

Formulation and Evaluation of Microemulsion Based Topical Gel of Carbamazepine

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ABSTRACT

Carbamazepine (CBZ) is a synthetic compound of the benzodiazepine class, used as an anticonvulsant and analgesic drug. Carbamazepine is relatively slowly but well absorbed after oral administration. Its plasma half-life is about 30 hours when it is given as single dose, but it is a strong inducer of hepatic enzymes and the plasma half-life shortens to about 15 hours when it is given repeatedly. Psoriasis is autoimmune disease in which genetic and environmental factors have a significant role. Carbamazepine was accidentally discovered to have antipsoriatic properties. Carbamazepine was obtained as a gift sample from Lupin. Characterization of carbamazepine was carried out by melting point and IR. Carbamazepine has limited aqueous solubility so in literature Self microemulsifying drug delivery system (SMEDDS) have been reported. In the present study, a topical microemulsion based gel of Carbamazepine was prepared. The pseudo ternary phase diagram was prepared to find the microemulsion region. Various microemulsion gel formulations were prepared using carbopol-974 and poloxamer-407 in varied concentrations. Prepared formulations (FG1 to FG10) were evaluated for various parameters like color, appearance, consistency, pH, spreadability and IR. The microemulsion based gels were found to have good spreadability and pH within the range of skin pH and thus suitable to use on skin.

Keywords: carbamazepine, psoriasis, microemulsion, gel.

INTRODUCTION

Psoriasis is a non-contagious, dry, inflammatory and ugly skin disorder, which can involve entire system of person¹. Psoriasis is a common chronic, recurrent, immune mediated disease of the skin and joints. It can have a significant negative impact on the physical, emotional, and, psychosocial well being of affected patients. Psoriasis is found worldwide but the prevalence varies among different ethnic groups. It has a strong genetic component but environmental factors such as infections can play an important role in the presentation of disease. There are several clinical cutaneous manifestations of psoriasis but most commonly the disease presents as chronic, symmetrical, erythematous, scaling papules and plaques. The epidemiology, clinical features, and impact on quality of life because of psoriasis are reviewed². Inverse psoriasis, also called flexural or intertriginous psoriasis, occurs commonly in infants and young children. In a survey of 1262 pediatric patients with psoriasis, approximately 4% had localized psoriatic diaper rash. Psoriatic diaper rash with dissemination occurs in up to 13% of patients with psoriasis. The mainstay of treatment for inverse psoriasis remains topical corticosteroids. Well documented adverse effects of long-term corticosteroid use include atrophy, telangiectases, and striae. Previous studies have shown systemic tacrolimus to be useful in the treatment of plaque-type psoriasis. However, later attempts to prove the drug's efficacy in chronic plaque-type

psoriasis were unsuccessful. More recently, topical tacrolimus ointment (0.1%) proved beneficial in the treatment of psoriasis involving the face and the intertriginous areas in adults³. Number of formulations is available in the market with variety of active pharmaceutical ingredients. Topical formulations available in the market are as follows: gel, cream and lotion, face wash or cleanser, face pack or mask⁴. The literature review showed that the carbamazepine shows the antipsoriatic effect⁴⁻⁵. Carbamazepine is water insoluble⁶. Topical formulation with very less quantity of water is reported in literature⁷. Microemulsion based gel can be good approach to formulate less soluble drugs⁸. So this study is aimed at development of oil in water microemulsion based gel formulation of carbamazepine.

MATERIAL AND METHOD

For the present study, Carbamazepine (CBZ) was obtained

Table 1: Composition of microemulsion formulation prepared

*Formulation Code	Capryol-90 (%)	**Smix (%)	Water (%)
M1	3	27	70
M2	3	40	57

*Each formulation contained 1% w/w of carbamazepine.

**Smix (Tween 80: Transcutol, 1:1)

Table 2: Formulae for poloxamer-407 and Carbopol 974 gels.

