

Enhancement of Percutaneous Delivery of Dapsone by Microemulsion Gel

Jayashri Gajananarao Mahore*, Suvarna Dinkarrao Suryawanshi, Satish Vasudeo Shirolkar, Sanjeevani Shekhar Deshkar

Department of Pharmaceutics, Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, PUNE-18.

ABSTRACT

Objective: The purpose of this study was to develop microemulsion based gel formulation for topical delivery of dapsone with an objective to increase the solubility and skin permeability of the drug for treatment of acne. **Methodology:** The solubility of dapsone in oils, surfactants and cosurfactants was evaluated by saturation solubility to screen the components of the microemulsion. The pseudoternary phase diagrams were constructed using capryol 90 and N-methyl-2 pyrrolidone as the oil phase, Kolliphor EL as surfactant and PEG 400 as the co-surfactant. The system were assessed for drug-loading efficiency and characterized for pH, conductance, viscosity, particle size, drug content, globule size, zeta potential and drug release. Optimized formulation systems were formulated into gel form by using poloxamer-407 and evaluated for viscosity, spreadability, drug content, stability, in-vitro skin permeation, steady state flux, permeability coefficient, enhancement ratio and skin irritation study. **Result and Discussion:** Globule size of optimized microemulsion (F2) was found to be 27.53 nm, zeta potential was found to be -14.6 mV, permeability of drug from microemulsion within 8h was observed 82%, In-vitro diffusion study

showed increase in flux of microemulsion based gel ($392.43 \mu\text{g cm}^{-2} \text{h}^{-1}$) to that of simple dapsone gel ($274.4 \pm 0.78 \mu\text{g cm}^{-2} \text{h}^{-1}$). Draize test revealed absence of irritation and inflammation on rat skin. **Conclusion:** Microemulsion based gel of dapsone formulation provided better application property and stability in comparison to simple gel.

Key words: Acne vulgaris, Dapsone, Flux, In-vitro skin permeation, Topical delivery.

Key Message: Microemulsion based gel improved the solubility and permeability of dapsone

Correspondence :

Jayashri G Mahore, Assistant Professor, Department of Pharmaceutics, Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, PUNE-18.

Phone: 09922943257

Email: jayashri_mahore@rediffmail.com

DOI: 10.5530/jyp.2017.9.99

INTRODUCTION

Acne is caused by the effects of hormones on the pilosebaceous unit, consisting of a hair follicle and sebaceous gland. The normal skin follicles were blocked and an overgrowth by bacteria, *Propionibacterium acnes* causes destruction of the lining of the follicle causes follicular material enter into the dermis, causing an inflammatory response.^{1,2} It is a multifactorial disease affecting the pilosebaceous follicles and arises from an enhanced sebum excretion.³ Mainly topical and systemic therapies are involved in the treatment of Acne vulgaris, which act either by inhibiting bacteria (*Propionibacterium acnes*) involved in acne. Systemic therapies include oral antibiotic like doxycycline, erythromycin, immediate or by extended-release minocycline and tetracycline. Side effects of systemic medication are stomach, dizziness and teratogenesis. Topical therapies include retinoid like tretinoin and isotretinoin which causes skin irritation, erythema and peeling. Extensive use of topical and oral clindamycin has resulted in increasing clindamycin resistant microorganism which has increased inappropriate therapeutic responses.⁴

Therefore, dapsone has been introduced in the management of acne. Dapsone has longer half-life, with least side effects and interactions with other drugs and safety in pregnancy.⁵ Dapsone (4-[4-aminobenzene] sulfonyl] aniline) is an antimicrobial agent with bacteriostatic action. It inhibits the synthesis of dihydrofolic acid by competing with para-aminobenzoic acid for the active site of dihydropteroate synthetase, thus resembling the action of sulphonamide.⁶ The mechanism of topical dapsone in treatment of acne vulgaris may result from a combination of both anti-inflammatory and anti-microbial effects.^{6,7} Dapsone is a BCS class II drug with low aqueous solubility.⁸ Oral administration of dapsone has several side effects, including hemolytic anemia, nausea and

