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FORMULATION AND EVALUATION OF DICLOFENAC DIETHYL AMINE MICEROEMULSION INCORPORATED IN HYDROGEL

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ABSTRACT

Transdermal delivery offer number of advantages over conventional systems. However, the major problem with transdermal delivery is skin which behaves as a natural barrier making difficult for most of drugs to be delivered into and through it. Microemulsions are low skin irritation, powerful permeation ability and high drug loading capacity. The low viscosity of microemulsion restrains its clinical application due to inconvenient use the problem of poor patient compliance, clinical application and stability can be overcome by formulating hydrogel thickened microemulsion using carbopol as a hydrogel thickening agent. Diclofenac diethylamine, a non-steroidal anti-inflammatory drug (NSAID) is topically very effective. The aim of the present research work was to formulate hydrogel thickened microemulsion with good solubility, powerful permeation ability and suitable viscosity for the topical delivery of ibuprofen using eutectic mixture of camphor and menthol as oily phase and also the solvent for the diclofenac diethyl amine with good penetration enhancer and imparts cooling effect to the skin. Carbopol 940 was used as a hydrogel thickening agent. The drug was found to be soluble in oil phase (the eutectic mixture containing equal parts of menthol and camphor) was >160mg/ml. Pseudoternary phase diagrams were constructed to obtain an optimum formula for DDEA. The pH values of the prepared DDEA microemulsion varied from 5.71-8.03 that are within the acceptable range for skin preparations. And the pH of gel observed is 5.8, drug content, drug release and viscosities are varies according formulations.

KEYWORDS: Diclofenac diethyl amine,menthol, camphor, tween 80, carbopol 940.

INTRODUCTION

Transdermal delivery offer number of advantages over conventional systems. However, the major problem with transdermal delivery is skin which behaves as a natural barrier making difficult for most of drugs to be delivered into and through it. In the last decade various attempts are made to deliver the drugs topically via microemulsions because of low skin irritation, powerful permeation ability and high drug loading capacity. Microemulsion is a dispersion of oil, surfactant, co surfactant and aqueous phase. Microemulsion is optically isotropic and thermodynamically stable liquid solution[(1)].

Microemulsion offers several advantages for topical preparations the low viscosity of microemulsion restrains its clinical application due to inconvenient use the problem of poor patient compliance, clinical application and stability can be overcome by formulating hydrogel thickened microemulsion using carrageenan, carbopol, hydroxypropyl methylcellulose and xanthan gum as a hydrogel thickening agent [(3)].

Diclofenac diethylamine, a non-steroidal anti-inflammatory drug (NSAID) is very effective for the systemic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Ibuprofen topical preparations may be beneficial to the patients since it reduces the adverse side effects and avoid the hepatic first-pass metabolism. But by topical delivery, it is difficult to maintain effective concentrations, since ibuprofen posses poor skin permeation ability [(5)].
The aim of the present research work was to formulate hydrogel thickened microemulsion with good solubility powerful permeation ability and suitable viscosity for the topical delivery of ibuprofen using eutectic mixture of camphor and menthol as oily phase, solvent for the DDEA, power penetration enhancer and imparts cooling effect to the skin. Carbopol 940 was used as a hydrogel thickening agent.

MATERIAL

Diclofenac diethylamine, Menthol, Camphor, Tween 80, Methanol AR grade, Ethanol (99.9%) Carbopol 940, Triethanolamine,Cellulose acetate membrane

METHODS

PREFORMULATION STUDIES

1) Determination of solubility of DDEA in eutectic Mixture

The solubility of DDEA was determined in the eutectic mixture consisting of equal parts of

camphor and menthol. An excess amount of DDEA was added to 35 ml of eutectic mixture and stirred at 100 rpm on a magnetic stirrer, for 30 m at o 35±2 in a closed vessel. The mixture was filtered through a 0.22 µm Millipore filter. The weight of undissolved solid was recorded.

