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Formulation and evaluation of a topical drug delivery system

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ABSTRACT

Topical drug delivery system is most preferred due to avoidance of first pass metabolism and gastro-intestinal incompatibility. Microemulsion is the most frequently preferred carrier systems for NSAIDs which are used in treatment of arthritis. This new drug delivery approach is jointly aiming at minimizing drug dose, diverting drugs to the target tissue by increased permeation, and enhancing efficacy in patients. In this work, the pseudo-ternary phase diagram were constructed using Tween 80, Ethyl oleate, Propylene glycol and water. Different batches of microemulsions were prepared by phase titration method. The batch which showed maximum *in vitro* drug release was formulated into gel using various concentration of polymer. EO was used as the oily phase of microemulsion due to powerful solubilization and permeation enhancing effect for Flurbiprofen. 0.75% carbopol 940 was considered as optimum gel matrix. Optimized batch of microemulsion gel was evaluated for pH, spreadability, % Drug content, Droplet size and Polydispersity-Index. The optimized batch was compared with marketed gel (5% gel). The in vitro permeation studies revealed that the prepared microemulsion-gel could be used as a potential carrier for the topical delivery of Flurbiprofen due to its permeation enhancing ability.

Introduction

Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes [1]. It is most preferred due to avoidance of first pass metabolism and gastro-intestinal incompatibility. Skin is one of the most readily accessible organs of human body for topical administration. Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. The main advantage of topical delivery system is that it has ability to deliver drugs more selectively to a specific site [2]. Percutaneous absorption involves passive diffusion of substances through the skin. The mechanism of absorption involves passage through the epidermis itself (Transepidermal absorption) or diffusion through shunts (Transfollicular absorption). In developing a topical delivery system, two criteria are considered: one is minimizing the lag time in skin permeation and the other is achieving adequate flux across the skin. One strategy overcoming this constraint is the incorporation of various chemical skin enhancers into the vehicle. Another strategy is a choice of an appropriate vehicle that corresponds to the drug being used for the dermal route of administration. These two criteria can be achieved by Microemulsion system.

Microemulsions can interact with the stratum corneum changing structural rearrangement of its lipid layers and consequently increasing transdermal drug permeation and so act as penetration enhancer [3]. Microemulsions have the ability to deliver larger amounts of topically applied agents into the skin than other traditional vehicles such as lotions or creams because they act as a better reservoir for a poorly soluble drug through their capacity for enhanced solubilization. Microemulsion is homogeneous, transparent, thermodynamically stable isotropic system with an average droplet diameter of 10 to 140 nm [4] in which two immiscible liquids (water and oil) are mixed to form a single phase by means of an appropriate surfactant and short to medium chain alcohols (co-surfactants) [5]. Interest in these versatile carriers is increasing due to their unique solubilization properties, small droplet size and thermodynamic stability.

The low viscosity of microemulsion restrains its application in pharmaceutical industry due to inconvenient use. Hence biocompatible hydrogels with weak interaction with surfactants have recently been found to change the rheology properties of microemulsion. The addition of hydrogels, e.g. carrageenan and carbomer 940 into microemulsion resulted in the formation of hydrogel-thickened microemulsion with a weak gel behavior and the change of viscosity.

Arthritis is a form of joint disorder that involves inflammation of one or more joints. The pain from arthritis is due to inflammation that occurs around the joint, damage to the joint from disease, muscle strains caused by forceful movements against stiff painful joints and fatigue. Flurbiprofen a non-steroidal anti-inflammatory drug (NSAID) having excellent anti-inflammatory and analgesic activity, hence used to treat arthritis. But it produces GIT ulceration, liver and kidney damage in case of oral administration [6]. Hence Topical preparation seems to offer an alternative application route for preventing systemic side effects of NSAIDs [7].

The aim of this work was to investigate the potential of microemulsion-gel system in order to reduce adverse effects associated with oral formulations as well as to enhance drug permeation into deeper layers of the skin and to sustained effect of drug.