headache. Adverse effects of dapsone are related to the production of metabolites. In the liver dapsone is acetylated by N-acetyltransferase which produces monoacetyldapsone, and upon enzymatic hydroxylation, dapsone hydroxylamine is produced, that is primarily responsible for the development of adverse effects.⁹ These side effects diminish its practicability to use it by the oral route for treating skin diseases. Because of unsuitability of dapsone for the oral route; topical route is another alternative. Dapsone is marketed as gel; the bioavailability of dapsone can be improved by incorporating drug in microemulsion based gel. Microemulsion as colloidal nanosize carrier system is a promising vehicle for topical administration of drug with poor water solubility. Microemulsion had demonstrated improved transdermal permeation, thermodynamically stable over conventional topical preparations such as gel, cream and ointment. Microemulsion acts as penetration enhancer by interacting with stratum corneum, changing structural organization of lipid layer and consequently increasing transdermal drug permeation.^{10,11} The viscosity played an important role in promoting the drug retention on the stratum corneum and viable epidermis. However, microemulsion had very low viscosity and cannot retain at the affected area. Retention time of microemulsion can be increased by adding gelling agent. Some of the gelling agent such as carbapol, HPMC K-15, poloxamer-407 have been selected to increase the appropriate viscosity of microemulsion to enhance skin permeation, retention and form microemulsion based gel to improve topical applicability. In the present study attempt was made to formulate microemulsion based gel of dapsone using oil- 6%, Smix- 32%, Water-62% and poloxamer 407-18% w/w as gelling agent. Prepared gel

was characterized for pH, viscosity, percent drug content, spreadability and *in-vitro* diffusion study.

MATERIALS AND METHODS

Materials

Dapsone was purchased from market. Capryol 90 provided as gift sample by Gattefosse India Pvt. Ltd., Mumbai, India. Kolliphor EL and Polaxomer 407 were provided as gift sample by BASF, Mumbai, India. N-methyl-2 pyrrolidone, PEG 400, Carbopol 934, Carbapol 940 and HPMC K100M were purchased from Research Laboratory, India. All other chemicals and reagents were of analytical grade.

Methods

Solubility of Dapsone

The saturation solubility of dapsone was determined by shaking method. Excess drug was added in 5 ml vial containing 2 ml distilled water and methanol. After proper mixing of the mixture the vial was kept in an orbital shaker at $37 \pm 1^\circ\text{C}$ for 24 h. The resulting solution was filtered through Whatman filter paper, diluted and absorbance was recorded at 296 nm.¹²

Formulation of Microemulsion of Dapsone Solubility study

The solubility of Dapsone was determined in various oils, surfactants, and co-surfactant. An excess amount of Dapsone was added in 2 mL of the selected oils, surfactants and cosurfactants taken in 5 mL stoppered vial separately, and mixed by vortexing. The vials were then kept at $37 \pm 1.0^\circ\text{C}$ in an orbital shaker for 48h to achieve equilibrium. The equilibrated samples were removed from shaker and centrifuged at $402\times g$ for 15 min. The supernatant was filtered through Whatman filter paper. The absorbance of these filtrates was noted using UV spectrometer and the concentration of dapsone was calculated.¹³

Construction of Pseudo-ternary phase diagram

Pseudo-ternary phase diagrams were constructed by titrating mixtures of oil and Smix (mixture of surfactant and co-surfactant) with water at room temperature. For this, the selected surfactant and co-surfactant were blended together in different ratios like 1:1, 1:2 and 2:1. Smix was mixed with oil phase to give weight ratio of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9 (w/w) by using magnetic stirrer. These mixtures were titrated slowly with distilled water taking care for proper stirring of liquid phases to achieve equilibrium. After being equilibrated, the mixtures were assessed visually for transparency and further titrated over the entire phase region. The pseudoternary phase diagram was constructed for each system by plotting concentration of oil, surfactant and cosurfactant, a proper region was selected for formulation of microemulsion system from constructed pseudoternary phase diagrams. Various pseudoternary phase diagrams consisting of different oil, surfactant and cosurfactant mixture, in different ratio were constructed by using *Triplot software* version 4.1.2.^{14,15}

Selection of formulation from Pseudo-Ternary Phase diagram

Pseudo ternary phase diagrams constructed using Capryol 90 and N-methyl-2 pyrrolidone as oil phase, Kolliphor EL as surfactant and Polyethylene Glycol 400 as co-solvent. Various compositions of oil, Smix and water were selected for microemulsion formulation based on following criteria:

- Considering the solubility of the drug in the selected oil (mg/mL), the concentration of oil had to be sufficient to solubilize the drug equivalent to dose (1 gm/100 gm of microemulsion)
- For formation of homogenous, clear, transparent microemulsion for selected quantity of oil, the optimum quantity of water and Smix had to be used for formulation of microemulsion.¹⁵

Preparation of Microemulsion

After the identification of microemulsion region in the phase diagram, the microemulsion formulations were selected at desired component ratios Table 1. Dapsone loaded microemulsion was prepared by dissolving dapsone in N-methyl-2 pyrrolidone + Capryol 90 (1:1) with stirring. The required quantity of surfactant and cosurfactant (Kolliphor EL + PEG 400) were added and the mixture was stirred to yield a homogenous solution. To this solution, water was added to yield a microemulsion.^{15,16}