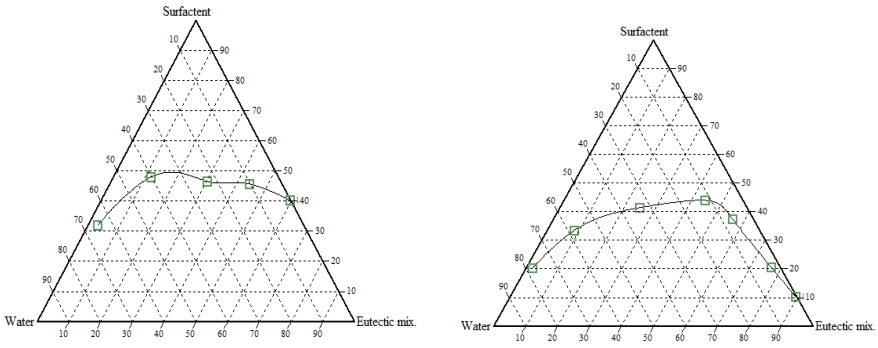
2) Melting point

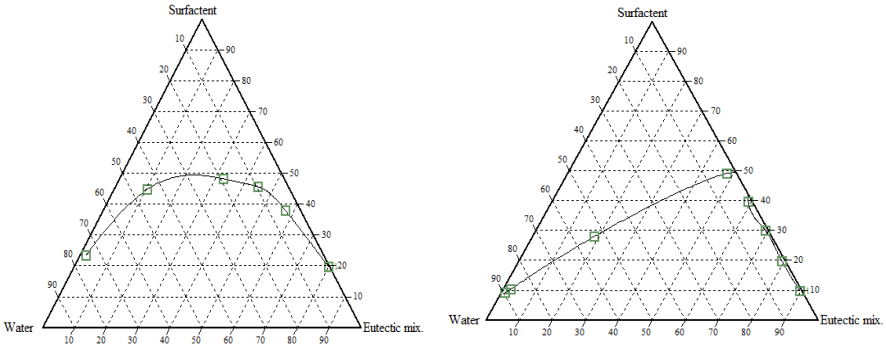
A small quantity of powder was placed into a fusion tube. That tube is placed in the melting point determining apparatus containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted. The malting point of DDEA detected is:- 149-152 ^{0}C.

3) Plotting of ternary phase diagrams

Ternary phase diagrams were constructed to obtain the components and their concentration ranges that can result in large existence area of microemulsion without the drug or containing 1.16% DDEA. Eutectic mixture consisting of equal parts of camphor and menthol was selected as the oily phase. Tween 80 was selected as the surfactant in the study as it was readily miscible with the eutectic mixture. When co-surfactant (ethanol) was used, the ratio of surfactant to co-surfactant was 1:1, 1:2 and 2:1. The ternary phase diagrams were constructed using water titration method at ambient temperature. For each phase diagram, the ratio of oil to surfactant or mixture of surfactant and co-surfactant was varied from 1:9 to 9:1. Water was added drop by drop, under gentle agitation, to each oily mixture until mixture become turbid. Transparent to translucent fluid systems were characterized as microemulsion. The ternary phase diagrams of eutectic mixture, tween 80 and water in presence and absence of co-surfactant (ethanol).

Psudoternary phase diagram:





"Fig. 1" The ternary phase diagrams of eutectic mixture, tween 80 and water in presence and absence of co-surfactant (ethanol); (a) co-surfactant free system,(b) 1:1 ratio of tween 80 and ethanol,(c) 1:2 ratio of tween 80 and ethanol, (d) 2:1 ratio of tween 80 and ethanol.

4) Determination of partition co-efficient

The partition coefficient (P) is the quotient of two concentrations and is usually given in the form of its logarithm to base 10 (log P). Partition coefficient of DDEA drug sample was determined by saturating 10 ml of n-octanol with 10 ml of phosphate buffer of 7.4 pH in a separating funnel. Intermediate shaking was done manually for 24 hrs. 10 mg of drug was added to a separating funnel and intermediate shaking was done for 6 hrs. The two solvent layers were separated through separating funnel and the amount of DDEA dissolved in each phase, was determined spectrophotometrically at 275.2nm against reagent blank prepared in the same manner on a UV-visible spectrophotometer.

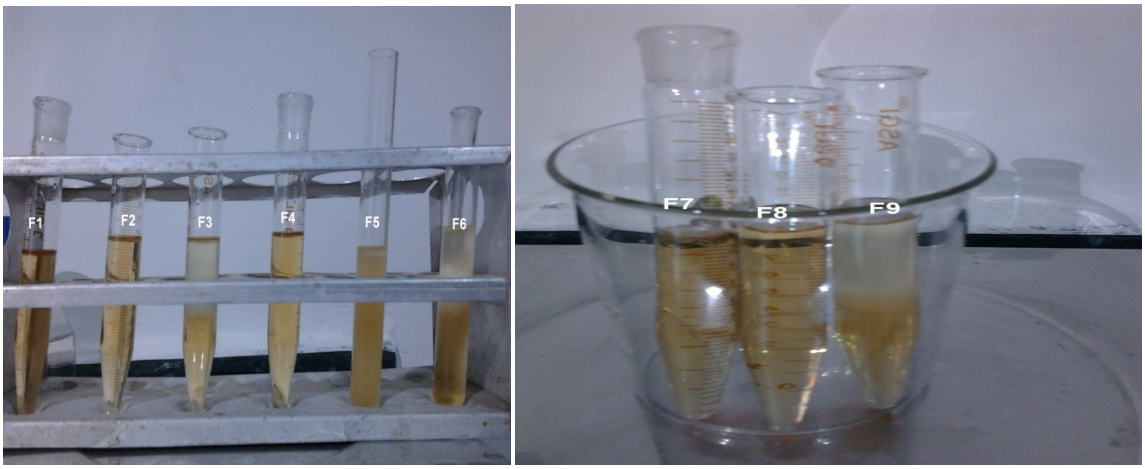
The partition coefficient obtained as logP of DDEA was 0.8 which was near to the value reported in literature.