Materials and methods:

Flurbiprofen was obtained as a gift sample from Sun Pharma. Ethyl oleate, Tween 80, Propylene glycol, carbopol 940 and other excipients were purchased from Molychem and dialysis membrane was purchased from Hi-Media.

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Solubility Studies:

To find out the suitable oil which can be used as the oil phase in microemulsion and provide excellent skin permeation rate of Flurbiprofen, the solubility of Flurbiprofen in various oils like Oleic acid, IPM, IPP, and EO was measured. The solubility of Flurbiprofen in surfactants (Tween 20, Tween 80, and Span 20) and co-surfactants (PG, Ethanol, PEG 400) was also measured. An excess amount of Flurbiprofen was added to each oil and surfactant, and then mixed by magnetic stirrer. After stirring for 72 h at 25°C, the equilibrated sample was centrifuged for 10 min at 10,000 rpm to remove the excess amount of undissolved Flurbiprofen. The known amount of supernatant (0.1ml) was pipetted out and was diluted with methanol and phosphate buffer saline. The concentration of Flurbiprofen was determined by UV-Visible Spectrophotometer.
Screening of surfactant and co-surfactant for emulsifying ability:

The turbidimetric method was used to assess the relative efficacy of the surfactant and co-surfactants to improve the microemulsification ability and also to select the best from the large pool available for topical delivery [8]. Screening of surfactants for emulsifying ability was carried out at 45-60°C. Briefly, 300 mg of surfactant, having good solubility, was added to 300 mg of the selected oily phase. The mixture was gently heated at 45-60° for homogenizing the components. For screening of co-surfactant, 0.2 g of surfactant was mixed with 0.1 g of co-surfactant and the mixture was homogenized with the aid of gentle heat (45-60°). The isotropic mixture, 50 mg, was accurately weighed and diluted with double-distilled water to 50 ml to yield a fine emulsion. The ease of formation of emulsions was monitored by noting the number of volumetric flask inversions required to give a uniform emulsion. The resulting emulsions were observed visually for the relative turbidity. The emulsions were allowed to stand for 2 h and their transmittance was assessed at 638.2 nm using double-distilled water as blank.

Construction of pseudo-ternary phase diagrams:

In order to find out the concentration range of components for the existence range of microemulsions, pseudo-ternary phase diagrams were constructed using water titration method at ambient temperature (25◦C). Three phase diagrams were prepared with the weight ratio of surfactant to co-surfactant (k_m) varied as 1:1, 2:1, 3:1. For each phase diagram at specific surfactant/co-surfactant weight ratio, the ratios of oil to the mixture of surfactant and co-surfactant were varied as 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9. A small amount of water was added drop wise into these mixtures. Following each addition, the mixtures were vortexed for 2-3 min and were allowed to equilibrate at 25° for few min. After equilibration, the mixtures were examined visually for phase separation and transparency. The point at which the mixture became turbid or showed signs of phase separation was considered as the end point of the titration. The area of microemulsion existence was determined and denoted as ME. The optimum surfactant/cosurfactant weight ratio (k_m) of microemulsion system was identified from the phase diagram having larger microemulsification region.

Preparation of Flurbiprofen-loaded microemulsion:

After the identification of microemulsion region in the phase diagram, the microemulsion formulations were selected at desired component ratios and different batches of microemulsions were prepared by phase titration method (Table 1). The preparation of selected microemulsion was simply performed by adding the weighed components together and adding an appropriate amount of water to the mixture drop by drop with constant stirring on a magnetic stirrer. The microemulsion containing Flurbiprofen was obtained by stirring the mixtures at ambient temperature [9]. All microemulsions were stored at ambient temperature

Preparation Of Microemulsion Gel:

Carbopol 940 was selected as the gel matrix to prepare the microemulsion-based hydrogel formulation. Carbopol 940 of varying concentration ratio was slowly mixed with one of the optimized batch of microemulsions under continuous stirring (Table 2). After carbopol 940 was entirely dissolved in the microemulsion, it was neutralized by using triethanolamine to obtain the gel.

