ABSTRACT

Curcumin Microemulgel

The present invention provides oil in water microemulsion of curcumin using novel oily phase containing 1:1 eutectic mixture of camphor and menthol. Further invention also provides topical formulations also known as microemulgels containing oil in water microemulsion of curcumin comprising 1:1 eutectic mixture of camphor and menthol . Microemulgels of curcumin comprises of novel polymer / emulsifier / gelling agent SEPINEO P 600. The invention also provides process of preparation of microemulsions and microemulgels.

Claims

We Claim,

1. Oil in water microemulsion of comprising from around 0.05 to 1 % w/w of Curcumin, from around 5 % to 15 % w/w of 1:1 eutectic mixture of camphor and menthol, from around 30% to 40 % w/w of mixture of surfactant and cosurfactant mixed in 2:1 w/w ratio and from around 50% – 70 % water or aqueous phase.
2. Oil in water microemulsion of curcumin according to claim 1 comprising from around 5 % to 15 % w/w of 1:1 eutectic mixture of camphor and menthol, from around 33% to 40 % w/w of mixture of surfactant and cosurfactant mixed in 2:1 w/w ratio and from around 50% – 60% water or aqueous phase.
3. Oil in water microemulsion of claim 1 wherein surfactant is Tween 80 and co-surfactant is Labrasol
4. Curcumin Microemulgel comprising oil in water microemulsion of from around 0.05 to 1 % w/w of curcumin.
5. Curcumin Microemulgel according to claim 3 or 4 comprising from around 40-60% of curcumin microemulsion, from around 1-10 % of gelling agent, from around 1-10 % of clarifying agent and from around 20-60 % of water.
6. Curcumin Microemulgel according to claim 5 wherein the gelling agent is SEPINEO P 600 and the clarifying agent is selected from polyethylene glycol and propylene glycol and mixtures thereof.
7. Curcumin Microemulgel according to claim 6 wherein SEPINEO P 600 is from around 3 % w/w to around 7 % w/w and clarifying agent is from around 5 % w/w to around 10 %w/w.
8. Curcumin Microemulgel according to claim 3 comprising 1:1 eutectic mixture of camphor and menthol as oily phase of microemulsion.
9. Process for preparing oil in water microemulsion of curcumin comprising following steps
    A. Mixing surfactant and co-surfactant in ratio of 2:1 to prepare premix.
    B. Mixing camphor and menthol in 1:1 w/w ratio to prepare Eutectic mixture

C. Mixing eutectic mixture and Surfactant Cosurfactant premix

D. Dissolving curcumin in the mixture of step C

E. Adding water and stirring to yield a clear transparent microemulsion.

10. Process for preparing Curcumin Microemulgelcomprising oil in water microemulsion comprising following steps

A. Preparing oil in water microemulsion of curcumin as per claim 9

B. Adding from around 1 – 10 % of Gelling agentinto water from around 20 – 60 % of total composition and stirring to obtain the gel / cream.

C. Adding 40 – 60 % microemulsion from step A to gel / cream of step B

D. Optionally adding preservative

E. Optionally adding clarifying agent

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P. S. Kharkar.

Ms. Kharkar Pallavi Shashikant

Applicants' Agent

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DESCRIPTION

FIELD OF INVENTION

The present invention relates toananti-inflammatory topical formulation containing oil in water microemulsion.The microemulsion of present invention incorporates eutectic mixture of camphor and menthol as oily phase which has surprisingly provided high solubility for many topical drugs, particularly curcumin. The topical formulation is in the nature of transparent or translucent gels collectively herein Microemulgel. The anti-inflammatory agent is curcumin. Further present invention relates to microemulgels of curcumin containing novel polymer.

BACKGROUND OF THE INVENTION

CN 101869692 patent discloses self-microemulsion of curcumin contain Curcumin matter, oil phase, Surfactant and Co-surfactant .No aqueous phase /gelling agent used in this art.

US20120052095 patent discloses a nanoemulsion formulation made up of curcumin or a curcuminoid along with at least one pharmaceutically acceptable excipient or inactive ingredient chosen from cream bases, emulsifiers, water washable bases, solid emulsifiers or nonionic surfactants, preservatives, emollients, collagen, flavoring agents and antiseptic agents. This is used in the treatment of skin disorders.

WO2007103435 patent discloses a microemulsion as one of the forms of delivery for a curcuminoid composition comprising a curcuminoid, an antioxidant, a water-solubilizing, pharmaceutically acceptable carrier, and optionally a glucuronidation inhibitor. No process of formation of microemulsion has been provided in the art and the focus is on the formation of solid lipid nanoparticle.

WO2007070983 patent discloses a topical delivery system in the form of a microemulsion for the transdermal delivery of pharmaceutically active agents.The microemulsions of the invention may be oil-in- water microemulsion, wherein the surfactant is preferentially soluble in water; water-in-oil microemulsion, wherein the surfactant is mainly in the oil phase; a three phase microemulsion wherein a surfactant rich middle phase coexists with water and oil phases; a bicontinuousmonophase; a single phase micellar solution that forms upon addition of a sufficient quantity of amphiphile (surfactant plus alcohol); or a swollen micellar solution but are prepared by methods previously known in the art. The invention basically claims the

use of a microemulsion in the preparation of a transdermally deliverable medicament in the treatment of a disease condition in a subject.

OBJECT OF THE INVENTION

The present invention attains one of the following objectives

First object of this invention is to provide microemulsion of an Anti-inflammatory agent, particularly curcumin, as intermediates in preparing topical formulations.

Second object of this invention is to provide microemulsion of curcumin containing novel oily phase made up of eutectic mixture of camphor and menthol.

Another object of the present invention is to provide transparent or translucent gels of curcumin collectively herein Microemulgels prepared by incorporating microemulsion of curcumin.

Yet another object of this invention is to provide microemulgels of curcumin incorporating novel polymer, Acrylamide/ SodiumacryloyldimethyltauratecopolymerIsohexadecane& Polysorbate 80, hereinafter Sepineo™ P600 or Sepineo P600.

One more object of this invention is to provide processes of preparation for microemulsion and microemulgels of curcumin.

SUMMARY OF THE INVENTION

According to first aspect of the present invention, there are provided oil in water microemulsions of curcumin as intermediates in the preparations of further topical formulations.

The second object of the present invention is to provide oil in water microemulsion of curcumin using novel oily phase made up of camphor and menthol.

In one more aspect of the present invention, there are provided topical formulations such as transparent and translucent gels collectively herein microemulgels containing oil in water microemulsion of curcumin.

According to yet another aspect of present invention, there are provided microemulgels of curcumin using novel polymer, Sepineo P600.

According to another aspect of the present invention, there were provided processes of preparation of oil in water microemulsion of curcumin and microemulgels of curcumin.