Preparation of microemulsion based gel

The poloxamer-407 as a gel matrix was used to prepare the microemulsion-based gel for improving the viscosity of microemulsion for topical delivery of dapsone. The poloxamer-407 (18% w/w) dispersed in water and then kept in freezer for 24 h. Then the poloxamer-407 solution was mixed with microemulsion under stirring. As the microemulsion was added to the solution of poloxamer-407, the viscosity of microemulsion based gel was increased. The gel was then subjected to physicochemical evaluation, diffusion study and stability studies.¹⁶⁻¹⁹

Evaluation of microemulsion and microemulsion based gel

Microemulsions were evaluated for percent transmittance, conductance, globule size and zeta potential measurement. Microemulsion and microemulsion based gel both were evaluated for pH, viscosity, percent drug content and spreadability study.^{20,21}

Stability study

Optimized formulation was stored at ambient environmental conditions $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH for 30 days. The samples were withdrawn on 0, 15 and 30 days of storage condition and evaluated for pH, drug content and *in-vitro* drug permeation study.²⁰

Table 1: Composition of microemulsion formulation prepared with Smix ratio.

Formulation code	Composition (%w/w) of different component in microemulsion with Smix		
	%Oil*	% Smix	% Water
F1	7	43**	50
F2	6	32**	62
F3	4	26**	70
F4	10	20***	70
F5	6	32***	53
F6	3	37****	60

* Oil- Capryol 90: N-methyl-2 pyrrolidone (1:1)

** Smix – KolliphorEL : PEG 400 (1:1)

*** Smix - KolliphorEL : PEG 400 (1:2)

**** Smix - KolliphorEL : PEG 400 (2:1)

Permeation study

In-vitro diffusion study of microemulsion and microemulsion based gel

The study was performed using Franz diffusion cells with dialysis membrane. The recipient compartment had total capacity of 35 mL. Microemulsion and microemulsion based gel equivalent to 10 mg of dapsone was placed on the donor compartment and the receptor compartment was filled with mixture of phosphate buffer solution (pH 7.4) and 30% methanol, maintained at $37 \pm 1^\circ\text{C}$. For *in-vitro* diffusion studies, artificial dialysis membrane was soaked in the same buffer solution for 24 h before mounting on the diffusion cells. Receptor liquid was withdrawn after each hour and sink condition was maintained by replacing liquid kept at same temperature. Dapsone concentration was assayed by UV spectrophotometer.²²

Ex-vivo skin permeation study

Male albino Wistar rats skin was used for permeation study. Skin permeation study was carried out as follows:

Abdominal skins were obtained from male rat after sacrificing by chloroform. The hair on the skin was removed. The skin was carefully excised and the subcutaneous tissue was removed surgically and the dermis side was wiped with isopropyl alcohol to remove adhering fat. Then the skin was washed with water, wrapped in aluminium foil and stored in freezer for further use. *In-vitro* skin permeation study was performed by using Franz diffusion cells with diffusion area of 4.9 cm^2 . The excised skin samples (dorsal side) of rat were placed between the donor and the receptor compartment of Franz diffusion cells with the stratum corneum facing the donor compartment. Then, 1 g of microemulsion based gel or simple dapsone gel containing 1% (w/w) dapsone was applied on the donor compartment. The receptor compartment was filled with phosphate buffer (pH 7.4) and 30% methanol maintained at $37 \pm 1^\circ\text{C}$ with stirring at 100 rpm. At predetermined time intervals (1 h), 1 mL receptor medium was withdrawn up to 8 h. All samples were analyzed by UV spectrophotometer.²³

Permeation data analysis

The cumulative amount of drug permeated per unit skin surface area plotted against time and slope of the linear portion of the plot was estimated as the steady state flux (Jss). Permeability coefficient was calculated as

$$K_p = J_{ss} / C_v$$

Where, C_v is the total donor concentration of the solute.

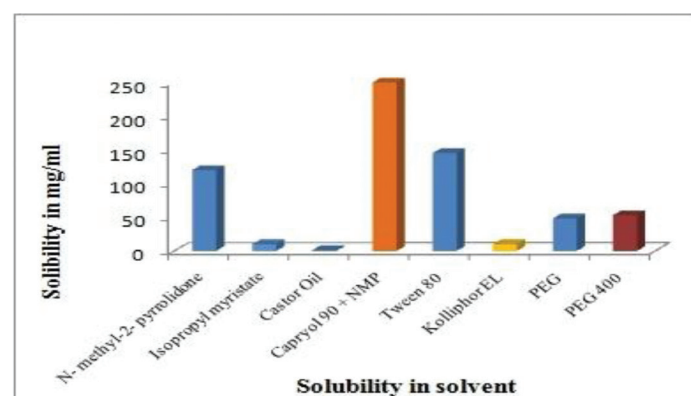


Figure 1: Solubility of dapsone in various solvent.