Evaluation of Microemulsion:

Prepared batches of microemulsions were evaluated for physical properties such as clarity, % Transmittance, translucency, dilutability, pH, Viscosity, Droplet size and Polydispersity-Index. Physical stability was assessed by Centrifugation and Freeze-Thaw Cycling. The drug release of Flurbiprofen from prepared microemulsions was evaluated using Franz diffusion cells.

The isotropic nature, Transparency and optical clarity of prepared microemulsion formulation were checked by measuring % transmittance at 638.2 nm using purified water as blank (UV Spectrophotometer UV-1601-220x). The formulations that showed maximum transmittance were considered as optimized formulation and subjected to further characterization.

The microemulsions formed were diluted in 1:10, and 1:100, ratios with double distilled water to check if the system shows any sign of separation and their transparency was assessed visually.

The selected formulations were subjected to different thermodynamic stability tests to assess their physical stability. Selected formulations were centrifuged at 3000 rpm for 30 min. The formulations having no phase separations were taken for the heating and cooling cycle (freeze thaw cycle). Three cycles between the temperatures 4°C (refrigerator) and 45°C in a hot air oven for not less than 24 h was done and assessed for physical instabilities such as phase separation and precipitation. [8] The formulations which were stable at these temperatures were evaluated for the viscosity using Brookfield viscometer and the pH using digital pH meter.

The droplet size and polydispersity index of the microemulsions were determined by photon cross-correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using NANOPHOX (NX0073, Sympatec, Germany).

An FTIR spectra of Flurbiprofen and optimized microemulsion formulation were obtained by means of a FTIR spectrophotometer and were compared with that of drug. Differential scanning calorimetry (DSC) was also performed on pure Flurbiprofen and optimized microemulsion formulation (F2) utilizing Perkin-Elmir DSC7.

The *in vitro* drug release study:

The *in vitro* drug release study was performed by using vertical Franz diffusion cell with an effective diffusion area of 3.56 cm^2 and 13 ml cell volume. The cellophane membrane was first hydrated in PBS solution at room temperature for 24 hours and then placed between donor and receptor compartment. The receptor compartment was filled with freshly prepared phosphate buffer saline (PBS)of pH 7.4 that was maintained at 32°C ± 0.5°C and the solution was stirred continuously at 300 rpm by magnetic stirrer. The microemulsion formulation (0.3gm) was gently placed in donor compartment. Samples were periodically withdrawn from the receptor compartment, replacing with the same amount of fresh PBS solution. Samples were analyzed by using a UV spectrophotometer at 247 nm after suitable dilution.

The cumulative amount of drug permeated through the membrane (µg/cm^2) was plotted as a function of time (*t*) for each formulation [10] . Drug flux (permeation rate) at steady state (J_{SS}) was calculated by dividing the slope of the linear portion of the graph by the area of the diffusion cell. The permeability coefficient (*P*) was calculated by dividing J_{SS} by the initial concentration of drug in the donor cell (C_0).

$P = Jss/C_0$.

Evaluation Of Microemulsion-Gel

The influence of the different concentrations of carbopol 940 on the viscosity as well as drug release profile of the optimized batch of microemulsion was evaluated. The formulation having suitable fluidity for topical application as well as maximum release rate was selected for further characterization. Optimized batch of microemulsion gel was evaluated for pH, spreadability, % Drug content, Droplet size and Polydispersity-Index.

This optimized batch was also compared with marketed gel (5% gel) for pH, spreadability, % Drug content and % drug release.

The *in vitro* drug release studies were performed by using vertical Franz diffusion cell as given for microemulsion. The viscosity was determined by using Brookfield viscometer. The pH was determined using digital pH meter.

An apparatus suggested by Mutimer *et al*. modified suitably in the laboratory and was used for spreadability study [8]. The spreadability was calculated by using the following formula:

$S = (m \times l)/t$

{S = spreadability; m= weight tied to the upper slides; l= length of glass slide, t = time taken}

Microemulsion-based hydrogel equivalent to 10 mg of drug was taken in 10 ml volumetric flask containing 5 ml methanol and stirred for 30 min. Volume was made up to 10 ml with methanol. From the above solution, 0.1 ml was further diluted with PBS solution. The resultant solution was filtered through Whatman filter paper and absorbance of the solution was measured at 247 nm using UV spectrophotometer.

