 10th hour which may be attributed to the globule size. These results are given in (**Table 16**).

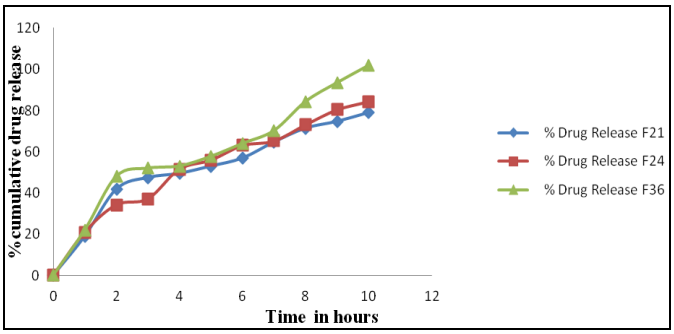

FIG. 10: *IN VITRO* DIFFUSION STUDY OF SMEDDS LOADED GEL

TABLE 16: *IN VITRO* DIFFUSION STUDY OF SMEDDS LOADED GEL

S. no.	Time (hours)	% cumulative drug release		
		F21	F24	F36
1	0	0	0	0
2	1	19±0.4	21±0.7	22±0.1
3	2	41.85±1.1	34.26±0.5	48±0.2
4	3	47.47±0.6	37.14±0.6	52±0.3
5	4	49.5±0.6	51.57±0.4	53±0.1
6	5	53.02±0.3	56±0.5	57.68±0.4
7	6	56.92±0.1	63.1±0.4	63.97±0.6
8	7	64.71±0.3	65.27±0.5	70.2±0.4
9	8	71.43±0.02	73.14±0.3	84.3±0.3
10	9	77.73±0.05	80.45±0.4	93.45±0.4
11	10	79±0.3	84.4±0.2	101.8±0.6

Values are reported as mean ± Standard Deviation, n = 3

***In vitro* Anti Arthritic Activity Study:** F21 and F24 had showed lower value as compared to F36. However all prepared gels has showed concentration gradient/dependent with increases the concentration, anti arthritic activity (% of inhibition) also increases. There is a concentration depended changes in the % inhibition. F36 gel was to found maximum inhibition as compared with other two formulations. F36 gel shows similar % of inhibition as that of Diclofenac sodium. Thus F36 prepared gel has promising anti arthtric activity through topical delivery.

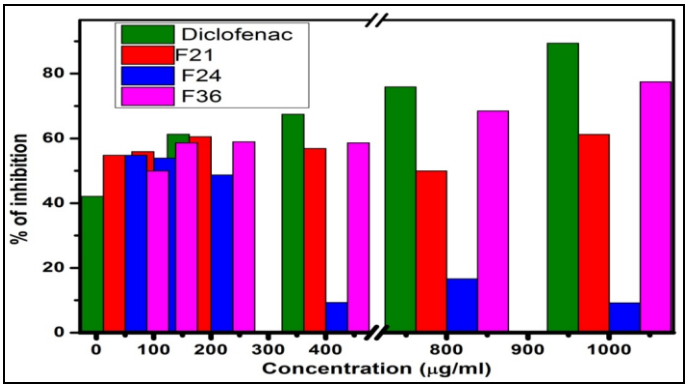

FIG. 11: *IN VITRO* ANTI ARTHRITIC STUDY OF SMEDDS LOADED GEL

Stability Study of Gel:

TABLE 17: STABILITY STUDY OF SMEDDS LOADED GEL

S. no.	Batch no.	Parameters	2nd Week		4th Week	
			Room temp.	40 °C / 75% RH	Room temp.	40 °C / 75% RH
1	F21	Appearance	White	White	White	White
		Drug content	65.3%	65.3%	58.4%	58.4%
		pH	6.6	6.6	6	6
		Appearance	White	White	White	White
2	F24	Drug content	71.3%	68.9%	64.3%	61.2%
		pH	6.7	6.5	6.4	6.2
		Appearance	White	White	White	White
3	F36	Drug content	78.9%	75.04%	70.5%	66.7%
		pH	6.8	6.6	6.8	6.4

At the end of one month stability studies on accelerated condition, all the batches complies with I.P. specification. Formulation did not show any deviation in assay and especially physical appearance. Hence it proves, the prepared formulations would withstand during shelf-life. From the above result it was found F36 was stable at all temperatures compared with other two formulations (F21 and F24).

CONCLUSION: The present research proves that the both formulated SMEDDS loaded with THDC4-0475RD (F21, F24 and F36) and their Gels, can be release the drug at target site; confirmed through *in vitro* diffusion study. Further, *in vitro* anti arthritic activity using BSA studies (results of F36 shows best among all) confirm the therapeutic efficacy of prepared SMEDDS and their gels, thus, its therapeutic efficacy would be more as compared to herbal drug (THDC4-0475RD) as such. Fabulous stability of prepared SMEDDS as well as the gel confirming that selected Drug: Surfactant: Co-surfactant: Oil ratio(s) through pseudoternary method are superior mixture, having high reproducibility. Thus, it concluded that SMEDDS loaded with herbal drug (THDC4-0475RD) can be delivered by topical as a gel formulation and would be stable throughout the shelf life.

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CONFLICT OF INTERSET: The authors have described no conflict of interest.

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