BRIEF SUMMARY OF THE DRAWINGS

The drawing 1/6 attached hereto describes four pseudoternary phase diagrams. The four pseudoternary phase diagrams are, as indicated in drawing 1/6, for the following :

1) Three phase system is oily phase, S_{mix} 1:1(Tween 80:Labrasol in 1:1 ratio) and water
2) Three phase system is oily phase, S_{mix}2:1(Tween 80:Labrasol in 2:1 ratio) and water
3) Three phase system is oily phase, S_{mix}3:1(Tween 80:Labrasol in 3:1 ratio) and water
4) Three phase system is curcumin containing oily phase, S_{mix}2:1(Tween 80:Labrasol in 2:1 ratio) and water

Oily phase is 1:1 Eutectic mixture of camphor and menthol. The shaded or grey region in each pseudoternary phase diagram indicates microemulsion region available for the said pseudoternary phase.

The drawing 2/6 attached hereto describes *In vitro* permeation data of 15 microemulsion batches.

The drawing 3/6 attached hereto describes overlay plot of batch number 23, proposed batch provided by Designexpert© Software as one of the best / optimized batch.

The drawing 4/6 attached hereto describes *In vitro* permeation (*In vitro* drug release) of curcumin from batch X (optimized batch) of microemulsion and from Microemulgel prepared from microemulsion of batch X.

The drawing 5/6 and 6/6attached hereto describes skin irritation study performed on the rabbit skin.

DETAILED DESCRIPTION OF THE INVENTION:-

Microemulsions are excellent candidate as potential drug delivery system because of their improved drug solubilization, enhanced penetration power, long shelf life and ease of preparation and administration.Also microemulsion have the ability to deliver larger amount of water and topically applied agents into the skin than water alone or other traditional vehicles such as lotions or creams because they act as a better reservoir for poorly soluble drug through their capacity for enhanced solubilization. The topical route of drug administration has been extensively studied where the drug transport from microemulsion was recorded usually better than that from other conventional topical preparations such as

ointments, gels and creams. Also the percutaneous absorption studies have been reported to be superior from the microemulsion formulation.

In addition, microemulsions fulfill requirements of potential drug delivery formulations entering the pharmaceutical market such as ease of production, applicability to as many drugs as possible, physical stability, excipients that are well tolerated and accepted by regulatory authorities and availability of large scale production allowable by regulatory authorities.

Curcumin is traditionally known anti-inflammatory and antioxidant agent. It has been incorporated in various cosmetics, herbal and consumer products for its benefits. It is highly insoluble in water thus making any aqueous based formulation almost impossible. It is soluble in organis solvents like acetone and DMSO which are highly undesirable in topical formulations. Many oils have poor solubility for Curcumin and hence they need to be incorporated in high amounts to dissolve curcumin. This might provide skin irritation. Various options tried by others include polymer dispersions of curcumin or molecular inclusion complex with cyclodextrins to enhance its solubility.

The present inventors have surprisingly found an oily phase containing combination of camphor and menthol to dissolve curcumin. This oily phase is a eutectic mixture of 1:1 camphor and menthol and has been surprisingly found to have good solubility for Curcumin. Thus oil in water microemulsions of curcumin have hereinafter become possible using eutectic mixture of camphor and menthol in 1:1 proportion as an oily phase. Further the inventors have used surfactants and co-surfactants suitable for curcumin and in optimized amount to enable preparation of oil in water microemulsion of curcumin.

Such microemulsions typically contain from around 2 % to 30 % and preferably from 4 % to 20 % and most preferably from 5 % to 15 % of oil. The amount of water is from 40 to 80 %, more preferably from 50 to 70 % and most preferably from 60 to 70 %. Further, microemulsions contain mixture of suitable surfactant to cosurfactant from 20 to 50 %, preferably from 25 to 45 % and most preferably from 30 to 40 %. These microemulsions show desired permeation after 24 hrs i.e. above 20 $\mu g/mlcm^2$, preferably above 30 $\mu g/mlcm^2$ and most preferably above 40 $\mu g/mlcm^2$. The flux of these microemulsions is more than 1 $\mu g/cm^2hr^-$, preferably more than 1.5 $\mu g/cm^2hr^{-1}$, most preferably more than 2 $\mu g/cm^2hr^{-1}$.

Inventors have successfully produced topical formulations from oil in water microemulsions collectively herein Microemulgels. Suitable gelling agent is SEPINEO P600 (Acrylamide/ SodiumacryloyldimethyltauratecopolymerIsohexadecane&Polysorbate 80). This polymer can act as thickner, emulsifier and stabilizer for oil in water emulsions.

The steps followed for preparing topical formulations of present invention included following steps:

1. Selection of representative Drug, oil phase, surfactant and cosurfactant,
2. Construction of blank pseudo-ternary phase diagrams to select optimum ratio of surfactant to cosurfactant.
3. Preparing pseudo-ternary plot with drug to select microemulsion region
4. Preparing Microemulsions of various compositions
5. Optimization by Design Expert 8.0 software
6. Preparation of optimized batch and checking for permeation and flux
7. Developing gels from microemulsions (collectively herein Microemulgels) incorporating oil in water microemulsions and checking for permeation and flux
8. Characterizing microemulsions and Microemulgels.

Selection of Drug:-

Based on following Criteria, curcumin is selected as Drug of choice.

Potent anti-inflammatory activity, Wide therapeutics index so that inter-individual varialbility in skin absorption must not pose too much of problem for refined dosage adjustment, Adequate skin acceptability, non-irritant, non-sensitizing and should not be metabolized by enzymes present in skin with the exception of prodrug, Daily dose is in the order of few milligrams, Ionized material generally penetrates the skin poorly compared to free acids or bases, Low molecular weight.

Curcumin extract is obtained from dried rhizome of Curcuma Longa Linn. Fam. Zingiberaceace. Curcuma longa has been known for its various properties such as anti-inflammatory, antioxidant, etc. Extract contains the major curcuminoids- Curcumin, Demethoxy curcumin and Bisdemethoxy curcumin. Curcumin, 1, 7 –bis (4-hyroxy-3-methoxyphenyl) 1E, 6E heptadiene-3, 5-dione, is found to have significant anti-inflammatory

activity comparable with hydrocortisone acetate and phenyl butazone. Curcumin is a polyphenol compound with poor water solubility.

Selection of Oil

The most important criteria for excipients selected were safe, nontoxic and non-irritant for topical use. The oil phase was selected depending upon the drug solubility. Labrafac lipophile WL 1349 which contains medium chain triglycerides is used as oily vehicle for forming fine dispersion such as microemulsion or self-emulsifying drug delivery systems. It has unique property of enhancing drug permeation. It is a good solvent for lipophilic active pharmaceutical ingredients. Capmul MCM is medium chain mono and di glycerides used as oily base similar to labrafac. Isopropyl myristate and ethyl oleate have oil consistency. Literature reported that it has been prior used for formation of curcumin microemulsion. These vehicles have penetration enhancer property. The eutectic mixture of camphor and menthol in the ratio of 1:1 is explored. As it was noted that both camphor and menthol have the property of lipid extarction from the skin, this facilitates the solute permeation. Camphor and menthol has cooling effects which enhance its applicability in topical formulation.