Microemulsion gel was sufficiently diluted with double-distilled water in a volumetric flask and gently mixed for droplet size analysis. The droplet size and poly-dispersity index of the microemulsion gel was determined by photon cross-correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using NANOPHOX (NX0073, Sympatec, Germany).

Stability Study:

The physical and chemical stability of optimized microemulsion-gel formulation was evaluated by storing it in well closed container for 3 months at 25 ± 1°C, 65 ± 5% RH and 40 ± 1°C, 75 ± 5% RH and samples were evaluated for physicochemical parameters like pH, % drug content, viscosity, and % drug release at one month interval

Results and Discussion

The solubility of Flurbiprofen in various oils, nonionic surfactants and co-surfactant was measured and the results are shown (Table 3). The solubility of Flurbiprofen in Ethyl Oleate was 120.36±0.5 mg/g, which was the highest amongst the oils investigated.

Emulsification studies were performed to evaluate the ability of various surfactants to emulsify the selected oily phase. The percentage transmittance values of various dispersions are given (Table 4, 5). Emulsification studies with various surfactants showed that Tween 80 had very good ability to emulsify Ethyl Oleate.

The pseudoternary phase diagrams were constructed in order to obtain the concentration range of components at which a stable microemulsion exists. The pseudo-ternary phase diagrams with various weight ratios of Tween 80 to PG are described (Figure1, 2 and 3).

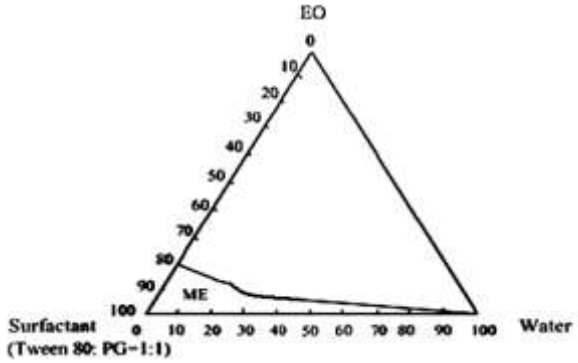

Figure 1: The pseudo-ternary phase diagrams of the oil-surfactant-water system at the 1:1 weight ratios of Tween 80 to Propylene Glycol (PG) at 25 ◦C (ME - microemulsion region).

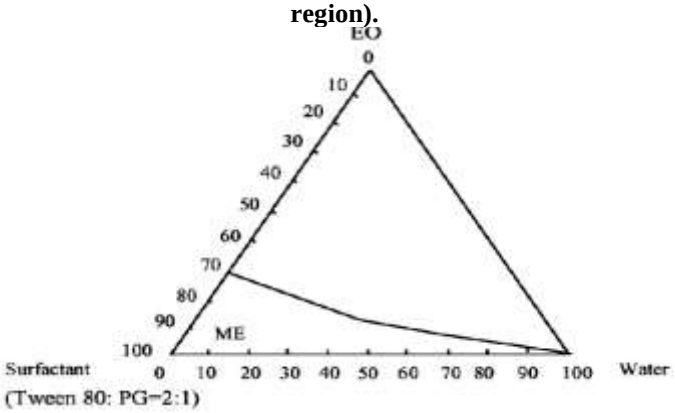

Figure 2: The pseudo-ternary phase diagrams of the oil-surfactant-water system at the 2:1 weight ratios of Tween 80 to Propylene Glycol (PG) at 25 ◦C (ME - microemulsion region).