FORMULATION AND EVALUATION OF MICROEMULSION

DDEA (1.16% w/w) was dissolved in eutectic mixture consisting of equal amount of camphor and menthol. The DDEA solution was then mixed with mixture of surfactant and co-surfactant. Finally, an appropriate amount of water was added to the ibuprofen solution mixture drop by drop to get microemulsion. The composition of the different formulated microemulsion (batches F1-F9) is shown in Table.

Table.1 Formulations of various microemulsions.

Batch code	Amount of each ingredient (%w/w)			
	DDEA	Eutectic (Oil phase)	Surfactent/cosurfactent 2:1	Water
F1	1.16	38.84	50	10
F2	1.16	38.84	40	20
F3	1.16	38.84	30	30
F4	1.16	28.84	50	20
F5	1.16	28.84	40	30
F6	1.16	28.84	30	40
F7	1.16	18.84	50	30
F8	1.16	18.84	40	40
F9	1.16	18.84	30	50



"Fig. 2"

1) Visual Appearance and Clarity

The appearance and clarity were determined visually. The formulations were clear and transparent.

Table.2 Visual appearance and clarity of various microemulsions

Formulation code	Visual Appearance	Clarity
F1	Yellowish Transparent	Clear
F2	Yellowish Transparent	Clear
F3	Yellowish Transparent (separated)	Clear
F4	Yellowish Transparent	Clear

F5	Yellowish Transparent (separated)	Cloudy
F6	Yellowish Transparent (separated)	Cloudy
F7	Yellowish Transparent	Clear
F8	Yellowish Transparent	Clear
F9	Yellowish Transparent (separated)	Clear

2) Measurement of droplet size and zeta potential

The average droplet size and zeta potential of the microemulsions were measured using a Zetasizer Nano-ZS (Malvern Instruments, UK). The measurement was performed at 25°C.

Table.3 Droplet size distribution

Formulation Code	Average droplet size (nm)
F1	83.67
F2	92.57
F4	76.89
F7	79.11
F8	79.78

3) Zeta potential [37]

It is used to identify the charge of the droplets. In the microemulsion prepared in the present study, the charge on the oil droplet is negative due to the presence of free fatty acids. Zeta potential determined by Zeta-meter was monitored at 25ºC(Zetasizer Malvern Insrument).

Table. 4 Zeta potential of microemulsions

Formulation code	Zeta potential
F1	-10.72
F2	-15.84
F4	-9.62
F7	-12.6
F8	-9.07

4) Determination of the amount of DDEA in microemulsions by Spectroscopic method

For determination of drug content about one gram of each ME was weighed and centrifuge, supernatant was taken in a 10 ml volumetric flask and dissolved in methanol. It was diluted appropriately and analyzed spectrophotometrically at 282.2nm. Appropriately diluted solutions of respective plain McE in methanol were taken as blank.

Table.5 Drug content of microemulsions.

S.No.	Formulation code	Drug content
1.	F1	94.25%
2.	F2	96.76%
3.	F4	92.45%
4.	F7	89.35%
5.	F8	92. 42%

5) Determination of pH

The pH values of the samples were measured by a pH meter (Mettler Toledo FE20 pH Meter) , at 20±1°C.

Table. 6 pH of various microemulsion.

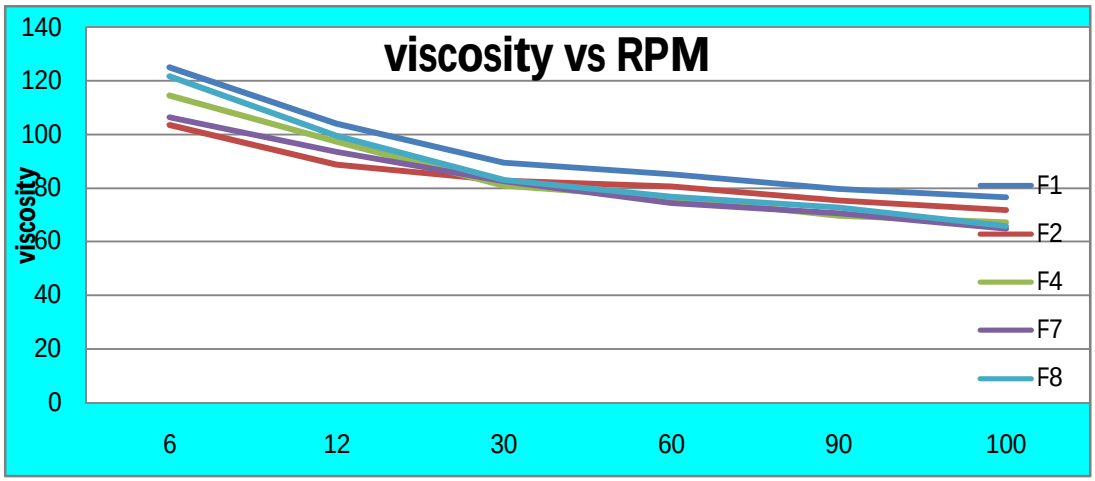
S.No.	Formulation code	PH
1.	F1	5.71
2.	F2	6.42
3.	F4	7.31
4.	F7	7.82
5.	F8	8.03

