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Formulation of Microemulsion Systems for Improvement of Nitrofurazone Permeation Through Silicon Membrane as Burn Wound Imitating Coverage

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Abstract: The basic objective of this study was to formulation of microemulsion for improvement of nitrofurazone permeation through silicon membrane and comparison between barrier properties of third-degree burned eschar and silicon as burn wound imitating coverage. Microemulsions were prepared with titration method and for evaluation the effect of parameter on barrier properties, three independent factors: proportion of surfactant/ co surfactant, percent of oil phase and Propylene Glycol (PG) as co surfactant were selected. The effect of independent variables on permeability parameters such as flux, D and T_{lag} were studied. Results showed, silicon performed less permeable membrane than eschar. The effects of microemulsion parameters on nitrofurazone permeability across silicon were not significant, but PG with effect on partitioning phenomena, increased flux and isopropyl myristate increased D.

Key words: Burn wound, imitating coverage, nitrofurazone, microemulsion, eschar, permeation

INTRODUCTION

Infection of burn wounds remains the single most important cause for multiple organ failure and death following severe burn. Early mortality relates to circulatory shock (Abbasi and Abbasi, 2007; Meyerholz *et al.*, 2009) and later mortality is attributed to sepsis (Apple *et al.*, 2002). As temperature increases, a process referred to as coagulation occurs. The central zone of wound called eschar where the heat energy is most intense.

This devitalized tissue, the burn eschar, is avascular and consists of denatured protein and cellular debris and provides an ideal environment for growth of microorganisms. The burned tissue is sterile immediately after burn. But, Gram-positive microorganisms grow in it and after 3 to 7 days superseded by Gram-negative species (Arturson, 1996). Eschar contains toxins and pathogenic microorganisms, which may diffuse into the circulation causing organ dysfunction and sepsis. Whilst, early burn excision is an ideal and practical solution for remove the agent responsible for immunosuppression and systemic sepsis, it is recognized that in some cases patients have injuries to other organs which prevent early operation under general anaesthesia (Ross *et al.*, 1993; Selvaggi *et al.*, 2007). Therefore, when early excision of

the eschar is not possible, treatment of eschar infection with effective topical antimicrobial agents can help to decrease the bacterial colonization in the tissue, which would otherwise lead to sepsis and so decrease rate of mortality and morbidity (Naoum *et al.*, 2004).

Any information about eschar barrier properties against antimicrobial permeation may be useful in predicting likely drug levels in the wound tissue, plasma and other tissues adjacent to the wound. These information are basic requires for development of effective topical antimicrobial formulations. For this purpose, mechanistic permeation studies using eschar tissue are necessary. There is little information in the literature about permeation of molecules with different physicochemical properties through eschar. Human eschar tissue for *in vitro* studies is usually obtained from cadavers or following plastic surgery. Setting up an *in vitro* study for evaluation of eschar permeation associated with some problems same as: particulate care is necessary in handling and working with eschar tissue. The duration and method of tissue storage may also causes variability and the tissue is infected by serious pathogenic microorganisms (Hettiaratchy and Dziewulski, 2004).

In the other hand, there is generally some variability in the age, race, sex, anatomical site and general health of donors. Permeation studies with synthetic membranes

instead of eschar may overcome these problems. So, such synthetic membranes are readily available, homogeneous, chemically pure and easier to handle. If good correlation between eschar and synthetic membrane permeation data for a especial compound is obtained, this membrane can be used instead of eschar in permeation study.

In the other hand, after debridman surgery especially when more than 50% of the surface of body is affected by deep burns, open wound should be closed with suitable membranes such as: autologous skin grafts and xenografts and tissue engineered biosynthetic products that achieve temporary wound coverage (Boyce and Warden, 2002). In many parts of the world, such expensive products are not available and early excision is limited (Garner and Heppell, 2005). Silicone (Atiyeh *et al.*, 2005) and Carbosil (Feldstein *et al.*, 1998) membranes are used as common burn wound coverage.