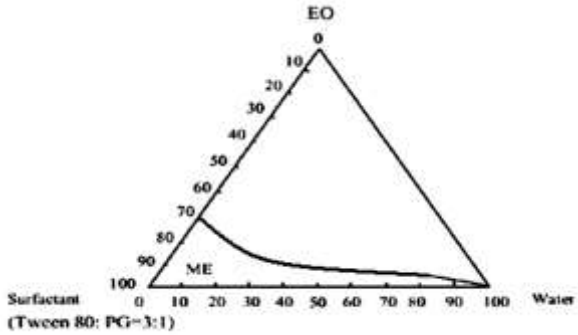

Figure 3: The pseudo-ternary phase diagrams of the oil-surfactant-water system at the 3:1 weight ratios of Tween 80 to Propylene Glycol (PG) at 25 ◦C (ME - microemulsion region).

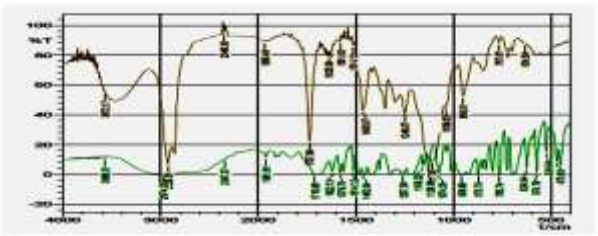

Figure 4: IR Spectrum of pure drug and optimized formulation (F2).

The transparent or translucent o/w microemulsion area is presented in the phase diagrams. The optimum surfactant/ cosurfactant ratio of micro emulsion system was found at k_m 2:1 for Ethyl Oleate -Tween 80- Propylene glycol-water system. The system at k_m 2:1 formed a larger single-phase region than

the systems at other k_m. It was reported that at the optimum k_m value, the cosurfactant gets entrapped into the cavities between the surfactant molecules, and the formed microemulsion will have the maximum solubilisation capacity. In the current investigation, due to larger microemulsion region Ethyl Oleate -Tween 80- Propylene glycol-water system at k_m value 2:1 was selected for further studies.

% Transmittance of prepared batches from F1 to F5 of microemulsion formulations were checked at 638.2 nm and were found to 96.76%, 99.12%, 98.86%, 97.74%,and 96.32 % respectively. It is reported that due to higher particle size, oil globules may reduce the transparency of microemulsion formulation and thereby values of %T [2]. Based on the maximum transparency F2, F3 and F4 batches were further characterized and investigated for droplet size analysis and drug release study

All batches of Microemulsions were found to be robust to all dilutions and did not show any separation after diluting with double distilled water [8].

No phase separation, creaming or drug precipitation was observed while performing thermodynamic stability tests. The results showed that all the formulations had a good physical stability. The results of viscosity and pH are given (Table 6).

The droplet size and polydispersity index of the selected batches of microemulsions are presented (Table 7). Graph representing droplet size is shown in figure 13, 14 and 15 for batch F2, F3 and F4 respectively. The polydispersity index (PDI < 1) showed that all the microemulsions have narrow size distribution and the thermodynamic stability. The amount of oil affected the globule size. The droplet size of Batch F4 was found to increase significantly compared to Batch F3 due to more oil in Batch F4, which can be attributed to the expansion of oil drop of microemulsion by increased amount of oil.

From the comparison of the FTIR spectra of optimized formulation (F2) with that of pure drug (Figure 4), it was found that the characteristic absorption peaks of drug were not affected in the formulation but only minor shifting of some peaks were seen. These minor shifts observed may be due to the formation of hydrogen bonds, van der Waals attractive forces or dipole moment, which are weak forces seen in the polar functional groups of drugs and surfactants. This indicates the compatibility of drug with surfactants.

Flurbiprofen showed a sharp peak at 117°C ± 0.1°C corresponding to the melting point of drug in crystalline form. The thermogram of the batch F2 did not show the melting peak for the Flurbiprofen around 117°C. This shows that Flurbiprofen was not in crystalline state but it is in amorphous state. These result suggested that there was absence of drug degradation or drug excipient molecular interaction in formulation F2. Similar results were reported by [12] Cavalli et al. 1997, stating that rapid quenching of the microemulsion does not allow the drug to crystallize.