Selection of Surfactant and Co-surfactants:-

The surfactant must be able to lower the interfacial tension to a very small value to aid the dispersion process during the preparation of the microemulsion, provide a flexible film that can readily deform around droplets, and be of the appropriate lipophilic character to provide the correct curvature at interfacial region for desired microemulsion type.

Various surfactants were chosen for studies which can be used for oil in water microemulsion. Labrasol (caprylocaproyl polyoxyl-8-glycerides NF) is used as o/w surfactant, used to solubilize active pharmaceutical ingredients and promote drug penetration. It is used to produce stable emulsion. Capmul MCM C8 which is glycerylmonocaprylate is explored for its surfactant property.Tween 80 is (Polyoxyethylene (20) sorbitanmonooleate)compatible, non-toxic surfactant widely used in topical formulation.

Lecithin, a mixture of polar and non-polar lipids is used as emulsifier. The surface-active properties which enable lecithin to make stable blends of materials that do not mix easily and tend to separate by forming layers.

Optimizing solubility of curcumin in oils, surfactants and co-surfactants

Curcumin solubility is checked in oils, surfactants and co-surfactants, hereinafter, vehicles. Only the dissolved fraction of a drug in a vehicle can enter the skin, making solubility one of the initial objectives for a topical formulation.

Procedure - Each of the vehicle (5ml) was added to each capped vial containing an excess of curcumin. After sealing, the mixture was sonicated to facilitate the solubilisation using a vortex mixer. Mixtures were shaken with mechanical shaker at 25°C for 48 hours. After reaching equilibrium, each vial was centrifuged at 3000 rpm for 15 min, then 1.0 ml supernatant was taken, suitably diluted with methanol and the content of curcumin was quantified by spectrophotometry at 425 nm.Amount of drug solubilised in various vehicles was quantified; the values are shown in Table 1.

Table 1 Solubility of Curcumin in various vehicles

Vehicle	Vehicle Type	Solubility(Average ±Standard deviation)mg/ml
EUTECTIC MIXTURE	Oil	19.19±0.6
ETHYL OLEATE	Oil	2.24±0.05
IPM	Oil	1.66±0.01
LABRAFAC	Oil	1.80±0.07
CAPMUL MCM C8	Surfactant	5.31±0.40
CAPMUL MCM	Surfactant	4.05±0.19
LABRASOL	Surfactant / Co-surfactant	23.43±0.11
TWEEN 80	Surfactant	8.81±0.06
LECITHIN	Cosurfactant	1.60±0.04

Amongst oils,Curcumin exhibited highest solubility (19.19±0.6mg/ml) in eutectic mixture of 1:1 camphor and menthol. Camphor is readily absorbed through the skin and produces a feeling of cooling similar to that of menthol and acts as mild local anesthetic and antimicrobial substance. Camphor and menthol are known for their dermal penetration enhancing property. Taking into consideration the property of camphor and menthol and their ability to form eutectic mixture having good solubility for curcumin, it was decided to use the eutectic mixture as the oily phase for preparing oil in water microemulsion.Tween 80

(solubility of Curcumin is 8.81±0.06 mg/ml) and Labrasol (solubility of Curcumin is 23.43±0.11 mg/ml) so they were chosen as surfactant and co-surfactant, respectively.

Construction of blank pseudo-ternary phase diagrams to optimize ratio of surfactant and co-surfactant

The blank pseudo-ternary phase diagrams of oil (a eutectic mixture of 1:1 camphor and menthol), mixture in various proportion of surfactant and co-surfactant i.e. Tween 80 and Labrasol respectively and water were constructed using water titration method. These phase diagram were constructed using triplot software.The three corners of the triangle are the highest concentration of the oil, Smix and water. The plots are called Pseudo-ternary as ratio of the two components i.e. surfactant and co-surfactant is kept constant.

Surfactant was blended with co-surfactant in fixed weight ratios (1:1, 2:1 and 3:1) and mixed throughly using cyclomixer. All surfactant, co-surfactant mixtures are termed Smix. Hence Smix are of 3 types, Smix 1:1(surfactant :co-surfactant 1:1), Smix 2:1(surfactant:co-surfactant 2:1) and Smix 3:1 (surfactant :co-surfactant 3:1)Aliquots of each Smix were then mixed with different quantities of the oil at room temperature. For each phase diagram, the ratio of the oil to the Smix was varied as 9:1,8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9 Therefore, for Smix 1:1, 9 different mixtures with the oils ranging from 9:1 to 1:9 as stated earlier are prepared. The same is done for Smix 2:1 and Smix 3:1. Following steps 1 – 7 were carried out

1) Water was added drop-wise to each oil-Smix mixture under vigorous stirring and then kept aside.

2) After equilibrium, the samples were visually checked for phase seperation, transparency and assigned as clear microemulsions or emulsions or gels.

3) In addition the mixtures were observed for the absence of liquid crystalline phase through the crospolarizer.

4) The addition of water was continued till the turbidity appears.

5) The samples were checked the following day for whether the turbidity persists or disappears due to equilibrium achieved.

6) The end-point was noted as the point where the turibidity persist for more than 24 hrs.

7) The entire composition of oil, Smix and water was calculated on percent weight basis and the pseudo-ternary plots were obtained.

Optimizing ratio of surfactant to co-surfactant

The ternary phase diagrams obtained from triplot software were as shown in Drawing 1. The shaded region represents the microemulsion area while the white region indicates the formation of macroemulsion. The optical isotrophy of the prepared microemulsion was checked using crospolarizer.

The areas of all the three pseudo-ternary plots were compared and it was observed that plots with Smix 1:1 and 3:1 have lesser microemulsion region as compared to plot with Smix 2:1. Hence this ratio is selected for further optimization with Drug containing mixtures.

Preparing pseudo-ternary plot with drug

From the pseudo-ternary phase diagram of blank microemulsion, the microemulsion region was identified for Smix 2:1. For preparing pseudo-ternary plot with drug, Smix 2:1 is chosen as it provided maximum microemulsion region. Mixtures of Oil and Smix 2:1 in ratio of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 , 1:9 (w/w) are prepared. Fixed weighted amount of curcumin was added to all the above mixtures and dissolved. Steps 1- 7 as mentioned under blank pseudo ternary plot construction were carried out. The resultant microemulsions were tightly stored at ambient temperature, and their physical stability was measured by observing periodically for the occurrence of phase separation if any.

Optimizing best proportion of oil, surfactant, co-surfactant and water for microemulsion

The result of blank microemulsion indicated that the Smix ratio of 2:1 is optimum for the selected oil phase. As shown in drawing 1 it could be concluded that o/w microemulsion can be formed using oil, Smix and water in concentration range of 2 to 30, 20 to 50 % and 40 to 80 % w/w respectively. The microemulsion prepared was also checked for its optical isotropy.