Any antimicrobial agent with good permeability through these membranes can effectively prevent microbial growth in wound and so prevent sepsis and organ dysfunction. Nitrofurazone is an effective antimicrobial agent that is used in burn wound treatment. There is little information about nitrofurazone permeability against eschar. In literature, nitrofurazone permeability through eschar is reported in intermediate level (Church *et al.*, 2006). But there is not any mechanistic study for nitrofurazone permeation parameters against eschar.

This study aimed firstly to characterize the permeability of nitrofurazone through silicon membrane and eschar that have not been studied. Secondly, we wish to investigate whether these membranes may be useful models of the barrier properties of eschar tissue. And thirdly we investigate the effect of microemulsion formulations on permeability of nitrofurazone through silicon membrane as imitating burn eschar coverage.

MATERIALS AND METHODS

This study was conducted in School of Pharmacy, Jundishapur University of Medical Sciences and London School of Pharmacy from July 2007 to 2008. Nitrofurazone was purchased from Aldrich (USA). Eschar tissue from patients with third degree burns was obtained from the Motahari Burn Center (Tehran, Iran). Silicone sheeting (0.007 cm) was obtained from Dow Corning (USA). Isopropyl myristate, propylene glycol and tween 80 were purchased from Aldrich (USA). Minitab 1 software was used for experimental design and the evaluation of the effect of variables on responses.

Solubility studies: Saturated solubility of Nitrofurazone in water, isopropyl myristate and propylene glycol was assessed by equilibrating an excess amount of drug in

medium solution using a stirrer at $37^{\circ}\text{C}\pm 0.5$ for 24 h. All samples were filtered through 0.45 μm , diluted and assayed by HPLC.

Isopropyl myristate-water partition coefficient calculation: Mixed isopropyl myristate with water at 37°C and stirrer for 24 h. drug dissolved in 5 mL of water (saturated with isopropyl myristate) and then added 5 mL of isopropyl myristate (saturated with water) and well stirred and stored for 24 h in 37°C and then concentration of drug in each phase was measured.

Drug analysis: A HPLC method was performed for analysis of nitrofurazone. This method used Hewlett Packard HPLC system with C18 column (length: 15 cm, 4.6 mm Id, 5 μ) with column temperature 50°C and UV detector at 374 nm. The mobile phase was water including acetonitrile (70:30) and a flow rate of 1 mL min^{-1} was used. A linear relationship ($R^2 = 0.9956$) between area under the curve and concentration in the range of $0.020\text{-}1400\ \mu\text{g mL}^{-1}$ was significant and the limit of quantification of this method was $20\ \text{ng mL}^{-1}$. Interday Interday Relative Standard Deviation (RSD) values were in the range of 1.0-1.9% and intraday RSD values were in the range 0.73-2.90%.

Microemulsions phase diagram and preparation: Microemulsions were prepared using the conventional titration method. Isopropyl myristate was used as oil phase, Tween 80 and Span 20 as surfactant and PEG400 and propylene glycol as co surfactant. To investigate, the microemulsion formation region, phase diagrams were constructed with this method: In set one; stock solution of surfactant and co surfactant were prepared and then IPM added with different ratio and stirred until clear and titrated with water, stirred until clear. In set two: mixtures of surfactant and co surfactant and water with different ratio and well stirred and then titrated with IPM. In third set; mixtures of IPM and water with different ratios were prepared and then titrated with different amount of surfactant and co surfactant. In the end point, composition of titrated samples and mass percent compositions of component were calculated and plotted in triangular co-ordinates to construct the pseudoternary phase diagram (Podlogar *et al.*, 2004).

Rheological measurement: For rheological measurement, the viscosity of microemulsions, were measured at different shear rates and constant temperature (25°C) using a viscometer (Brookfield Viscometer, Model LVT, USA). Rheometer equipped with data processing software. The rheological behavior of disperse systems was examined by constructing rheograms shear stress against shear rate.