The permeation ability of the various microemulsions was evaluated using the in vitro permeation experiments. It was observed that maximum drug release was achieved from microemulsion Batch F2 within 8 h. The cumulative release profile of the drug from Batch F2, F3 and F4 formulation is shown (Figure 5).

A steady increase of drug in the receptor chamber with time was observed. The permeation profiles of microemulsions followed zero order release kinetics.

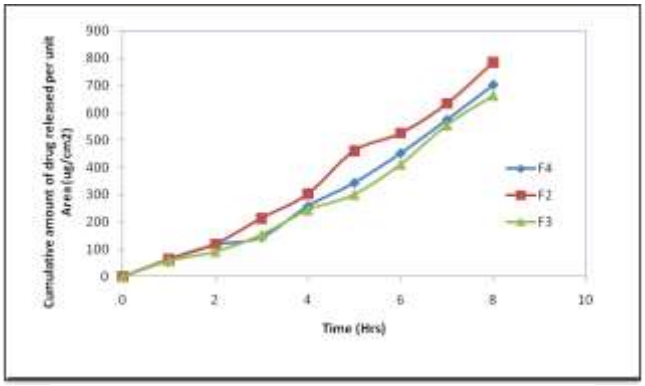

Figure 5: Diffusion profile of Flurbiprofen from microemulsion batches F2, F3 and F4

The increase of oil in Batch F4 resulted in a significant increase of permeation rate of drug compared to batch F3 but it showed no significant increase of permeation rate when compared with Batch F2. It is possible that the high concentration of surfactant and co-surfactant in Batch F4 as compared to Batch F2 might result in a relatively low thermodynamic activity. Even though Batch F4 had higher concentration of oil than Batch F2, the low thermodynamic activity might did not increase the penetration rate when compared with Batch F2. The increased concentration of surfactant and co-surfactant in Batch F3 compared to Batch F2 may have retained the drug in droplets of microemulsion formulation and hence decrease its penetration rate.

The slope of the steady-state portion of the permeation curve created by plotting the cumulative amount of drug permeated in micrograms versus time in hours is the Steady State Flux (J_{SS}). The permeation parameters of the tested microemulsion batches are presented (Table 8).

Batch F2 was formulated into gel because as compared to other two batches, it contains low oil as well as surfactant and co-surfactant concentration, it has small droplet size and it showed good permeation profile.

Carbopol 940 as an aqueous gel matrix in continuous phase, displayed non-covalent intermolecular associations deriving from disparate forces such as coulombic, van der waals and hydrogen-bond interaction and showed a weak gel behavior. These physical interactions could lead to the formation of the three-dimensional gel network and the dispersed oil droplets were reasonably hosted within the meshes of the three-dimensional gel network. Diffusion of the drug incorporated into an o/w microemulsion is affected by the partitioning of the drug between the internal oil phase and the external aqueous phase.

The drug release profile of Batch G1, G2, and G3 of gel shown (Figure 6).

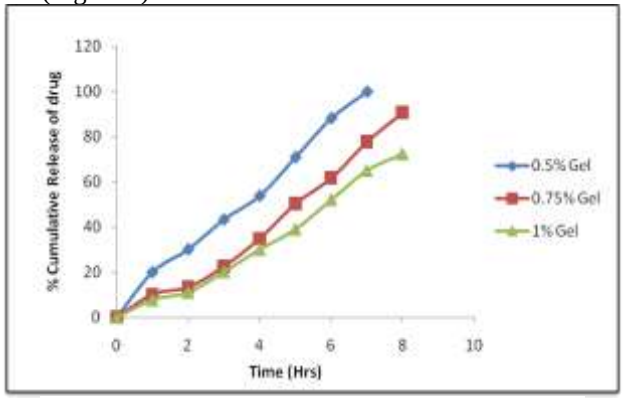

Figure 6: Diffusion profile of Flurbiprofen from microemulsion Gel batches G1, G2 and G3

Batch G1 showed higher fluidity and less viscosity compared with the batch G2 and G3 and demonstrated faster and higher release profile. Large concentration of carbopol 940 in the G3 batch resulted into excessive network structure in the external phase that impedes the free drug movement and hence drug release was too slow and took longer time for diffusion. G2 batch of the microemulsion-Gel (having 0.75% carbopol concentration) showed the sustained release of drug from the formulation compared with other batches of gel.