Enhancement ratio (Er) was calculated by dividing the Jss of the respective formulation by the Jss of control formulation: $Er = J_{ss} \text{ of formulation} / J_{ss} \text{ of control}$.^{24,25}

Skin irritation test

Skin irritation study of dapsone loaded microemulsion based gel was carried out by using Draize patch test on Albino Wistar rats of 180-250 g weight. Rats were selected in two groups of five animals each under laboratory condition of temperature and light/dark cycle. Back side of rat was shaved and optimized gel was applied on area of $2 \times 2\text{ cm}$ to study skin irritation study for three days. Approximately 24, 48 and 72h after application, animals were examined for signs of irritation.^{26,27}

RESULTS

Saturation solubility of dapsone in solvent, oil, surfactant and cosurfactant:

Being a BCS class II drug dapsone has very low solubility in water. The saturation solubility of Dapsone in distilled water was found to be $0.24 \pm 0.056\text{ mg/mL}$ and in methanol was $49.76 \pm 0.68\text{ mg/mL}$.

Because of poor water solubility, solubility of dapsone in the oily phase of microemulsion is very critical because it may affect the stability as well as the percutaneous delivery performance of the formulation. To screen appropriate solvents for the preparation of microemulsions, the solubility of dapsone in various oils, non-ionic surfactants and co-surfactant was measured Figure 1. The solubility of dapsone in N-methyl-2 pyrrolidone was 120 mg/mL but solubility of dapsone in blend of Capryol 90 and N-methyl-2 pyrrolidone was 250 mg/mL. Use of N-methyl-2 pyrrolidone provided a greater microemulsion region and higher solubilization of Dapsone. So, to improve the solubility of dapsone the blend of N-methyl-2 pyrrolidone + Capryol 90 (1:1) was used. Amongst the various surfactants and cosurfactants screened, dapsone exhibited good solubility in nonionic surfactants such as Tween 80. Though dapsone was showing less solubility in Kolliphor EL than Tween 80, it was decided to select kolliphor EL further study as it was giving better transparent region in pseudoternary plot.

Construction of pseudoternary phase diagram

The phase diagrams of Capryol 90+ N-methyl-2 pyrrolidone+Kolliphor EL+ PEG 400+water was shown in Figure 2. The transparent o/w microemulsion area was presented as a shaded region in the phase diagrams. The Smix ratio 1:1 had larger microemulsification region as compared to 1:2 and 2:1. The emulsified area was the lowest at ratio of 2:1 as the concentration of co-surfactant was less. From the microemulsion regions in the phase diagrams, the microemulsion formulations were selected at different component ratios. The microemulsions containing excess amount of drug were prepared and evaluated. The effect of amount of

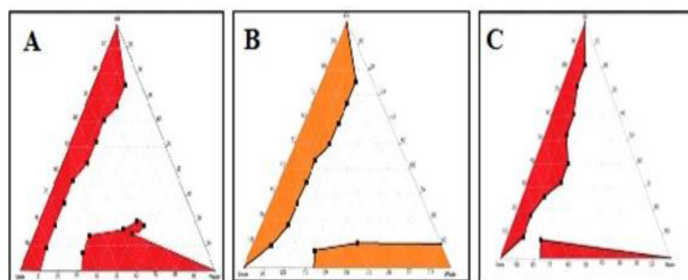


Figure 2: Pseudo-ternary phase diagram showing microemulsion region of oil, water and Smix (Kolliphor EL: PEG 400) with different ratio of Smix (surfactant: Co-surfactant) A 1:1, B 1:2, C 2:1.

Table 2: Data for evaluation of different microemulsion.

Code	Appearance and Clarity	pH	Conductance ($\mu\text{S}/\text{cm}$)	Percent drug Content (%) *	Percent Transmittance (%) *	Particle Size (nm)
F1	+++	5.8	14	92.99 $\pm$ 0.025	97.95 $\pm$ 0.11	30.34
F2	+++	6	15.3	97.99 $\pm$ 0.040	99.14 $\pm$ 0.29	27.53
F3	+++	5.8	15.8	92 $\pm$ 0.06	97.93 $\pm$ 0.83	49
F4	+++	5.6	14.2	92.01 $\pm$ 0.055	97.95 $\pm$ 0.27	64.40
F5	+++	5.7	15.1	83.63 $\pm$ 0.54	97.96 $\pm$ 0.078	31
F6	+++	5.8	13	96.65 $\pm$ 0.092	97 $\pm$ 0.035	64.09

* Mean $\pm$ SD; n=3, Microemulsion marked as Turbid (-), Slightly turbid (+), Clear (++), Clear and transparent (+++).