Permeation studies: Large eschar tissue samples were obtained from 7 donors, 5 males (mean age of 39±10 years) and 2 female (age; 33±1 years) patients 20-27 days post burn at the time of surgical debridement. In all cases, burns resulted from exposure to flames and only the samples from abdominal and leg regions were collected for this study. Tissue samples were stored at -20°C until use. Samples were thawed initially and then washed with water. The samples were then cut into smaller pieces suitable for permeation studies reported previously (Kasting *et al.*, 1994). Eschar samples used for this study had a measured thickness of 0.17±0.02 cm. Eschar tissue and silicone membranes were soaked overnight in receptor solution prior *in vitro* permeation studies. Permeation studies were performed in Franz-type diffusion cell with a diffusion area of 2.5 cm² for Eschar samples and 1 cm² for silicone. Eschar tissue and silicone membranes were mounted between the donor and receptor chambers. One milliliter aqueous saturated solutions of nitrofurazone were applied to eschar samples and Silicone membranes and 1 mL of different microemulsion formulations of nitrofurazone with concentration of 100 µg mL⁻¹ for silicon membranes. The receptor chambers were filled with 25 mL for eschar studies and 3 mL for silicone, of buffer phosphate (pH = 7), to ensure sink condition. The receptor chambers were maintained at 37±0.5°C by a thermostatted water bath. At 1, 2, 3, 4, 5, 6 and 8 h after application 300 µL were withdrawn from receptor chambers and replaced with the same volume of fresh receptor medium. The effect of formulation parameters on nitrofurazone permeation parameters through membranes was evaluated with factorial experimental design.

Data analysis: In this study, the cumulative amount of nitrofurazone permeating through eschar and silicon membrane was plotted as a function of time and experimental data were processed using scientist® (Micromath Inc.), with finite dosing. Numerical inversion of the Laplace domain for steady-state diffusion solution was used to obtain the physicochemical parameters such as K and D for drug diffusion through the membranes and drug permeation was subsequently calculated using Eq. 1 (Okamoto *et al.*, 1986). Diffusional path-length of eschar is not known, therefore the parameters P₁ and P₂ were used to solve this problem. For Silicone, because the real thickness is defined so we can use directly K, D and L in this Eq. 1:

$$\bar{Q} = \frac{P_1 A C_0}{s \sqrt{s/P_2} \sinh \left(\sqrt{s/P_2} \right)} \quad (1)$$

P₁ and P₂ are defined as: P₁ = Kl and P₂ = D/l², where, D is the diffusion coefficient and K is the membrane/donor phase partition coefficient of a membrane with a diffusion area (A) and an effective length (l), following application of a concentration of drug (C₀) in the donor chamber and s is the Laplace variable. Q is mass permeated per area unit.

This equation was used to fit the permeation data and the permeability coefficient was calculated with P₁ and P₂ (K_p = P₁/P₂). Flux also was calculated with fick's first law (J = K_p · C₀) and T_{lag} with (T_{lag} = 1/6 P₂). Evaluation of diffusion coefficient of drug through Escher, with this equation is not possible, because real thickness of eschar is indefinite. However, thickness of Escher (0.17±0.020 cm) can be used to provide an apparent diffusion coefficient.

Statistical analysis: All statistical analyses were conducted using the SSPS software (SPSS 13.0 for Windows, SPSS Inc., Chicago, IL, USA). Five experiments were performed for eschar and silicone membranes and results were compared with t-test statistical test. The results were considered significant for p<0.05, with 95% confidence intervals.

RESULTS

Solubility and oil/water partition coefficient of nitrofurazone: The results of the solubility of nitrofurazone in various solvents at room temperature shown in Table 1 suggest that nitrofurazone has greater solubility in PG than water (W) and isopropyl myristate (IPM). The IPM/W Partition coefficient of drug shows that nitrofurazone tends to water more than isopropyl myristate.

Phase behavior for microemulsion preparation: The aim of the construction of pseudo-ternary phase diagram was to getting knowledge about range of microemulsion. The pseudo-ternary phase diagrams with various weight ratios of Tween 80 and Span 20 (1:1) as surfactant, PG and polyethylene glycol 400 as co surfactant and isopropyl myristate as oil phase as shown in Fig. 1 presents microemulsion region. Microemulsion formation was distinguished with transparent, one- phase and low viscosity system. Microemulsion formation occurred only with high concentration of surfactant+cosurfactant concentration