FORMULATION DEVELOPMENT

Following criteria was set before selecting different formulations of microemulsion region of phase diagram.

1. Oil concentration should be such that it solubilizes the drug completely depending on the solubility of the drug in the oil.
2. Maximum percent of oil to be incorporated in the microemulsion should not cause skin irritation.

3. Percentage of surfactant mixture (Smix) required for any percent of oil selected for microemulsion formulation should not exceed 50%.

The microemulsion was optimized using a three-factor, three-level Box-Behnken design. In statistics, **Box–Behnken designs** (BBD) are experimental designs for response surface methodology, devised by George E. P. Box and Donald Behnken in 1960.The three factors are the three independent variables of the design. Three levels are the three levels of the three factors (independent factors). The responses are the dependent factors controlled by the said independent factors. In present case, the three independent factors are i) oily phase ii) Smix2:1, and iii) water. The three levels are the three levels or three amounts of i) oily phase ii)Smix2:1 and water. The two dependent factors i.e. responses are the i) in vitro permeation and ii) flux. The complete factorial design includes all combinations known as runs i.e. 3 independent factors X 3 levels i.e $3^3 = 27$ runs. However it is possible to just include 15 runs (less than complete factorial plan) and subject the dáta from 15 runs to the software Design Expert® to arrive at optimized batch of microemulsion.The Data which is required to be subjected to the software include level of independent factor and corresponding dependent factor. For example, amounts of oily phase, Smix2:1 and water used in microemulsion batch (run) and the corresponding permeation and flux. Each batch of microemulsion can be defined by levels of its components and the permeation and flux produced from each such batch. After subjecting such data from 15 batches (runs) to the software, software provides various batch compositions (levels of independent factors) and corresponding calculated permeation and flux (responses). Depending on the requirement of permeation and flux, optimized batch composition can be determined and corresponding batches can be manufactured.

Preparation of different microemulsion batches

Process

The different batches of micro emulsions (runs) were prepared by dissolving weighed amount of (40 mg) curcumin in specified amount of oil and Smix mixture as per the table 2 and 3. The mixture was sonicated till curcuminwas dissolved in it. The water was added later with continuous stirring using magnetic stirrer to yield a clear transparent microemulsion.

Table 2 – Composition of 15 runs (15 batches) of microemulsions wherein Levels of oils, Smix2:1 and water can be referred from table 3.

RUNS	RATIO		
	OIL	Smix	WATER
1	0	0	0
2	1	0	-1
3	-1	0	1
4	0	-1	-1
5	1	-1	0
6	0	0	0
7	-1	0	-1
8	0	0	0
9	-1	-1	0
10	-1	1	0
11	1	1	0
12	1	0	1
13	0	-1	1
14	0	1	1
15	1	0	1

Table 3 – Levels and amounts of each of oil, Smix and water in microemulsion batch

Ingredient/Levels	-1	0	1
	Parts		
Oil	5	10	15
Smix	30	35	40
Water	50	60	70

For example, Run 1 has 0 levels of each of oil, Smix 2:1 and water means microemulsion having 10 parts of oil or 1 g oil, 35parts of Smix or 3.5 g of Smix and 60 parts of water or 6g of water. The curcumin present in each run is constant which is 40 mg.

Fifteen batches (Runs) with various above combinations of oil, Smix2:1 and water were formulated and their responses, R_1-permeation in 24 hrsand R_2-flux were obtained as follows: calculated.

Permeation in 24 hrs[18]

Invitro permeation study was performed using Franz diffuison cell (capacity 20 ml) with surface area of 3.142 cm^2. The temperature was maintained at 37±0.5°C. The dialysis membrane (cellulose membrane, molecular weight cut-off between 12000 to 14000 dalton pore sizes 2.4 nm) was used. 20 ml of 50% methanol was used as the receptor compartment to maintain sink condition. The membrane was presoaked in receptor medium for 24 hrs was mounted on receptor compartment followed by donor compartment placed on it and clamped. 2 ml of microemulsion was placed in donor compartment. The aliquot (2ml) was withdrawn at specified intervals of 2,4,6,8 and 24 hrs from receptor compartment. It was filtered and analysed after suitable dilution at 425 nm using HPLC (Jasco).

Flux

The flux was calculated by plotting the amount permeated to time in hrs. The slope of the linear portion of the graph indicates the flux.

The batch composition and corresponding permeation and flux are as reported in Table 4.

Table 4: 15 Microemulsion batch compositions and corresponding permeation and flux

ME Batches	**Levels; amounts in grams**			**Batch size (with 40 mg drug)**	**Permeation in 24 hrs(µg/mlcm^2)**	**FLUX (µg/cm^{2}hr^{-1})**
	Oil	Smix	Water			
1	0 1g	0 3.5g	0 6.0g	10.54g	12.764	0.465
2	1 1.5g	0 3.5g	-1 5.0g	10.04g	8.823	0.357
3	-1 0.5g	0 3.5g	1 7.0g	9.04g	1.667	0.036

4	0 1g	-1 3.0g	-1 5.0g	 9.04g	35.43	1.297
5	1 1.5g	-1 3.0g	0 6.0g	 10.54g	44.42	2.184
6	0 1.0g	0 3.5g	0 6.0g	 10.54g	12.71	0.467
7	-1 0.5g	0 3.5g	-1 5.0g	 9.04g	31.27	1.382
8	0 1.0g	0 3.5g	0 6.0g	 10.54g	12.69	0.465
9	-1 0.5g	-1 3.0g	0 6.0g	 9.54g	10.4	0.445
10	-1 0.5g	1 4.0g	0 6.0g	 10.54g	18.67	5.874
11	1 1.5g	1 3.5g	0 6.0g	 11.04g	51.327	1.519
12	1 1.5g	0 3.5g	1 7.0g	 12.04g	44.42	1.58
13	0 1.0g	-1 3.0g	1 7.0g	 11.04g	12.09	0.496
14	0 1.0g	1 4.0g	1 7.0g	12.04g	80.25	2.398
15	0 1.0g	1 4.0g	-1 5.0g	10.04g	70.877	2.748

Batches 14 and 15 were most promising.

The above responses are subjected to Designexpert© Software to get the following data provided in Table 5 and 6 along with the detailed data.

Table 5: Model summary statistics for permeation in 24 hrs (R_1)

For Response R_1

SOURCE	STD. DEV	R2	ADJ R2	PREDICTED R2	PRESS	

Linear	21.04	0.3981	0.2339	-0.2061	9760.24	
2FI	20.34	0.5910	0.2842	-0.8291	14802.64	
Quadratic	9.78	0.9409	0.8346	0.0547	7650.39	Suggested
Cubic	0.038	1.0000	1.0000	+	+	

Detailed data obtained from the software for table 5

- The "Pred R-Squared" of 0.0547 is not as close to the "Adj R-Squared" of 0.8346 as one might normally expect. This may indicate a large block effect or a possible problem with model and/or data. Things to consider are model reduction, response transformation, outliers, etc.
- "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Ratio of 9.808 indicates an adequate signal. This model can be used to navigate the design space
- The Model F-value of 8.85 implies the model is significant. There is only a 1.36% chance that a "Model F-Value" this large could occur due to noise.
- Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case B, AC, B^2, C^2 are significant model terms.