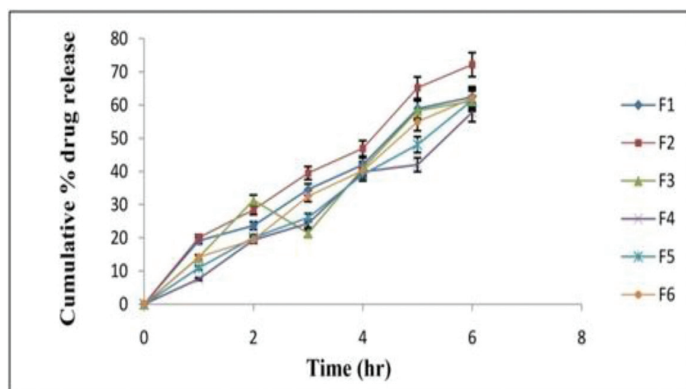


Figure 3: In-vitro drug permeation dapsone loaded microemulsion through dialysis membrane.

surfactant: cosurfactant and oil phase on globule size of drug-loaded microemulsions were investigated.

Evaluation parameter for microemulsion

Microemulsion had pH values from 5.8 to 6. pH of all these formulations were in the range of pH of skin (4 to 7).

The conductance of microemulsion formulations was measured using conductometer. It was observed that as the percentage of water was increased in microemulsion, the electrical conductivity also increased. The conductance of microemulsions was found in Table 2 the range of 14-16 (microsiemens/cm). Estimation of dapsone content in microemulsion formulation was carried out by the UV spectrometric method. The content of dapsone in various microemulsion was found to be in range of 80- 100%. Percent transmittance in microemulsion formulation was carried out by UV spectrometric method at 630 nm. The percentage transmittance of dapsone microemulsion formulations was found to be in the range of 97-100%.

Droplet size of microemulsion formulation is critical parameter. The smaller the droplet size, the larger will be interfacial surface area provided for drug permeation.^{21,27} Globule size of (F2) formulation was found to be 27.53 nm Table 2. The viscosity of optimized microemulsion (F2) was found to be 120 cps at 100 rpm which was determined by using Brookfield viscometer (DV II + PRO) with small sample volume adaptor. Zeta potential of optimized microemulsion (F2) was found was found to be -14.6 mV.

In-vitro diffusion of microemulsion

Figure 3 represent the cumulative percent drug permeated from the formulation F1 to F6 in 6 h through dialysis membrane shows that drug permeation greatly depends on the composition of microemulsion.

Table 3: Data for evaluation of different microemulsion based gel.

Formulation	pH	Spreadability gm cm/sec	Percent drugcontent *
FG1	5.8	14.42	91.27 $\pm$ 0.34
FG2	6	25	97.06 $\pm$ 0.21
FG3	5.8	21.42	80.65 $\pm$ 0.56
FG4	5.7	15	86.96 $\pm$ 0.081
FG5	6	18.75	94 $\pm$ 0.025
FG6	6.2	20.83	96.97 $\pm$ 0.073

*Mean $\pm$ SD; n= 3

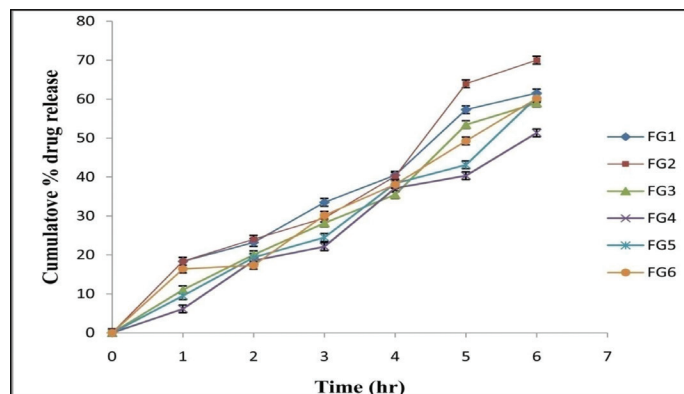


Figure 4: In-vitro drug permeation dapsone loaded microemulsion based gel through dialysis membrane.

After 6 h of permeation study through dialysis membrane, amount of drug permeated (72.20%) was maximum for F2 formulation.

Evaluation parameter for microemulsion based gel

The pH of all the microemulsion based gel formulation was found to be in the range of 5.8-6.2. These pH values were considered to be acceptable since the skin pH ranges between 4-7. Although good spreadability was observed for all the formulations, the formulation gelled with polaxamer - 407 showed better spreadability in range of 14- 30 gm/cm/sec. Estimation of drug content in microemulsion based gel formulation was carried out by UV spectrophotometer. The content of dapsone in various microemulsion based gel was found to be in range of 80- 97% Table 3. Drug content study revealed that no degradation of drug was observed when formulated as microemulsion based gel.