Table 1: Calculated physicochemical properties of nitrofurazone

Properties	Values (n=3)
Saturated solubility in water	329±6.98 (µg mL ⁻¹)
Saturated solubility in Propylene Glycol (PG)	3238±175.01 (µg mL ⁻¹)
Saturated solubility in IPM	248±7.16 (µg mL ⁻¹)
IPM/W Partition coefficient of drug	-0.122±0.008

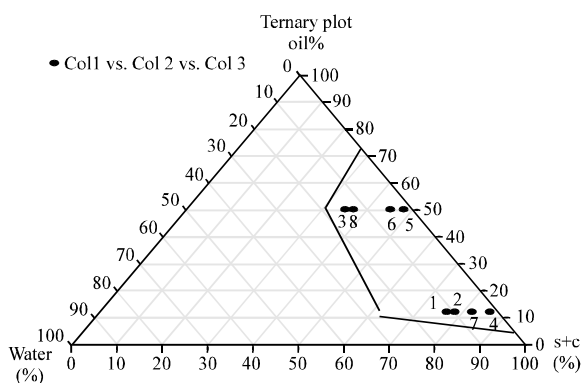


Fig. 1: The pseudo-ternary phase diagrams of the microemulsion composed of oil (isopropyl myristate) surfactant (Tween 80+Span 20) cosurfactant (PG+ polyethylene glycol 400) and water

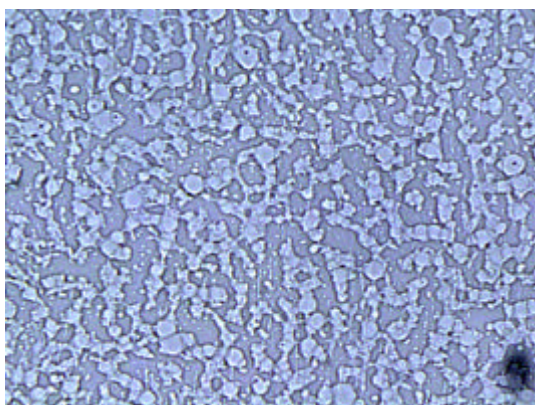


Fig. 2: Microscopic picture of microemulsion (formulation number 3, 4 and 5)

and low amount of water. Microscopic pictures of microemulsion suggests bicontinuous structures for formulations number 3, 4 and 5 (Fig. 2) and non bicontinuous structures for formulations number 1, 2, 6, 7 and 8 (Fig. 3).

For evaluation of the effect of formulation parameters on nitrofurazone permeation through membranes factorial experimental design (3 factors and 2 levels) was used. Factors and their levels were: Surfactant/co surfactant ratio (4/1, 2/1), oil % and PG (with or without). Formulations of different microemulsion based on factorial design (Table 2) were selected from microemulsion region (Fig. 1).

Rheology: Based on results presented in Table 3, the highest viscosity belongs to formulation 3 with bicontinuous structure (Fig. 2) that in it 3 factors are in

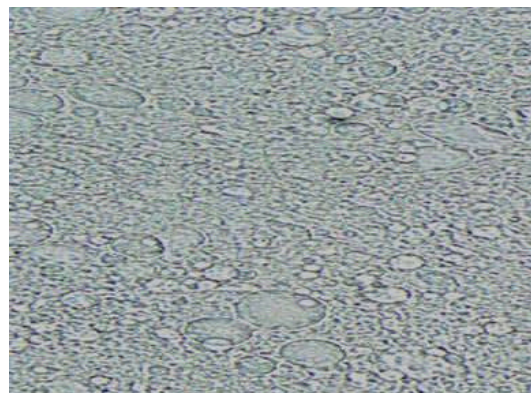


Fig. 3: Microscopic picture of microemulsion (formulation number 7, 8, 1, 2 and 6)

Table 2: Nitrofurazone microemulsion of different compositions for permeability studies

Formulation	S/coS	% (W/W) IPM	% (W/W)		Factorial
			PG	W	
Micro 1	4	12	2	3.599	++
Micro 2	4	12	-	5.599	+-
Micro 3	4	50	2	9.999	+++
Micro 4	2	12	2	3.68	-+
Micro 5	2	50	-	6.899	+-
Micro 6	2	50	2	4.899	+-
Micro 7	2	12	-	5.699	---
Micro 8	4	50	-	11.998	+++