Values greater than 0.1000 indicate the model terms are not significant.

R1 = +12.72 +6.90 * oil +18.81* Smix - 0.99* water +7.59 *oil *Smix +16.3 *oil *water +8.18 * Smix * water - 8.78 *oil^2 +19.33 * $Smix^2$+17.60 * $water^2$ ....(II)

Conclusions for response R1 - permeation

The equation obtained indicates the effect of various factors on the permeation of the drug in 24 hrs. The components oil and Smix have positive effect on the permeation. Smix phase has the highest effect due to its surfactant property it can be assumed to alter the permeation. The equation indicates the interaction of two components of the formulation and its contribution to permeation. The interaction between oil and water has maximum positive effect. The oil phase used has permeation enhancing property while water helps in hydration thus the optimum concentration of oil and water has positive effect on permeation. The quadratic terms also indicates the interaction and its effect on permation.

Table 6: Model summary statistics for flux(R_2)

For Response R_2

SOURCE	STD. DEV	R2	ADJ R2	PREDICTED R2	PRESS	
Linear	1.69	0.1420	-0.0920	-0.7382	63.44	
2FI	1.32	0.6167	0.3293	-0.6236	59.26	
Quadratic	0.27	0.9898	0.9715	0.8374	5.94	Suggested
Cubic	1.155	1.0000	1.0000	1.0000	+	

Detailed data obtained from the software for table 6

- Tthe model is significant. There is onlya 0.02% chance that a "Model F-Value" this large could occur due to noise.
- Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case B, AB, AC, A^2, B^2, C^2 are significant model terms.
- Values greater than 0.1000 indicate the model terms are not significant.
- The "Pred R-Squared" of 0.8374 is in reasonable agreement with the "Adj R-Squared" of 0.9715.
- "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Ratio of 25.565 indicates an adequate signal. This model can be used to navigate the design space. R2 = +0.46 - 0.03* oil + 0.78 * smix - 0.15 * water - 1.97 * oil * Smix + 0.64 * oil * water +0.11 * Smix * water + 0.79* oil^2 + 1.69 * $Smix^2$ - 0.42* $water^2$ .....(III)

Conclusions for response R2 - flux

The equation obtained indicate the effect of various factor on the flux of the drug. The Smix has positive effect on the flux. Oil and water phase has the negative effect on the flux of the formulation. The equation indicated the interaction of two components of the formulation and its contribution to flux. The interaction between oil and water has maximum positive effect while the design suggest that oil and Smix has negative effect on flux this may contribute for retaintion on the skin. The design also suggest that oil has negligible effect on the flux.

Further, the software provided 37 batch compositions with predicted permeation and flux, provided herein under Table 7 to further support optimization studies.Most batch compositions so provided had permeation in 24 hrs above 20 µg/mlcm^{2}and flux above 1.5 µg/cm^{2}hr^{-1}.

Table 7: Batch compositions from Designexpert© Softwarefor optimization.

Sr. No.	Oil	Smix	Water	Permeation in 24 hrs	Flux
1	0.00	0.00	0.00	22.96	2.14
2	-1	0	-1	20.28	2.13
3	1	0	-1	21.85	2.48
4	1	1	0	35.44	2.56
5	1	0	1	43.06	2.15
6	0	1	1	49.42	2.13
7	-1	1	0	21.97	2.46
8	-1	-1	0	30.34	2.89
9	0	-1	1	32.35	2.56
10	-1	0	1	24.71	2.17
11	1	-1	0	24.64	2.18
12	0	-1	-1	39.31	2.14
13	0	-0.59	-0.21	21.8	2.15
14	-0.72	0.16	-0.67	23.89	2.63
15	-0.65	0.38	-0.09	23.72	2.17
16	0.15	0.36	0.70	36.77	2.78
17	0.67	-0.75	-0.37	27.57	3.12
18	-0.06	-0.73	0.96	30.34	2.69
19	0.61	-0.35	0.43	25.46	2.54
20	0.32	0.87	0.97	59.16	1.48
21	-0.9	0.54	-0.94	22.01	2.74
22	0.00	-0.51	-0.07	25.14	2.96
23	**-0.25**	**0.99**	**0.86**	**51.229**	**2.945**

24	0.83	0.81	0.02	33.75	2.16
25	-0.68	-0.38	0.36	24.83	2.51
26	-0.20	0.38	0.09	32.42	3.0
27	-0.20	-0.3	0.54	21.14	2.34
28	0.87	-013	-0.57	23.56	2.5
29	-0.81	-0.2	-0.76	22.07	2.13
30	0.61	0.92	0.69	55.68	1.115
31	-0.39	0.47	0.21	25.82	4.1
32	0.86	-0.71	-0.6	29.31	2.15
33	0.19	0.59	0.42	36.74	2.46
34	-0.52	0.02	0.85	27.57	2.30
35	-0.4	-0.2	0.95	32.57	2.60
36	0.3	0.41	0.29	21.14	4.20
37	-0.67	-0.76	-0.35	25.45	2.114

Further, Designexpert© Software provided 37 overlay plots to determine the amount of oil, Smix and water so as to have flux not less than 1.5 μg/mlcm^2 and permeation not less than 20 μg/ml cm^2 in 24 hrs. The overlay plots provided solutions to give the optimum ratio of Smix, oil and water which can produce best result for permeation in 24 hrs and flux. Each overlay plot for example, as provided in drawing 3, indicate three region with colour codes gray, dark yellow and golden yellow. The solution point present in golden yellow region are more desirable while those in gray should be ignored.

Amongst all the batches, batch 23with following amounts of oil, Smix and water is found to be the best with respect to permeation and flux. The batch 30 showed best permeation whereas batch 36 showed best flux. Batch number 20, provides desired permeation but borderline flux as shown in table 8.

Table 8:- Comparison of best and borderline batches

Sr. No.	Oil	Smix	Water	Permeation in 24 hrs	Flux
23	-0.25	0.99	0.86	51.229	2.945
30	0.61	0.92	0.69	55.68	1.115

36	0.3	0.41	0.29	21.14	4.20
20	0.32	0.87	0.97	59.16	1.48

With the help of data of earlier 15 prepared batches and new data provided by the software for 37 new batch compositions, one can arrive at composition of microemulsion of desired permeation and flux.