6) Viscosity measurement

Viscosities of microemulsions were measured using Brookfield viscometer DV-E with spindle 2 at 6, 12, 30, 60, 100 rpm. The developed formulation was poured into the small adaptor of the brook field synchroelectric viscometer and the angular velocity increased gradually

Table. 7 Viscosity of the formulations before gelation at 25°C

RPM	Viscosity (cps) (Before gelling) using spindle—2				
	F1	**F2**	**F4**	**F7**	**F8**
6	125.08	103.56	114.56	106.43	121.78
12	103.98	88.77	97.34	93.54	99.43
30	89.35	82.85	80.98	82.49	82.93
60	85.07	80.55	76.34	74.32	76.87
90	79.56	75.32	69.77	70.65	72.67
100	76.56	71.72	67.34	64.88	65.76



"Fig. 3" Viscosity graph of microemulsions.

7) Refractive index

Refractive Index Measurements. Refractometry is the method of measuring substances' refractive index in order to assess their composition or purity. A refractometry measures the extent to which light is bent (i.e. refracted) when it moves from air into a sample and is typically used to determine the index of refraction of a liquid sample, to find out drug loading has no significant effect on the refractive index of the microemulsion system [34,35]

Table. 8 Refractive index of microemulsions.

S.N.	Formulation code	Rf.
1.	F1	1.46
2.	F2	1.43
3.	F4	1.44
4.	F7	1.42
5.	F8	1.41

8) Determination of conductivity of microemulsion

To find out microemulsion type and the effect of the amount of water phase of microemulsions was monitored quantitatively by measuring the electrical conductivity. The water phase was added drop by drop into the mixture of oil phase and surfactant phase.

Table. 9 Conductivity of microemulsion.

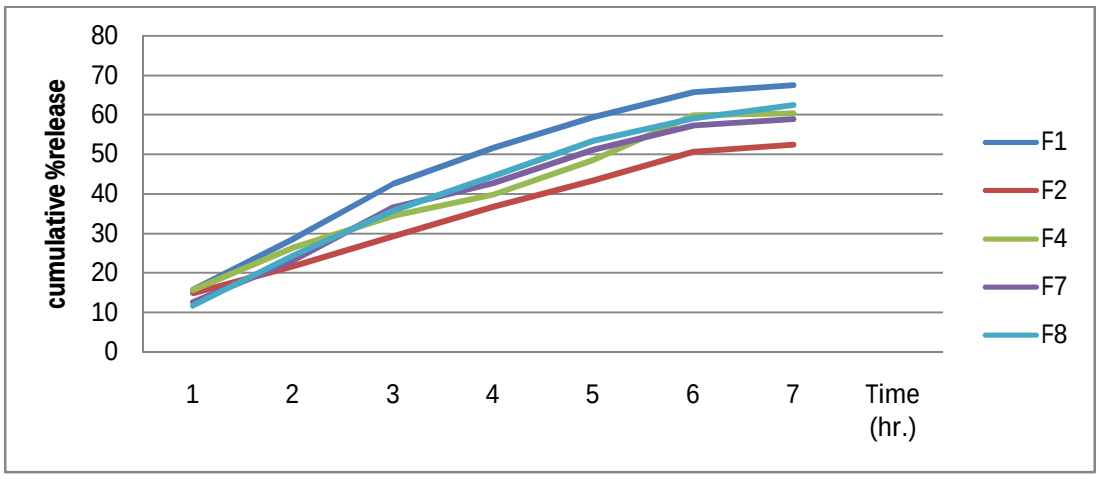
S.N.	McE batch	Conductivity σ (µS/cm)	Water content Φ (wt %)
1.	F1	70.4	10
2.	F2	138.8	20
3.	F4	126.5	20
4.	F7	176.3	30

9) *In vitro* permeation study [2,7]

The permeation and the diffusion of DDEA from prepared microemulsions were evaluated using Franz diffusion cells (surface 2 cm2 receiver liquid volume 7 mL) in a 37^0c thermostatic bath. The receiver liquid contains phosphate buffer of pH = 7.4. It was used a cellulose acetate membrane with the pore size of 0.45µm as diffusion barrier. This membrane was hydrated for 24 hours with phosphate buffer pH=7.4 at 20^0c. The donor compartment contains 0.1083 gm of microemulsion. It was collected 1.5mL of sample at every hour from the receiver compartment and it was established the amount of DDEA delivered and diffused. After each sample was collected the same volume of phosphate buffer solution in the receiver compartment was added.

Table. 10 Cumulative percentage release rate.