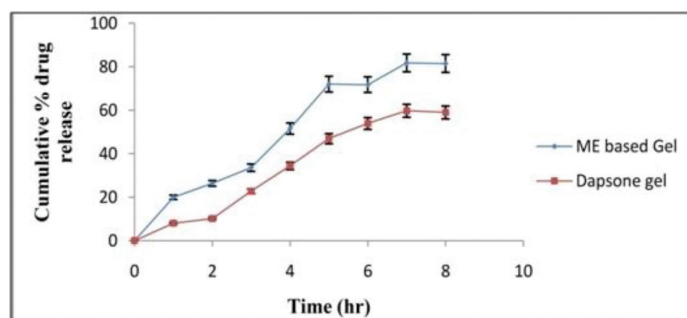
Rheological study

Viscosity of all gels was determined by Brook filed viscometer by using spindle S- 94. Viscosity of all gel at 20 rpm was found to be FG1-32890, FG2-48500, FG3-78900, FG4-30300, FG5-33000 and FG6-65200 cps.

Table 4: Stability testing of FG2 after 15 days interval.

Time interval (days)	pH	Drug content*	<i>In vitro</i> diffusion study*
0	6	97.99±0.040	70±0.09
15	5.9	97.20±0.020	69.96±0.03
30	5.8	96.86±0.020	69.76±0.10

*Mean ± SD; n= 3

**Figure 5:** Comparison of *in-vitro* drug permeation of plain dapsone gel and microemulsion based gel through rat skin.

In-vitro diffusion of microemulsion based gel

The results of *in-vitro* diffusion study of microemulsion based gel through dialysis membrane using Franz diffusion cell are shown in Figure 4.

Among all the microemulsion based gel formulations, formulation FG2 (Oil: 6%, Smix: 32%, Water: 62%) showed good permeation rate through dialysis membrane (70 ± 0.09%), spread easily and it was found to be stable formulation and hence was selected as optimized formulation.

Stability study

The result of stability study Table 4 revealed that there was no significant change in the microemulsion based gel formulation, no phase separation and no sign of precipitation of drug. Stability studies indicated that the preparation was stable at room temperature over the period of one month.

Ex-vivo skin permeation study

Ex-vivo skin permeation study showed higher drug release for microemulsion based gel (81.51 ± 0.42 %) as compare to simple gel of dapsone (58.98 ± 0.36%) at the end of 8 h Figure 5. This might be due to decreased globular size of microemulsion droplets (F2- 27.53 nm).

Kinetics of drug release from microemulsion and microemulsion based gel

The cumulative amount of drug released from selected dapsone microemulsion and microemulsion based gel formulation at different time interval was fitted to different models to find out the mechanism of drug release.

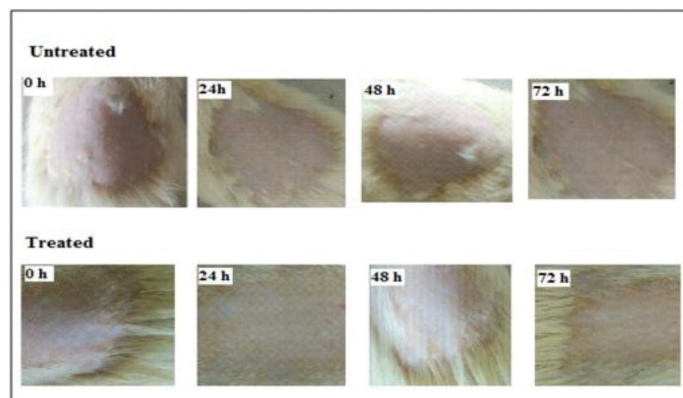
The correlation coefficients Table 5 showed that the kinetic of drug release from microemulsion and microemulsion based gel followed zero order model of kinetics.

Permeation analysis

The permeability parameters of different formulations are given in Table 6. Flux is the amount of drug permeated per unit area in unit time. The

Table 5: Release Kinetics of microemulsion and microemulsion based gel.

Code	Zero Order		First order	Matrix		Peppas		Hix – Crow
	R ²	K	R ²	R ²	K	R ²	n	R ²
F2	0.9808	12.69	0.9352	0.9162	25.91	0.9477	0.78	0.9565
FG11	0.9818	12.47	0.9329	0.9113	25.41	0.9537	0.81	0.9551

**Figure 6:** Skin irritation test for microemulsion based gel of dapsone on rat skin.

results showed that the optimized microemulsion formulation when gelled with poloxamer-407, the flux (J_{ss}) and permeability coefficient (K_p) was greatly increased as compared to simple dapsone gel. At the end of 8 h microemulsion based gel showed flux of $392.43 \pm 0.814 \mu\text{g}/\text{cm}^2/\text{h}$ and cumulative drug release was found to be $81.51 \pm 0.42\%$. Increase in flux as compare to simple dapsone gel with highest enhancement ratio (Er) 1.430, which indicates faster drug release from microemulsion based gel.

Skin irritation study of microemulsion based gel on rat

Frequent use of some topical formulation can induce irritation and damage the skin. Therefore, skin irritation studies are developed for topical formulation.

Treatment groups not showed any signs of skin irritation as reddening and inflammation at the site of application. Skin of rat was found to be free of any signs of irritation Figure 6. Thus it can be concluded that all selected microemulsion based gel of dapsone are safe for topical application.