The addition of carbopol 940 into microemulsion increases its viscosity and transforms it into lamellar structure or a highly ordered microstructure. The viscosity of all three batches is given (Table 9). Batch G1 containing 0.5% carbopol 940 had a relatively high fluidity. However 1% carbopol 940 in batch G3 resulted in a too high viscosity and Batch G2 containing 0.75% carbopol 940 had a most appropriate fluidity for topical administration. So 0.75% carbopol 940 was consider as optimum gel matrix.

Hence Batch G2 was further evaluated for pH, spreadability, % Drug content, and compared with marketed gel (Table 10).

The droplet size of the G2 batch of microemulsion gel was 70nm and its polydispersity index was 0.08.

Release profile of FLURBIPROFEN was carried out from optimized microemulsion-gel and Marketed gel (5% gel) and the results are shown (Figure 7).

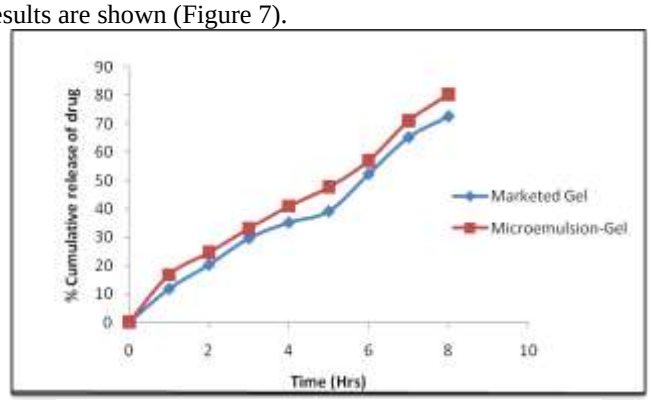

Figure 7: Diffusion profile of Flurbiprofen from microemulsion-Gel (G2) and Marketrd gel.

From this study it can be concluded that the extent of diffusion of Flurbiprofen from microemulsion-gel is comparatively greater than Marketed gel. Steady State Flux (J_{SS}) of microemulsion-gel and Marketed Gel was 9.74 $\mu g.cm^{-2}hr^{-1}$ and 8.47 $\mu g.cm^{-2}hr^{-1}$ respectively.

The values of measured spreadability indicate that the microemulsion-gel is easily spreadable. Spreadability of marketed gel was 5.5g.cm/sec while that of batch G2 was 6.5g.cm/sec; indicating spreadability of microemulsion-gel was good as compared to the marketed gel. The pH of marketed gel was 6.90 ± 0.06 while that of batch G2 was 6.70 ± 0.02.

Stability study of microemulsion-gel (Batch G2) was carried out for three months at 25 ± 1°C, 65 ± 5% RH and 40 ± 1°C, 75 ± 5% RH. Results of stability studies of optimized microemulsion-gel for physicochemical parameters like pH, % drug content, viscosity, and % drug release are shown (Table 11). No change of phase separation was observed during 3 months. The results suggested that the formulations did not show significant difference ($p > 0.05$) in drug release profile compared to that of initial drug release profile indicating that microemulsion-gel was stable up to 3 months.

Given the results of this study, it is clear that microemulsion-gel loaded with Flurbiprofen is potentially useful for permeation of Flurbiprofen in topical delivery. The skin permeability of Flurbiprofen was significantly increased by microemulsion-gel, which might result from the special characteristics of microemulsions (i.e. enhanced solubilization and penetration). It is promising that the concentration of Flurbiprofen used to treat inflammatory conditions of joints could be decreased due to the high permeation ability of Flurbiprofen microemulsion-gel and side effects of Flurbiprofen might be reduced. Thus, this study suggests that, Microemulsion-gel system can be an alternative to a gel for enhanced delivery of Flurbiprofen.