+: Upper level; -: Lower level

Table 3: Viscosity properties of Microemulsions (n = 4)

Formulation No.	Dyn viscosity (mPa.s)	Kin viscosity (mm ² sec ⁻¹)	Density (g cm ⁻³)
1	184.37±0.30	227.35±8.42	0.811±0.0088
2	181.75±4.03	219.24±4.59	0.829±0.0074
3	213.95±7.26	268.77±9.38	0.796±0.0059
4	154.95±1.36	181.87±1.22	0.852±0.0066
5	47.60±0.24	53.48±0.71	0.890±0.008
6	50.23±0.53	57.95±0.68	0.884±0.0092
7	188.86±5.75	240.18±11.09	0.778±0.0043
8	103.58±0.38	117.98±3.52	0.878±0.0079

high amount. Multivariate regression was used for the evaluation of the correlation between independent variables and microemulsion's viscosity.

Table 4 and Fig. 4 show the effect of main factors (S/C, oil, PG) and their interaction on kinematics viscosity of Microemulsions. The amount of PG and s/c had more effect on viscosity. Higher amount of PG and s/c performed higher viscosity.

Linear equation which takes into account all the main effects for viscosity is: Viscosity = 82 + 24.9 s/c - 1.17 oil + 25.9 PG.

Analysis of variance is shown that correlation between viscosity and independent variable are not significant (p>0.05) and these equations can not predict correlation. Independent variable with these levels can not predict responses and then optimization technique can not perform.

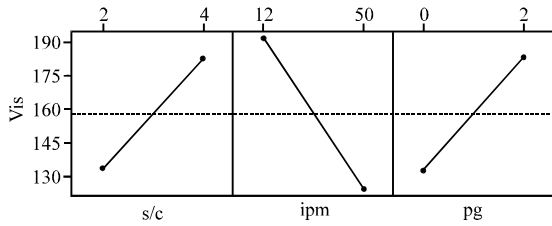


Fig. 4: The effect of main effect of independent variables on viscosity

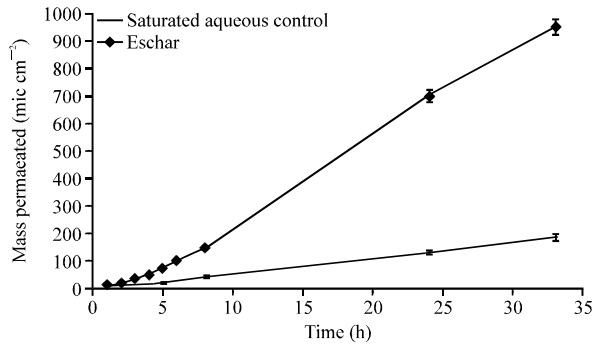


Fig. 5: Permeation of nitrofurazone through Eschar and silicone membranes (for eschar and control, donor was saturated aqueous of nitrofurazone and for silicon was microemulsion) (n = 5)

Table 4: Magnitudes of the main effects and interaction of the factors on viscosity in factorial experimental design

Response	Effect			Interaction			
	s/c	Oil	PG	s/c×Oil	s/c×PG	oil×PG	s/c×oil×PG
Viscosity	49.75	-67.25	51.75	88.25	78.25	26.25	-5.25

Table 5: Permeation parameters of nitrofurazone through membranes (n = 5)