Comparing the four batches, one can note that by increasing the oily phase, one can increase permeation whereas optimum Smix is essential for flux. After this, inventors could design one more batch, batch X having following parameters, very close to batch no. 23. except the amount of oil is further low. The reasons were as follows:

1) Oil should be minimum to dissolve curcumin and to obtain desired permeation

2) More oil may produce skin irritation

Batch X is subjected to permeation studies, and flux is calcuated. The permeation was observed to be around 80 µg/ mlcm^2 and the flux obtained was 2.98 µg/hrcm^2. The same is provided in drawing 4.

Sr. No.	**Oil**	**Smix**	**Water**	**Permeation in 24 hrs**	**Flux**
23	**-0.25**	**0.99**	**0.86**	**51.229**	**2.945**
Batch X	**-0.50**	**0.99**	**0.86**	**80**	**2.98**

The most optimized batches have following compositions as in table 9

Table 9 – Optimized microemulsion compositions of Curcumin

Sr. No.	**Oil** **In grams** **In %**	**Smix** **In grams** **In %**	**Water** **In grams** **In %**	**Total batch size in grams with 40 mg of curcumin**	**Permeation in 24 hrs**	**Flux**
23	-0.25 0.875g 7.434%	0.99 3.99g 33.942%	0.86 6.86g 58.283%	11.765	51.229	2.945
Batch X	-0.50 0.75g	0.99 3.99g	0.86 6.86g	11.64	80	2.98

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	6.444%	34.278%	58.934%			
14 Curcumin = 0.332%	0 1.0g 8.306%	1 4.0g 33.222%	1 7.0g 58.14%	12.04g	80.25	2.398
15 Curcumin = 0.398%	0 1.0g 9.960%	1 4.0g 39.841%	-1 5.0g 49.801%	10.04g	70.877	2.748

Thus, most optimized microemulsions are prepared when oily phase is from 6 – 10 %, Smix is from 33 – 40 % and water is from 50 – 59%.

Testing of Microemulsions

Methods

1. Transparency

The droplet of microemulsion being smaller than ¼ th the wavelenght of visible light, permit white light to pass through the disperseed system making it transparent.

The microemulsion systems were inspected for optical transparency and homogeneity by visual observation against light. The system were also checked for presence of undissolved drug or solid ingredient.

2. Optical Birefringence

The microemulsion was placed between two polarizing plates in a series and then observed for light transmittance. After this, one of the plates was rotated relative to other through 90° (crossed polarizers) and then examined. Presence of liquid crystalline phase shows the occurrence of birefringence and reduces the possibility of microemulsion formation.

3. A. Photon correlation spectroscopy:

Photon correlation spectroscopy (PCS) is a technique employed to determine themean particle size (PCS diameter) and size distribution (poly-dispersity index, PDI). It is a light scattering experiment in which the statistical intensityfluctuations in light scattered from the particles are measured. These fluctuations are due to the random brownian motion of the particles.

B. Zeta potential and electro-phoretic mobility:

Measurement of zeta potential has become inextricably connected with the studyand characterization of colloidal dispersions, as this parameter is highly useful forthe assessment of the physical stability of colloidal dispersions. In the presentwork, for the zeta potential measured using Malvern Zetasizer.

4. Percentage transmittance:

The percentage transmittance of the systems was measured at 650 nm usingUV Visible spectrophotometer keeping distilled water as a blank(Zhang, 2004).

%T= Anti log [2- A] .....(IV)

Where, A= absorbance; T= transmitance

5. Dilution potential:

The prepared microemulsion based systems were diluted 10 times with water and the effect of dilution on phase separation andpercentage transmittance was observed.

6. Specific Gravity:

The specific gravity of microemulsion was measured using specific gravity bottle. The weight of empty specific gravity bottle (10 ml) was noted. It was filled with water and weighed. Same procedure was used for microemulsion. The difference between empty and filled bottle was used to calculate the weight of water and formulation. The specific gravity and density was calculated using following formula.

$$Specific\ gravity = \frac{Weight\ of\ formulation}{Weight\ of\ water} \quad .....(V)$$

$$Density = \frac{Weight\ of\ formulation}{Volume\ of\ formulation} \quad .....(VI)$$

7. Entrapment efficiency

The entrapment efficiency of curcumin microemulsion was determinedby centrifugation method. 10 µl of 0.1N HCl was added into drug loadedmicroemulsion. The entire system was then centrifuged for 20 min at 3500 rpmusing REMI Centrifuge. The supernatant was separated. Free drug concentration was determinedby UV spectrophotometric analysis.The

entrapment efficiency and drug loading of curcumin microemulsion wascalculated according to the following equations:

Percent Entrapment efficiency= $\frac{W_a - W_s}{W_a} x100$ .....(VII)

Percent drug loading= $\frac{W_a - W_s}{W_a - W_s + W_L} x\ 100$ .....(VIII)

Where,

W_a= amount of drug added to formulation.,

W_s= amount of free drug.

W_L = weight of oil.

8. *pH of microemulsion:*

pH of all the microemulsions were determined using digital pH meter.

9. Physical stability

The microemulsion formulated was centrifuged at 3500 rpm for 30 min. It is a quite simple and inexpensive technique to determine behaviour of small particles in gravitational field i.e. their separation rate, providing a rapid full-proof identification of the system as microemulsion.

10. Invitro permeation studies

Invitro permeation study was performed using Franz diffuison cell (capacity 20 ml) with surface area of 3.142 cm^2, temperature was maintained at 37±0.5°C. The dialysis membrane (cellulose membrane, molecular weight cut-off between 12000 to 14000 dalton, pore sizes 2.4 nm) was used. 20 ml of 50% methanol was used as the receptor compartemnt to mainatin sink condition. The membrane presoaked in receptor medium for 24 hrs, was mounted on receptor compartment, donor compartment was placed over it and clamped. 2 ml of microemulsion was placed in donor compartment. The aliquot (2ml) was withdrawn at specified intervals of 2,4,6,8 and 24 hrs from receptor compartment. It was filtered and analysed after suitable dilution at 425 nm using HPLC (Jasco).

11. Flux

The flux was calculated by plotting the amount permeated to time in hrs. The slope of the linear portion of the graph indicates the flux

Table 10Summary of evaluation parameters of microemulsion

Sr. No.	Test	Result
1	**Transparency**	Clear
2	**Optical Birefringence**	No birefringence
3A	**Photon correlation spectroscopy**	Particle size of the optimized microemulsion was determined by light scattering based on laser diffraction using Malvern Zetasizer Ver. 6.34 after suitable dilution. The average size was observed 222 nm. The microemulsion showed *polydispersity index* 0.344
3B	**Zeta potential**	The microemulsion analysed for its surface potential at 25° C. The microemulsion had -7.90mV zeta potential. The surface charge helps the small particles of microemulsion to be dispersed in the continous phase.The electric potential at the boundary of the double layer is known as the zeta potential of the particles and has values that typically range from +100mV to -100mV.
4	**Percentage transmittance**	It was observed that microemulsion had 99.5405 % transmittance. It confirmed the transparency of microemulsion.
5	**Dilution Potential**	It was observed that microemulsion had 1,000 times dilution potential and percent transmittance increased on dilution and no phase seperation was observed till 1,000 times dilutions.
6	**Specific Gravity and Density**	The specific gravity was noted to be 1.034 and density was found to be 0.986 gm/ml.
7	**Entrapment efficiency and drug loading**	The entrapment efficiency was found to be 93.275 % and drug loading was 16.596%.
8	**pH of microemulsion**	The pH of the microemulsion was found to be 4.63

9	**Physical stability**	No sign of separation of phases of microemulsion formualtion were observed after centrifugation of the formulation at 3500 RPM for 30 min.
10	**In-vitro drug release**	For Optimized batch Theamount of drug permeated through the membrane was evaluated at various time intervals. The permeation was observed to be around 80 µg/ mlcm^2. The flux was observed to be 2.98 µg/hrcm^2.