Time (Hrs)	Cumulative % Release (n=3)				
	F1	F2	F4	F7	F8
1	15.76 ± 0.45	14.93 ± 0.51	15.82 ± 0.41	12.72 ± 0.17	11.7 ± 0.30
2	28.52 ± 0.43	21.79 ± 0.40	26.42 ± 0.37	23.3 ± 0.39	24.41 ± 0.20
3	42.51 ± 0.45	29.39 ± 0.30	34.46 ± 0.34	36.7 ± 0.42	35.76 ± 0.25
4	51.54 ± 0.24	36.82 ± 0.19	39.77 ± 0.35	42.8 ± 0.34	44.6 ± 0.21
5	59.32 ± 0.55	43.3 ± 0.34	48.56 ± 0.27	51.28 ± 0.37	53.41 ± 0.38
6	65.72 ± 0.36	50.66 ± 0.33	59.83 ±0.38	57.3 ± 0.25	59.18 ± 0.25
7	67.43±0.45	52.43±0.36	60.32±0.59	58.98±0.22	62.56±0.26



"Fig. 4" Cumulative percentage drug release Vs time graph

10) Stability studies

The physical stability was evaluated by visual inspection for physical changes such as phase separation and drug precipitation. The physical stability study was also done at 4°C, 25°C and 45°C for 45 days at 75 % RH.

FORMULATION OF HYDROGEL THICKENED MICROEMULSION [6, 7, 8]

The selected microemulsion is incorporated in hydrogel for better and long term retention of preparation on skin.

Carbopol 940 was hydrated in fixed amount of water for at least 4 h and then previously formulated microemulsion was gradually added with continuous stirring till clear viscous solution was obtained. Finally, fixed amount of Triethanolamine was added to get hydrogel thickened microemulsions.

The hydrogel thickened microemulsions were characterized for pH, viscosity, spread ability, and in vitro drug transport, stability studies, and drug content.

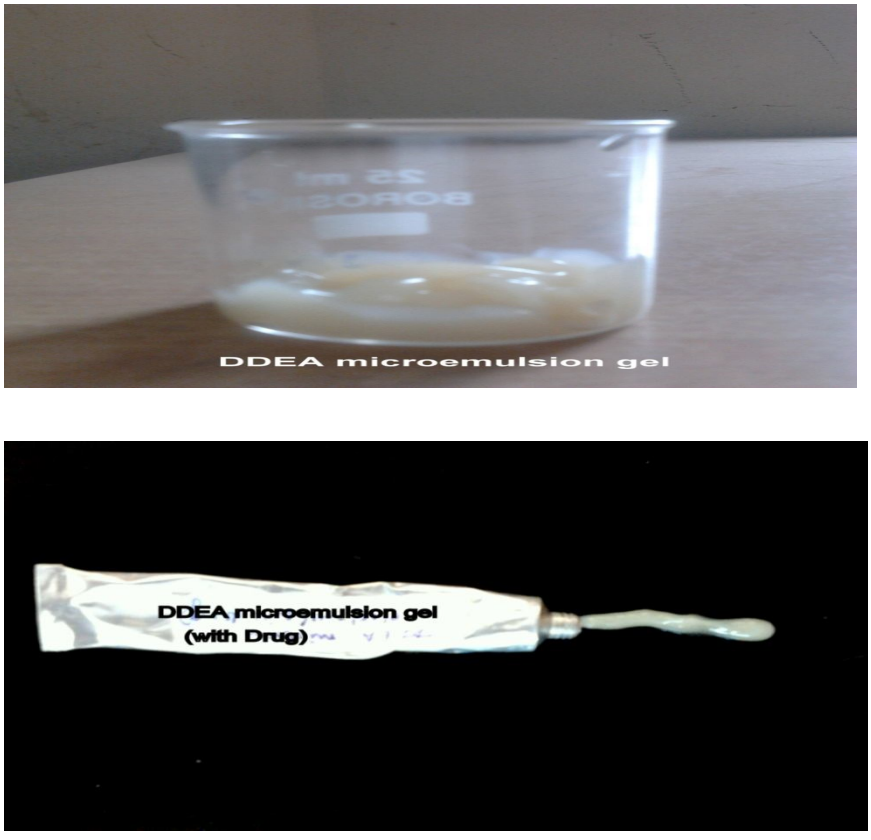


Fig. 5 Images of Microemulsion gel.

EVALUATION OF HYDROGEL THICKENED MICROEMULSION

1) Color, odor, appearance and feel

The evaluation of organoleptic properties is usually subjective in nature. Changes in color and odor can be indicative of oxidation in gels, while changes in appearance can provide valuable information about product throughout its shelf life. The formulated gel was

inspected visually for color, presence of any clog and to evaluate the feel the formulated gel were applied on cellophane and feel was experienced.

Table. 11 Evaluation of organoleptic properties of gel

S.No.	Parameter	Gel
1	Color	yellow
2	Clogging	-
3	Odor	pleasant
4	Feel	smooth

2) pH

The skin has a pH of 4-6, and topical are designed to be in that pH range. The pH of product can influence not only the solubility of drug in the formulation, but may also affect its potential to cause skin irritation. Changes in pH throughout the shelf life of product may also be indicative of stability problem.