Condition	Permeation parameters			
	D (cm ² h ⁻¹)	kp (cm h ⁻¹)	Flux (µg cm ⁻² h)	Tlag (h)
Eschar	0.0016±0.0002	0.1450±0.016	33.00±3.70	3.000±0.20
Control (water)	0.50×10 ⁻⁴ ±0.6×10 ⁻⁵	0.0310±0.002	10.20±0.68	0.163±0.18
Formulation 1	0.18×10 ⁻⁴ ±0.7×10 ⁻⁵	0.0027±0.0002	0.27±0.014	0.450±0.03
Formulation 2	0.30×10 ⁻⁴ ±0.9×10 ⁻⁵	0.0028±0.0002	0.28±0.016	0.270±0.019
Formulation 3	0.70×10 ⁻³ ±0.4×10 ⁻⁶	0.0081±0.0006	0.81±0.05	1.160±0.077
Formulation 4	0.70×10 ⁻⁴ ±0.35×10 ⁻⁵	0.0125±0.0009	1.25±0.12	0.110±0.009
Formulation 5	0.60×10 ⁻⁴ ±0.65×10 ⁻⁵	0.0060±0.048	0.60±0.04	0.130±0.01
Formulation 6	0.20×10 ⁻⁴ ±0.24×10 ⁻⁵	0.0040±0.00035	0.430±0.033	0.410±0.021
Formulation 7	0.20×10 ⁻³ ±0.5×10 ⁻⁴	0.0029±0.0002	0.290±0.025	0.037±0.0018
Formulation 8	0.19×10 ⁻³ ±0.58×10 ⁻⁴	0.0068±0.0003	0.680±0.07	0.045±0.0022

Table 6: Magnitudes of the main effects and interaction of the factors on response in factorial experimental design

Response	Effect			Interaction			
	s/c	Oil	PG	s/c×Oil	s/c×PG	oil×PG	s/c×oil×PG
Flux	-0.132	0.107	0.227	0.362	-0.167	-0.247	0.317
D	-2.6E-05	-0.00001	-9.1E-05	0.000085	-6E-06	-0.00002	-6.5E-05
T _{lag}	0.31	0.219	0.412	0.023	0.023	0.285	0.182

In vitro permeation studies: The permeation profiles of nitrofurazone through third degree burn Eschar and silicone membranes (Fig. 5) demonstrated steady state region that used for estimation of permeation parameters (Table 5).

Table 6 shows the effect of main factors (S/C, oil, PG) and their interaction on responses (flux, diffusion coefficient, lag time) for Microemulsions. Results suggested that for flux: higher effect belongs to PG that 2 percent of PG increased flux compares with zero percent of PG. interaction between s/c and oil was more important than other interactions. In the proportion of s/c=4 with increasing of oil amount from 12 to 50 percent, flux increases significantly (p<0.05). For D and T_{lag}: all factors show indirect correlation with diffusion coefficient and direct correlation with T_{lag}. Same as flux, PG has more effect on D and T_{lag} and it can be seen that the most important interaction for D is the interaction between s/c and oil percent and for T_{lag} is interaction between oil and PG percent.

Linear equation which takes into account all the main effects and interaction for flux, D and T_{lag} are:

$$\text{Flux} = 0.574 - 0.066 \text{ s/c} + 0.0028 \text{ oil} + 0.114 \text{ PG} + 0.181 \text{ s/c} \times \text{oil} - 0.084 \text{ s/c} \times \text{PG} - 0.124 \text{ oil} \times \text{PG} + 0.159 \text{ s/c} \times \text{oil} \times \text{PG}$$

$$D = 0.000168 - 0.000013 \text{ S/C} - 0.0000001 \text{ oil} - 0.000046 \text{ PG} + 0.000042 \text{ s/c} \times \text{oil} - 0.000003 \text{ s/c} \times \text{PG} - 0.00001 \text{ oil} \times \text{PG} - 0.000033 \text{ s/c} \times \text{oil} \times \text{PG}$$

$$T = 0.523 + 0.155 \text{ s/c} + 0.0058 \text{ oil} + 0.206 \text{ PG} + 0.011 \text{ s/c} \times \text{oil} + 0.117 \text{ s/c} \times \text{PG} + 0.143 \text{ oil} \times \text{PG} + 0.091 \text{ s/c} \times \text{oil} \times \text{PG}$$

Analysis of variance shows that correlation between response and independent variable are not significant and these equations can not predict correlation. Independent variable with these levels can not predict responses and then optimization technique can not perform. In the other hand, result indicates that all drug permeation parameters across eschar tissue are higher than silicone. These differences are very highly significant ($p < 0.0001$). The average diffusivity of drug across silicone is $0.5 \times 10^{-4} \pm 0.6 \times 10^{-5}$ for aqueous control (aqueous saturated of drug in donor). Because, the real thickness of eschar was not defined, apparent diffusion coefficient of drug across the eschar was calculate. Mass permeated through Eschar is approximately 3 times greater than silicone membrane in controls and 10 times greater than Microemulsions. Nitrofurazone diffused across eschar faster than silicone but, because thickness of eschar was greater than silicone, T_{lag} for eschar membranes were greater than silicon membranes.