Formulation of Microemulgels

Further, microemulgels can be prepared from the microemulsions of present invention. The microemulgels include gels prepared by incorporating oil in water microemulsion of present invention.

Apart from microemulsions, other components of microemulgels are gelling agents, preservatives,clarifying agents and cooling agents.

Gelling agent - Gelling agents explored are hydroxyl propyl methyl cellulose (HPMC) grades K4M and K 15M, Poloxamer 407, and Novel cream-gel base SEPINEO P 600 which is a concentrated dispersion of acrylamide/sodium acryloyldimethyltaurate copolymer in isohexadecaneisand used to for its unique property of ready to use polymer/ emulsifier/thickening agent. These gelling agents give transparent glassy gels.

Preservatives - The parabens which are commonly used as preservative in topical formulation are not used due to incompatibilities reported in literature. Thus an alternative preservative benzalkonium chloride was used.

Development of Microemulgels

Development batches as per table 11were prepared.

The optimized batch containing oil, Smix and water was further subjected to gelling. This microemulgel was designed to facilitate ease of application and dispensing. The various gelling agents explored were poloxamer 407, HPMC K 4M, HPMC K 15 M, SepiNeo P 600. In all the formulations benzalkonium chloride was used at the concentration of 0.05% w/w.

A]Gelling using HPMC - HPMC K 4M and HPMC K 15 M gel was prepared by hot method. The fixed amount of water was measured and added to the beaker and heated on the hot plate

upto 70°C. HPMC was added slowly to the hot water and stirred continously. This solution is allowed to cool to room temperature. Microemulsion was added to HPMC gel thus formed.

B] Gelling using Poloxamer 407 - Weighed amount of poloxamer was added to specific amount of water and allowed to cool in freezer for overnight. This solution was then allowed to achieve room temperature. This procedure produced poloxamer gel by cold method. Microemulsion was then incorporated into the gel.

C] Gelling using SepiNeo P 600 - SepiNeo P 600 is used as thickening-emulsifying polymer. The gelling agent was added to weighed quantity of water and stirred to obtained cream base. The clarifying agents like Propylene Glycol (PG) and Poly ethylene Glycol- 400(PEG-400) were used. This gel base so prepared was subjected to addition of microemulsion.

Table 11- Development of Microemulgel

Components in grams	**In grams per Batchsize of 100 gm of gel**								
	I	II	III	IV	V	VI	VII	VIII	IX
Microemulsion	50	50	50	50	50	50	50	50	50
HPMC K4M	2	2.5	3	--	--	--	--	--	--
HPMC K 15 M	--	--	--	2	2.5	3	--	--	--
Poloxamer 407	--	--	--	--	--	--	10	15	20
Sepineo P 600	--	--	--	--	--	--	--	--	--
PEG-400	--	--	--	--	--	--	--	--	--
Propylene Glycol	--	--	--	--	--	--	--	--	--
Benzalkonium Chloride	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Components in grams	**In grams per Batchsize of 100 gm of gel**							
	X	XI	XII	XIII	XIV	XV	XVI	XVII
Microemulsion	50	50	50	50	50	50	50	50
HPMC K4M	--	--	--	--	--	--	--	--
HPMC K 15 M	--	--	--	--	--	--	--	--

Poloxamer 407	--	--	--	--	--	--	--	--
Sepineo P 600	3	5	6	7	3	5	6	7
PEG-400	q.s	q.s	q.s	q.s	--	--	--	--
Propylene Glycol	--	--	--	--	q.s	q.s	q.s	q.s
Benzalkonium Chloride			q.s	q.s	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Optimising the gelling agent

A] Gelling using HPMC - Both the grades of HPMC (HPMC K4 M and HPMC K 15 M) produced good glassy gels with plain water but lacked compatibility with microemulsion. When microemulsion was incorporated into the gel, it resulted into seggregation of gel mass and liquid phase immediately. This phenomenon was observed at all concentrations of both grades of HPMC.

B] Gelling using Poloxamer 407 - Poloxamer gel produced by cold method had the problem of air entrapment. When microemulsion was incorporated into gel it formed microemulgel. This gel was kept overnight in a container. It was observed that the gel and microemulsion were seperated into two distinguished layers. The seperation was observed at all the three different levels of concentrations of poloxamer used.

C] Gelling using SepiNeo P 600 - SepiNeo P 600 gel was quite stable and had high incorporation potential. The entire amount of microemulsion was incorporated into the gel without seggregation or seperation of the gel and microemulsion. This gel was however creamy in nature and appearance. This is cream base.Further clarifying agents are added to this gel. The clarifying agents used are propylene glycol and polyethylene glycol. The clarifying agent around 5 – 10 g is added to around 100 g of cream base so obtained. Addition of 5 – 10 g of propylene glycol led to completely transparent gel. The addition of 5 – 10 g of polyethylene glycol led to transluscent gel. Both these gels are Microemulgels.

The preservative used for the formulation was benzalkonium chloride at the concentration of 0.05 %w/w.

Table 12 - Summary of the evaluation parameters

<table>
<tr><th>Sr. No.</th><th>Test</th><th>Result</th></tr>
<tr><td>1</td><td>Colour