The pH of DDEA gels were determined using digital pH meter, pH found of gel is: 5.8

3) Spreadability

Spreadability is an important property of topical formulation from a patient compliance point of view. Application of the formulation to inflamed skin is more comfortable if the base spreads easily, exhibiting maximum “slip” and “drag.” [(36)]

An excess of gel sample (4 gm) was placed between two slides and a 1Kg weight was placed on upper slide for few minutes to compress and uniformly spread the gel between the slides. A weight of (60 gm) was placed on the pan. The time required to separate the two slides was taken as measure of spreadability. It was calculated using the formula,

$S = M .L / T$

Where,

S = Spreadability L = length of the glass slide

T = time in sec M = weight tied to the upper slide

Length of the glass slide was taken 11.3 cm and weight tied to upper slide was taken (60 gm) throughout the experiment. Results are shown above.

Table. 12 spreadability of microemulsions gel.

S.No	Formulation	1	2	3	Spreadability (gm.cm/sec)* n=3
1	F_1	20.60	21.37	22.60	21.52±0.45

4) Viscosity

Viscosity measures the flow characteristics of topical formulation. Changes in viscosity of the product are indicative of changes in stability or effectiveness of the product. Viscosity of the DDEA gels were determined using Brookfield viscometer using spindle No S96 at 25˚C

Table. 13 viscosity of gel.

RPM	Viscosity (cps) using spindle-S96
1.5	6317.16
2.5	4715.86
3.5	4223.76
4.5	4113.86
5.5	3915.86
6.5	3723.43

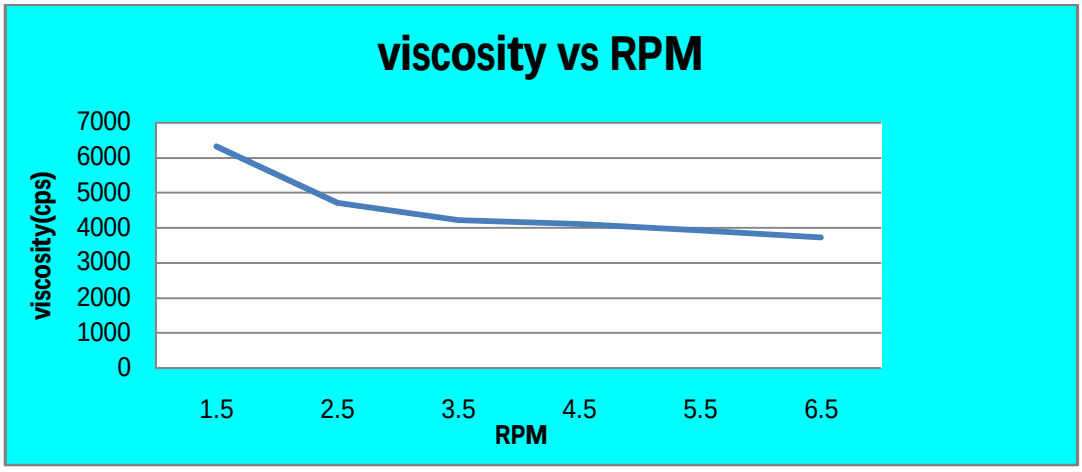


Fig. 6 Graph of gel viscosity.

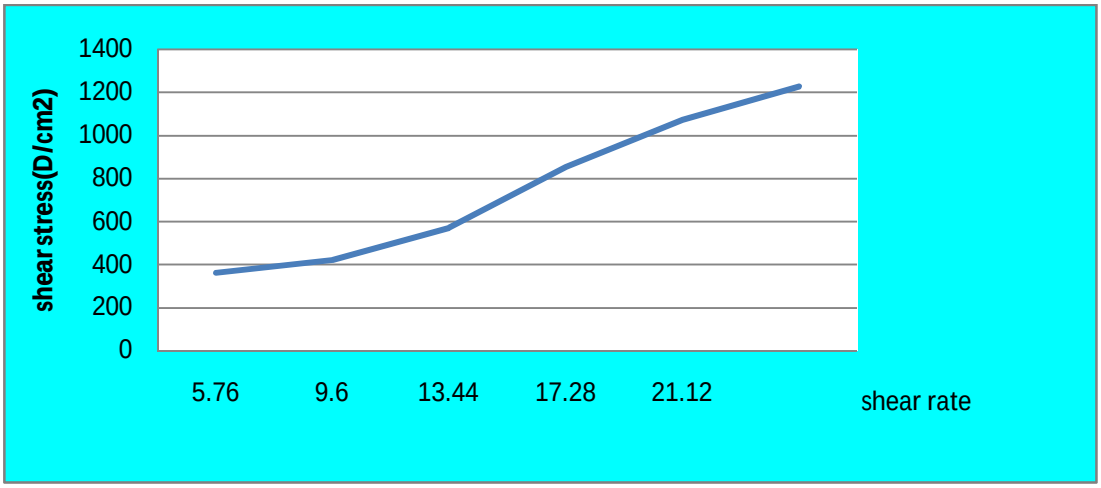


Fig. 7 Graph between shear rate and shear stress of hydrogel.