DISCUSSION

Capryol 90 + N-methyl-2 pyrrolidone as oil phase (1:1) and Kolliphor EL + PEG 400 as the Smix for microemulsion showed better transparent region, because dapsone has good solubility in these solvents, which helped to get the transparent region in pseudo-ternary phase diagram. It was evident from the results that the droplet size is inversely proportional to the concentration of Smix and directly proportional to concentration of oil. A decrease in particle size with increase in Smix may be the

Table 6: Permeability parameters of formulation.

Formulations	Flux ($J_{ss} \pm SD$) ($\mu\text{g cm}^{-2} \text{h}^{-1}$)	Permeability coefficient (K_p) (cm h^{-1})	Enhancement ratio (Er)
Dapsone microemulsion based gel	392.43 ± 0.814	0.03922 ± 0.0065	1.430
Dapsone gel	274.4 ± 0.78	0.02474 ± 0.0078	

result of more non-ionic surfactants (Smix) being available to solubilize the oil/water interface.

Sticking of particles to each other (aggregation, coagulation and flocculation) or to the surrounding surface causes microemulsion instability. Sticking can be counteracted by strong electrostatic repulsion and the strength of that repulsion can be measured by the zeta potential. Negative zeta potential showed that globules of microemulsion had no charge, the system was stable. It was observed from the result of viscosity measurements that viscosity values of all microemulsion formulation were increased slightly with increase in concentration of Smix. Conductivity studies showed that addition of the appropriate amount of water phase into the formulation had no negative effects on system stability. In an unstable microemulsion system the conductivity values were reduced because of phase separation. Good spreadability is because of the loose gel matrix nature of microemulsion based gel. Increase in shear causes alignment of random molecules of gelling material thus decreasing internal resistance of material. The pH range for skin is 6-8. Measured pH values of all formulations were found to be compatible for topical formulations.

Higher percent drug permeation of F2 formulation was might be due to change in concentration of oil, Smix and water. Smaller particle size of F2 formulation permeated better drug as compared to other formulations. It has been shown that release rate from microemulsion based gel was higher as compared to simple dapsone gel. Greater permeability of drug from microemulsion based gel may be attributed to different factors, such as a) microemulsion with reduced particle size provides more surface area to release drug, thereby increase the rate of drug release, and b) various components of microemulsion also have penetration enhancing effect.

Enhance steady state flux of Microemulsion gel over the simple gel could be due to the permeation enhancer property of surfactant and cosurfactant present in microemulsion. Permeation enhancer causes reduction in diffusional barrier and disturbance in the stratum corneum structure. The microemulsion may simultaneously alter both the lipid and the polar pathways as a combined effect of both the lipophilic and hydrophilic domains of microemulsions. The lipophilic domain of the microemulsion can interact with the stratum corneum and facilitate permeation. The hydrophilic domain causes the hydration of the skin, which plays an important role in the percutaneous uptake of poorly soluble drug. When the aqueous fluid of the microemulsion enters the polar pathways, it increases the interlamellar volume of stratum corneum lipid bilayers, resulting in disruption of the interfacial structure. Since some lipid chains are covalently attached to corneocytes, hydration of these proteins will also lead to disorder of lipid bilayers. Similarly, swelling of the inter-cellular proteins may also disturb the lipid bilayers; a lipophilic drug like dapsone can then permeate more easily through the lipid pathway of the stratum corneum.²⁸

CONCLUSION

The study revealed that microemulsion based gel prepared with Poloxamer-407 (18%) as a gelling agent imparts viscosity to the preparation to sustain the action of the drug by increasing the residence time. The contents of the microemulsion based gel was composed of Dapsone (1% w/w), N-methyl-2 pyrrolidone- Capryol 90 (1:1), (6% w/w), Kolliphor EL (32% w/w), poloxamer-407 (18% w/w) and water (62% w/w). The increased permeability of dapsone microemulsion based gel was observed 81.51 ± 0.42 % within 8 h compared to simple gel $58.98 \pm$

0.36%. There was no change in drug content, *in-vitro* diffusion study of the microemulsion based gel after 30 days of stability testing. Conclusively, microemulsion based gel could be one of the approach to enhanced the solubility and to improve permeability of dapsone.