Acknowledgements:

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Table 1: Composition of microemulsion formulations (%w/w).

Batch	Flurbiprofen	Ethyl Oleate	Tween 80:PG (2:1)	Water
F1	1	8	33	58
F2	1	8	42	49
F3	1	8	54	37
F4	1	10	54	35
F5	1	12	54	33

Table 2: Composition of microemulsion-gel (%w/w).

Batch	Flurbiprofen	Ethyl Oleate	Tween 80:PG (2:1)	Water	Carbopol 940
G1	1	8	42	49	0.5
G2	1	8	42	49	0.75
G3	1	8	42	49	1.0

Table 3: Solubility of flurbiprofen in various solvents at 25°c (mean ± s.d., n=3)

Solvents	Solubility (mg/g)
Oleic Acid	98.12 ± 0.5
Ethyl Oleate	120.36 ± 0.5
Iso Propyl Palmitate	72.60 ± 0.5
Iso Propyl Myristate	83.24 ± 0.5
Tween 20	859.84 ± 0.5
Tween 80	912.48 ± 0.5
Span 20	195.12 ± 0.5
Propylene Glycol	253.24 ± 0.5
PEG 400	192.96 ± 0.5
Ethanol	950.72 ± 0.5

Table 4: Emulsification efficiency of surfactants

Surfactants	%transmittance
Tween 20	98.5
Tween 80	99.8
Span 20	48

Table 5: Emulsification studies on surfactant/co-surfactant combinations.

Co-surfactants	%transmittance
Propylene Glycol	98.6
PEG 400	78.4
Ethanol	92.8

Table 6: Physiochemical parameters of the tested microemulsion formulations

Batch	% transmittance	Dilutability	Viscosity (cp)	Ph
F1	96.76	No Phase Separation	153	5.70
F2	99.12	No Phase Separation	207	5.20
F3	98.86	No Phase Separation	273	5.40
F4	97.74	No Phase Separation	287	5.10
F5	96.32	No Phase Separation	273	5.40

Table 7: Physiochemical parameters of the selected microemulsion formulations.

Batch	Droplet size (nm)	Polydispersity index
F2	44.84	0.181
F3	64.68	0.205
F4	66.55	0.292

Table 8: Permeation Parameters Of Microemulsion Batches F2, F3, F4

Batch	Steady State Flux J_{SS} ($\mu g.cm^{-2}hr^{-1}$)	Permeability Coefficient P ($\times 10^{-3}cm\ h^{-1}$)	Lag Time (hrs)
F2	98.36	32.78	0.45
F3	82.18	27.39	0.48
F4	86.90	28.97	0.51

Table 9: Viscosity (Pa.S) Of Prepared Batches Of Microemulsion-Gel

Batches	Viscosity (Pa.S)
G1	42
G2	47.60
G3	58.5

Table 10: Evaluation parameters of microemulsion-gel (g2) and marketed gel.

Parameters	G2 batch of Gel	Marketed Gel
pH	6.70	6.90
Drug content(%w/w)	98.97%	99.20%
Spreadability (g.cm/sec)	6.5	5.5
Steady State Flux J_{SS} ($\mu g.cm^{-2}hr^{-1}$)	9.74	8.47

Table 11: Evaluation parameters of microemulsion-gel (g2)- stability studies.

Temperature / Parameters	25 ± 1°C, 65 ± 5% RH			40 ± 1°C, 75 ± 5% RH		
	1 Month	2 Months	3 Months	1 Month	2 Months	3 Months
pH						
Viscosity (Pa.S)	6.75	6.60	6.55	6.60	6.70	6.40
% Drug content	48.30	47.78	47.37	46.24	45.68	45.95
% Drug Release	98.13%	97.38%	97.32%	97.91%	98.28%	97.73%
At the end of	90.20%	89.60%	89.84%	90.60%	89.06%	89.01%
8 Hrs						

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