Transparency</td><td>The formulation prepared were golden yellow in colour. All the three concentration of the SepiNeo P 600 produced the same shade coloured gel.
The gel prepared were transparent / translucent to naked eye</td></tr>
<tr><td>2</td><td>Consistency</td><td>Consistency was dependent on amount of SepiNeo P 600. Optimum consistency was obtained from 3 – 6 % of SepiNeo P 600.</td></tr>
<tr><td>3</td><td>pH</td><td>SepiNeo P 600
5 % 5.54±0.005; 6 % - 6.83±0.005; 7% -6.90±0.005</td></tr>
<tr><td>4</td><td>Extrudability</td><td>The extrudate obtained after applying pressure at the tube end was evaluated for its ability to form uniform cylinder devoid of air voids. Microemulgel with 5 % gelling agent was the best.</td></tr>
<tr><td>4</td><td>Spreadability</td><td>It was observed that gel prepared with 5% concentration had good spreadability than gels with 6 % and 7% concentration.
<table>
<tr><th>Concentration of SepiNeo P 600 (% w/w)</th><th>Spreadability (gm.cm/sec)</th></tr>
<tr><td>5</td><td>5.78±0.11</td></tr>
<tr><td>6</td><td>0.79±0.03</td></tr>
<tr><td>7</td><td>0.45±0.07</td></tr>
</table></td></tr>
<tr><td>5</td><td>Drug Content</td><td>The drug content was evaluated using Jasco HPLC. Drug content was found to be 99.9%.</td></tr>
<tr><td>6</td><td>Viscosity</td><td>The viscosity of microemulgel was measured by Brookfield Viscometer. The viscosity of the gel at 2 RPM was observed to be 347639.5±55.86 cps.</td></tr>
<tr><td>7</td><td>Diffussion studies</td><td>The diffusion studies performed to know the amount of drug permeated across the dialysis membrane. The drawing 4 indicates the release pattern of drug from the gel. The amount of drug permeated through the membrane has decrease in microemulgel as compared to microemulsion alone. This</td></tr>
</table>

		effect was observed as the microemulsion has been embeeded into the gel matrix. It has to partition and travel across the barrier of gel and then into the membrane.
8	**Photon correlation spectroscopy**	It was observed that there is no major significant increase in the particle size of the microemulgel as compared to microemulsion. This indicate the microdroplet have maintained their integrity in the gel formulation and have not aggregated or collapsed. The average particle size was observed to be 260 nm. The microemulgel showed polydispersity index 0.395.
9	**Skin Irritation Test**	The skin irritation study was perform on the rabbit skin. The drawing 5 and 6 are photos taken at various stages of the experiment. No skin irritation is caused by the Microemulgel. Refer drawing 5 and 6.

Table 13 - Microemulgel Composition

Sr. No.	**Ingredient**	**% Composition**
1	Microemulsion	40 – 60 %
2	Gelling agent	1 – 10%
3	Clarifying agent	1 – 10 %
4	Preservative	0.05 %
5	Water	20 – 60 %

Following are the non-limiting examples of the present invention

Example: 1 – Manufacturing of microemulsion for Optimized batch X

		Batch 23		Optimize Batch X	
Sr. No.	Ingredients	Weight in grams	Percentage (%)	Weight in grams	Percentage (%)
1	Curcumin	0.04g	0.34%	0.04g	0.343%

2	Eutectic mixture of camphor and menthol (1:1)	0.875g	7.434%	0.75g	6.443%
3	Smix 2:1 (Tween 80 : Labrasol)	3.995g	33.942%	3.99g	34.278%
4	Water	6.86g	58.283%	6.86g	58.935%
	Total	**11.765**	**99.999%**	**11.64**	**99.999%**

Process:-

1) The premix of Tween 80 and Labrasol is prepared in 2:1 ratio and the required quantity from the premix is weighed. This is Smix.
2) 1:1 Eutectic mixture of camphor and menthol is prepared by mixing the two and the required quantity of eutectic mixture is weighed from it. This is oily phase.
3) The Smix of step 1 and oily phase of step 2 are mixed
4) Curcumin is dissolved in the mixture Smix and oily phase.
5) Water is added and stirred with magnetic stirrer to yield a clear transparent microemulsion.

Microemulgel

Example 2 - Manufacturing of Microemulgel from microemulsion of example 1.

Sr. No.	Ingredients	Weight (g)	Weight (g)	Weight (g)
1	Microemulsion	50	50	50
2	SepiNeo P 600	5	5	5
3	Propylene Glycol (PG)	-	10	-
4	Poly ethylene Glycol- 400(PEG-400)	-	-	10

5.	benzalkonium chloride	0.05	0.05	0.05
6	**water**	45	45	45
	Visual Observation	cream base	transparent gel	transluscent gel

Process

1. SepiNeo P 600 is added to 45 gm. of water and stirred to obtain cream.
2. 50 gm of Microemulsion was added to cream of step 1 under constant stirring.
3. Benzalkonium chloride was added. This is cream base.
4. Clarifying agent is added to product of step 3. Depending on the type of clarifying agent, end product is transparent Microemulgel or transluscent Microemulgel.

Similarly batches with 3 %, 6 % and 7 % SepiNeo P 600 are prepared.

Claims

We Claim,

1. Oil in water microemulsion of comprising from around 0.05 to 1 % w/w of Curcumin, from around 5 % to 15 % w/w of 1:1 eutectic mixture of camphor and menthol, from around 30% to 40 % w/w of mixture of surfactant and cosurfactant mixed in 2:1 w/w ratio and from around 50% – 70 % water or aqueous phase.
2. Oil in water microemulsion of curcumin according to claim 1 comprising from around 5 % to 15 % w/w of 1:1 eutectic mixture of camphor and menthol, from around 33% to 40 % w/w of mixture of surfactant and cosurfactant mixed in 2:1 w/w ratio and from around 50% – 60% water or aqueous phase.
3. Oil in water microemulsion of claim 1 wherein surfactant is Tween 80 and co-surfactant is Labrasol
4. Curcumin Microemulgel comprising oil in water microemulsion of from around 0.05 to 1 % w/w of curcumin.
5. Curcumin Microemulgel according to claim 3 or 4 comprising from around 40-60% of curcumin microemulsion, from around 1-10 % of gelling agent, from around 1-10 % of clarifying agent and from around 20-60 % of water.
6. Curcumin Microemulgel according to claim 5 wherein the gelling agent is SEPINEO P 600 and the clarifying agent is selected from polyethylene glycol and propylene glycol and mixtures thereof.
7. Curcumin Microemulgel according to claim 6 wherein SEPINEO P 600 is from around 3 % w/w to around 7 % w/w and clarifying agent is from around 5 % w/w to around 10 %w/w.
8. Curcumin Microemulgel according to claim 3 comprising 1:1 eutectic mixture of camphor and menthol as oily phase of microemulsion.
9. Process for preparing oil in water microemulsion of curcumin comprising following steps
    A. Mixing surfactant and co-surfactant in ratio of 2:1 to prepare premix.
    B. Mixing camphor and menthol in 1:1 w/w ratio to prepare Eutectic mixture

C. Mixing eutectic mixture and Surfactant Cosurfactant premix

D. Dissolving curcumin in the mixture of step C

E. Adding water and stirring to yield a clear transparent microemulsion.

10. Process for preparing Curcumin Microemulgelcomprising oil in water microemulsion comprising following steps

A. Preparing oil in water microemulsion of curcumin as per claim 9

B. Adding from around 1 – 10 % of Gelling agentinto water from around 20 – 60 % of total composition and stirring to obtain the gel / cream.

C. Adding 40 – 60 % microemulsion from step A to gel / cream of step B

D. Optionally adding preservative

E. Optionally adding clarifying agent

Dated this 4th day of December 2013

P. S. Kharkar.

Ms. Kharkar Pallavi Shashikant

Applicants' Agent

4 DEC 2013