DISCUSSION

Full factorial design were applied for the evaluation of permeability of nitrofurazone in microemulsion across silicon membrane and analysis of variance indicated that selected independent variable (proportion of surfactant/ co-surfactant, amount of oil phase and the amount of propylene glycol) are insufficient for prediction of flux, diffusion coefficient and lag time. More parameter or different levels of previous parameters have to apply for this purpose. But, with obtained results in this study, between selected independent variables, for flux, the amount of PG and interaction between s/c and oil, for D: amount of PG and interaction between s/c and oil and for Tlag the amount of PG and interaction between oil and PG had more effects. It seems that PG increased flux due to improve diffusion because PG improved tends of drug into microemulsion and so decreased the partitioning phenomena. In agreement with the present study Wang *et al.* (2004) showed that the nature of solvent played an important role in the interactions between the fatty acids and the intercellular lipids in the SC. These findings would make an important contribution to the choice of solvent in transdermal drug delivery systems.

El-Maghraby (2008) investigated the effects of cosurfactants on the transdermal delivery of hydrocortisone (model drug) from eucalyptus oil microemulsion. The presence of cosurfactant and its type can thus affect both the phase behavior and the transdermal delivery potential of microemulsion. Present study showed the comparison between different microemulsions showed significant below order in

calculated flux: $F_4 > F_3 > F_5$, $F_8 > F_6 > F_1$, F_2 , F_7 . In formulation 4 and 3, the amount of PG were high and in formulations 1, 2 and 7 the amount of oil (isopropyl myristate) were low. In formulations 5, 8, 6, the amount of oil phase was high. It is indicated PG and IPM both increased flux but the effect of PG was more than IPM. Increasing in percent of IPM reduced the solubility of nitrofurazone and so increased activity of drug. This significant order for diffusion coefficient was: $F_7, 8 > F_6, 1 > F_4, F_5 > F_2 > F_3$.

El Maghraby (2008) conducted study was to select the best vehicle as the first step in optimization of tadalafil transdermal delivery. Binary combinations of ethanol with either IPM or EO provided the first step forward toward the development of transdermal delivery system. The present study showed the comparison between both orders indicates that PG increased in flux with increasing partitioning phenomena in formulations 4 and 3 because, the amount of D in these formulations is low.

Nitrofurazone has intermediate lipophilic. IPM/water partition coefficient of drug and solubility in different solvents indicate that affinity of drug in water is more than IPM and in PG more than water. In comparison between microemulsion 3 and 8; amount of IMP and s/c ratio in both is equal, but formulation No. 3 has PG and No. 8 doesn't. High amount of IPM in 3 and 8 create high Q_{33} . PG in 3, causes higher Q_{33} and lower D, in comparison with 8. Formulations 3 indicated bicontinuous structure and so IPM is not external phase but in formulation 8 that is w/o microemulsion, IPM plays as external phase and contact with membrane and can effects on membrane and cases higher amount of D comparison with formulation 3. Mostly, nitrofurazone is in the surfactant film in the microemulsion formulations. Solubility of drug in IPM is low and drug in external phase is saturated and has maximum thermodynamic activity. PG present in 1,3,4, in external phase decreased the effect of IPM on membrane and therefore induced lower D. It seems that s/c ratio can not effect on permeation parameters. These results that obtained in this study are contrary to other researches that showed the effect of microemulsion on skin permeation (Rhee *et al.*, 2002; Peltora *et al.*, 2003).

CONCLUSION

In comparison between eschar and silicon, it seems that silicon can not present barrier properties of eschar. Eschar is more permeable than silicon. Silicon can reduce the permeability of microorganisms, drugs and other molecules through burn skin. In the other hand, microemulsions that were applied in this study decrease the permeability of silicon comparison with saturated aqueous solution.

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