5) Drug Contents [32]

Shake a quantity of gel containing 50 mg. of DDEA with 50 ml of acetone for 10 min. filter and evaporate the filterate to dryness. Dissolve the residue in 10 ml. of a mixture of, 40 volumes water and 60 volumes of methanol, and sonicate, now dilute 1 volume of this solution to 5 volumes with mobile phase and filter through a glass fiber filter, this solution contain 0.005% w/v of Diclofenac Sodium (1 % diclofenac sodium is equivalent to 1.16% diclofenac diethylamine) .Now take 1 ml of this solution and dilute upto 100 ml with mobile phase. Take absorbance at 282.2 nm

6) Drug Diffusion studies (in vitro penetration studies) [2,7]

The permeation and the diffusion of DDEA from prepared microemulsions were evaluated using Franz diffusion cells (surface 2 cm2 receiver liquid volume 7 mL) in a 37^0c thermostatic bath. The receiver liquid contains phosphate buffer of pH = 7.4. It was used a cellulose acetate membrane with the pore size of 0.45µm as diffusion barrier. This membrane was hydrated for 24 hours with phosphate buffer pH=7.4 at 20^0c. The donor compartment contains 1gm of gel. It was collected 1.5mL of sample at every hour from the receiver compartment and it was established the amount of DDEA delivered and diffused. After each sample was collected the same volume of phosphate buffer solution in the receiver compartment was added.

Permeation Data Analysis [38]

The cumulative amount of drug permeated through the skin (mg/cm2) was plotted as function of time (t) for each formulation. Drug flux (permeation rate) at steady state (Jss) was

calculated by dividing the slope of the linear portion of the graph by the area of the diffusion cell. The permeability coefficient (Kp) was calculated by dividing Jss by the initial concentration of drug in the donor cell (C0).

$$Kp = Jss/C0$$

Table. 14 Permeability parameters of different formulations.

Formulation	Jss (mg /cm 2 per h)	Kp X 10 -3 cm/h
GF1	1.819	0.346
Mky.Prt.	1.495	0.258

Table. 15 *In vitro* permeation studies of microemulsified gel and marketed product.

Time (Hrs)	Cumulative % Release n=3	
	GF1	Mkt.Prt.
1	14.73 ± 0.34	11.64 ±0.26
2	23.65 ± 0.22	17.49 ±0.26
3	30.21 ± 0.55	23.45 ±0.16
4	36.53 ± 0.424	28.63 ±0.27
5	41.32 ± 0.45	32.58 ±0.28
6	42.86 ± 0.12	34.43 ±0.31

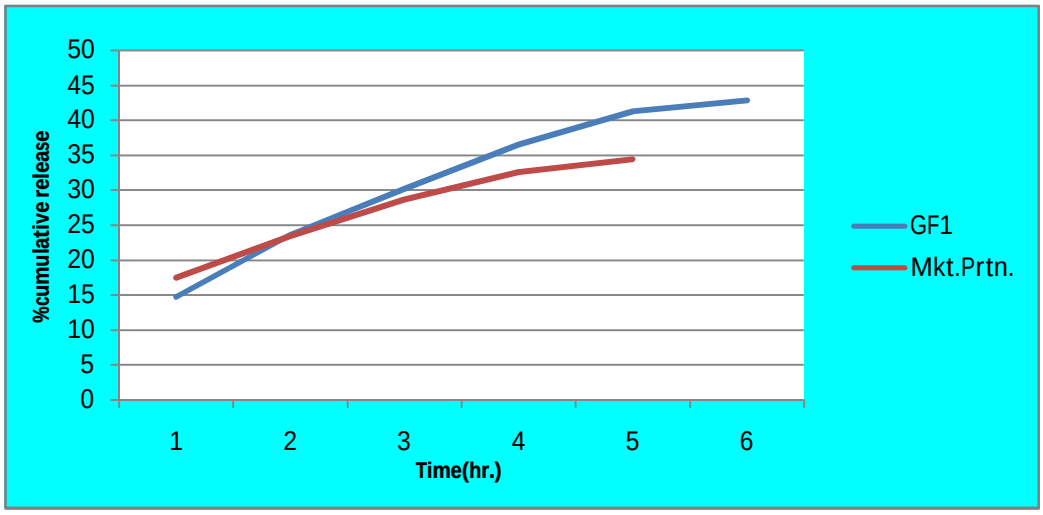


Fig. 8 Graphical representation of cumulative %release of microemulsified gel and marketed product.

For GF1

y=5.7137x+ 11.552

R^2 =0.9597

For mkt.prtn.

Y=4.697x+8.2633

R^2 =0.9742

7) Short term stability studies

Short term stability study of the hydrogel thickened microemulsion of gel was carried out for two months at 25±2 and 60% RH. The pH, drug content and viscosity of the hydrogel thickened microemulsion shows no any significant change at the end of stability study, and no significant change of phase separation was observed during 2 months.