REFERENCES

1. Degitz K, Borelli C. Pathophysiology of Acne. J Dtsch Dermatol Ges. 2007;5(4):316-25.
2. Jonnet K, Michae S. An Update on management of Acne Vulgaris. Clin Cosmet Invest Dermatol. 2009;2:105-10.
3. Stern RS. Dermatologists and office-based care of dermatologic disease in the 21st century. J Investigative Dermatol Symposium Proc. 2004;9(2):126-30.
4. Guy F, Webster MD. Pathology and Principles of Acne Treatment. Adv Stud Nursing. 2005;3(7):228-33.
5. Adele S, Beatrice T, Ponti D, Penna L. An Innovative Approach in the Topical Treatment of Acne. Clin Cosmet Invest Dermatol. 2015;8:179-85.
6. Tan J. Dapsone 5% gel: A New Option in Topical Therapy for acne. Skin Therapy Lett. 2012;17(18):1-3.
7. Falcocchio S, Ruiz C, Francisco IJ. Propionibacterium acnes GehA lipase, an enzyme involved in acne development, can be successfully inhibited by defined natural substances. J Mol Catal B Enzym. 2006;40(3):132-7.
8. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res. 1995;12(3):413-20.
9. Wozel VE. Innovative use of dapsone. Dermatologic Clinics. 2010;28(3):599-610.
10. Prabhjyotkaur, Loveleenpreetkaur, Khan MU. Topical Formulation and Hydrogel: An Overview. Inter J Adv Pharm Biology Chem. 2013;2(1):201-6.
11. Lawrence MJ, Rees GD. Microemulsion based media as novel drug delivery systems. Adv Drug Delivery Rev. 2000;45(1):89-121.
12. Choi SY, Oh SG, Bae SY, Moon SK. Effect of short chain alcohols as co-surfactant on pseudo-ternary phase diagrams containing lecithin. Korean J Chemical Eng. 1999;16(3):377-81.
13. Date AA, Patravale VB. Microemulsion: Application in transdermal and dermal delivery. Critical Rev Thera Drug Carrier Syst. 2007;24(6):547-596.
14. Zhu VW, Gou C, Yu A. Microemulsion based hydrogel formulation of penciclovir for topical delivery. Inter J Pharm. 2009;378(1):152-8.
15. Khandavilli S, Panchagnula R. Nanoemulsions as versatile formulation for paclitaxel delivery: peroral and dermal delivery studies in rats. J Invest Dermatol. 2006;127(1):154-62.
16. Vintiloiu A, Leroux CJ. Organogels and their use in the drug delivery-A review. J Control Release. 2008;125(3):179-92.
17. Mou D, Che H, Du D. Hydrogel-thickened nanoemulsion system for topical delivery of lipophilic drugs. Inter J Pharm. 2008;353(1):270-6.
18. Kantaria S, Rees GD, Lawrence MJ. Formulation of electrically conducting microemulsion-based organogels. Inter J Pharm. 2003;250(1):65-83.
19. Ghosh V, Mukherjee A, Chandrasekaran N. Mustard oil microemulsion formulation and evaluation of bactericidal activity. Inter J Pharm Pharma Sci. 2012;4(4):497-500.
20. Spiclin P, Homar M, Zupancic-valant A, Gasperlin M. Sodium ascorbyl phosphate in topical microemulsions. Inter J Pharm. 2003;256(1):65-73.
21. Anjali CH, Dash M, Chandrasekaram N, Mukherjee A. Anti-bacterial activity of sunflower oil microemulsion. Inter J Pharm Pharma Sci. 2010;2:123-8.
22. Patel RM, Patel BR, Parikh RJ. Investigating the effect of vehicle on *in vitro* skin permeation of ketoconazole applied in o/w microemulsion. Pharm dev Technol. 2011;16(3):250-8.
23. Shinde U, Pokharkar S, Modani S. Design and evaluation of Microemulsion Gel system of Nadifloxacin. Indian J Pharm Sci. 2012;74(3):237-47.
24. Ghosh B, Reddy HL. Effect of physicochemical parameter on skin permeability of antihypertensive. Indian J Exp Biol. 2001;39:710-4.
25. Khanna S, Katara OP. Lecitinised microemulsion for topical delivery of tretinoin. Inter J Drug Dev Res. 2010;2:711-9.
26. Yi T, Wan J, Xu H, Yang X. A new solid self-microemulsifying formulation prepared by spray drying to improve the oral bioavailability of poorly water-soluble drugs. Euro J Pharm Biopharma. 2008;70(2):439-44.
27. Gannu R, Palem C, Yamsani V, Yamsani S, Yamsani M. Enhanced bioavailability of lacidipine via microemulsion based trasdermal gel: Formulation optimization, *ex vivo* and *in vivo* characterization. Inter J Pharm. 2010;388(1-2):231-41.
28. Shinde U, Pokharkar S, Modani S. Design and Evaluation of Microemulsion Gel System of Nadifloxacin. Indian J Pharm Sci. 2012;74(3):237-47.

Article History: Submission Date : 24-06-2017 ; Revised Date : 15-07-2017; Acceptance Date : 31-07-2017.

Cite this article: Mahore JG, Suryawanshi SD, Shirolkar SV, Deshkar SS. Enhancement of Percutaneous Delivery of Dapsone by Microemulsion Gel. J Young Pharm. 2017;9(4):507-12.