RESULT AND DISCUSSION

Solubility studies indicated that DDEA display sparingly soluble in water. The solubility of DDEA in oil phase (eutectic mixture of menthol and camphor) was estimated. The DDEA was found to be soluble in oil phase (the eutectic mixture containing equal parts of menthol and camphor) was >160mg/ml .

Pseudoternary phase diagrams were constructed to obtain an optimum formula for DDEA in situ gel microemulsion. These diagrams were constructed to obtain the components and the concentration ranges that produced the microemulsion. Based on these findings, appropriate oil and surfactant-cosurfactant with selected percentage ratios (2:1) were used in the preparation of microemulsion.

FTIR studies shows that there is no interaction between drug and excipients.

The **appearance and clarity** were determined visually. The formulations were found to be clear and transparent and the gel shows yellowish color and smooth feeling.

Droplet size and zeta potential was observed with the help of Malvern Zetasizer. The average particle size was taken into consideration. The average diameter of droplet was in micro size range. From the observation it was clear that as the micro size range is dependent on the concentration of surfactant and co-surfactant ratio, these smaller size droplet are capable of better drug release.

zeta potential of the liquid formulations is of considerable importance from the stability point of view. In the study the zeta potential was less than -15 mV which are considered to be stable.

The **pH** of the formulations was determined by using pH meter. The skin has a pH of 4-6, and topical are designed to be in that pH range. The pH of product can influence not only the solubility of drug in the formulation, but may also affect its potential to cause skin irritation. Changes in pH throughout the shelf life of product may also be indicative of stability problem. The pH values of the prepared DDEA microemulsion varied from 5.71-8.03 that are within the acceptable range for skin preparations. And the pH of gel observed is 5.8

Viscosities of formulations were measured before and after gelation using Brookfield viscometer with spindle 2 for microemulsion and S96 for gel at various rpm at temperature 25±0.5 ºC .All the formulations exhibited Newtonian and psudoplastic flow characteristics before and after gelling respectively.

Drug content: of the formulation increases with increase of droplet size. The drug content of the formulation F1 and F2 was higher as compare to other formulations because of their maximum droplet size; F7 and F8 formulation have very low drug content probably due to

minimum droplet size. Drug content observed in hydrogel thickened microemulsion of batch F1 was 93.5%

Drug release: As the droplet size decrease, surface is increased allowing more dissolution and drug release. The formulations F-1 shows more drug release as compared to other microemulsion formulations. On the basis of microemulsion flux study, formulation F1 is chosen best, which is used for gel incorporation.

Gel formulation, which is compared with marketed preparation. The results shows, The significant difference ($P<0.05$) in drug permeation between gel containing microemulsified diclofenac diethyl amine formulation, and marketed gel was probably due to the considerable reduction in mean size of internal phase droplets, which is present significantly in microemulsion. The maximum drug release could be due to smallest droplet size and lowest viscosity and incorporation of oil phase (camphor + menthol) and ethanol as permeability enhancer, in comparison to marketed formulation. Permeability parameters like steady state flux (Jss) and permeability coefficient (Kp) significantly increased in microemulsion formulation in comparison to marketed formulation. This is because of the combined effects of different aspects of microemulsion as described above and components used which acts as permeation enhancers.

Short term stability study of the hydrogel thickened microemulsion of gel was carried out for two months at 25±2 and 60% RH. The pH, drug content and viscosity of the hydrogel thickened microemulsion shows no any significant change at the end of stability study.
and no significant change of phase separation was observed during 2 months.
The **stability** of microemulsion was evaluated by visual inspection for physical changes such as phase separation and drug precipitation. The study was done at 4°C, 25°C and 45°C for 45 days at 75 %. All the formulation was found to be stable.

SUMMARY AND CONCLUSION

Microemulsions can be defined as systems of at least two nearly immiscible fluids dispersed one into another with a remarkable small droplet size (in the nanometer range, e.g.20-200 nm). These are transparent or translucent systems, which show thermo-dynamic equilibrium between components present in the different phases. Gelling microemulsion drug delivery system is a novel approach for the formulation of drug compounds for transdermal. This approach combines advantages of both solutions and gels, such as accuracy and facility of

administration of the former and prolonged residence time of the later. Thus, gel-forming system prolongs the residence time of the drug and improves transdermal bioavailability. The principal advantage of this formulation is the possibility of administering accurate and reproducible quantities with increased penetration, in contrast to the already existing gelled formulations and moreover promoting retention on skin.

Microemulsion is one of the most promising approaches towards overcoming the formulation difficulties of hydrophobic/lipophilic drugs.

Formulating Diclofenac diethylamine in gel microemulsion form successfully, is expected to enhance the therapeutic efficacy of this drug relative to either simple drug solution or the market drug product. This might be due to greater penetration of the drug from microemulsion because of the presence of surfactants and Cosurfactants that increase the membrane permeability, thereby increasing drug uptake. Thus the need of frequent application and hence the risk of side effects can be overcome. Furthermore, the presence of the gelling polymers in this microemulsion is expected to prolong residence on the skin.

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