Batches	Ingredients				Gelling agent		
	Drug(gm)	Capryol-90 (gm)	Tween-80 (gm)	Transcutol (gm)	Water(gm)	Poloxamer-407(gm)	Carbopol-974(gm)
FG1	0.1	0.3	1.35	1.35	7	2.5	-
FG2	0.1	0.3	1.35	1.35	7	2.4	-
FG3	0.1	0.3	1.35	1.35	7	2.2	-
FG4	0.1	0.3	1.35	1.35	7	-	0.1
FG5	0.1	0.3	1.35	1.35	7	-	0.3
FG6	0.1	0.3	2	2	5.7	2.5	-
FG7	0.1	0.3	2	2	5.7	2.4	-
FG8	0.1	0.3	2	2	5.7	2.2	-
FG9	0.1	0.3	2	2	5.7	-	0.1
FG10	0.1	0.3	2	2	5.7	-	0.3

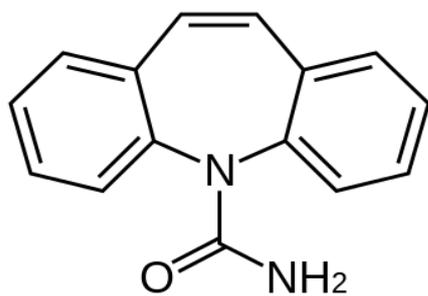


Figure 1: Structure of Carbamazepine.

Table 3: Characteristic frequencies of IR spectrum of Carbamazepine.

S. No	Frequencies cm-1	Assignment
1	3452.34	NH ₂ Asymmetric
2	3330.36	NH ₂ Symmetric
3	3150.51	Aromatic C-H Stretching
4	1676.20	Amide – I
5	1600.97	Amide – II
6	1489.10	C=C Aromatic

from Lupin Pvt. Ltd, (India) as a gift sample. Capryol 90 was obtained from Gattefose as a gift sample. Poloxamer 407 was obtained from BASF as a gift sample. Carbopol 974 was obtained from Lubrizol. Tween-80 and Transcutol P were purchased from Himedia.

Characterization of Carbamazepine

Melting Point

Melting point of carbamazepine was determined by open capillary method using a programmable melting point apparatus (Make-Veego). Drug filled capillary was placed in melting point apparatus containing silicon oil as a heating medium and the melting point was noted. The stirrer was kept on while recording the melting point to ensure uniform heat transfer.

Fourier Transform Infrared Spectroscopy (FTIR)

IR absorption spectrum of carbamazepine was recorded by potassium bromide dispersion technique in which mixture of drug and potassium bromide was placed in sample holder and infrared spectrum was recorded using FTIR (Shimadzu, Japan). The identified peaks were compared with principal peaks of reported IR spectrum of carbamazepine and the sample was authenticated.

Determination of λ_{max} and standard curve of Carbamazepine in methanol, water and Phosphate Buffer pH 7.4

UV spectrum of carbamazepine was carried out in methanol, water and phosphate buffer pH 7.4. Carbamazepine (10 mg) was weighed accurately and transferred to a 100ml volumetric flask. 50 ml of methanol was added and sonicated for 10 minutes so as to dissolve completely. Final volume was made up with methanol, from this 1ml is taken and diluted upto 10 ml to get concentration of 10 μ g/ml. From this, 1, 2, 3, 4, 5 ml were taken and diluted upto 10 ml with methanol in volumetric flasks. The methanol was used as blank solutions and all the solutions were scanned in the range of 400 to 200 nm (UV- visible spectrophotometer). Similarly standard curves were prepared in water and phosphate buffer pH 7.4.

Solubility study

The solubility of drug was determined in water and pH 7.4 buffer at 37°C. Excess quantity of drug was suspended in respected media. The vials were shaken in temperature controlled shaker for 24 hrs. After 24 hrs samples were filtered. Filtrate was diluted and the absorbance was measured at 284 nm. Solubility was calculated using calibration curve.

Construction of Pseudo-ternary phase diagram

Pseudo-ternary phase diagram was constructed by titrating mixtures of oil and Smix (mixture of surfactant and co-surfactant) with water at room temperature. For this, the selected surfactant (Tween 80) and co-surfactant (Transcutol) were blended together in ratio 1:1. Every mixture was mixed with selected oil (caoryol-90) 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 by plotting concentration of oil, surfactant and co-surfactant. A proper monophasic region was selected for formulation of microemulsion system from constructed pseudoternary phase diagram.

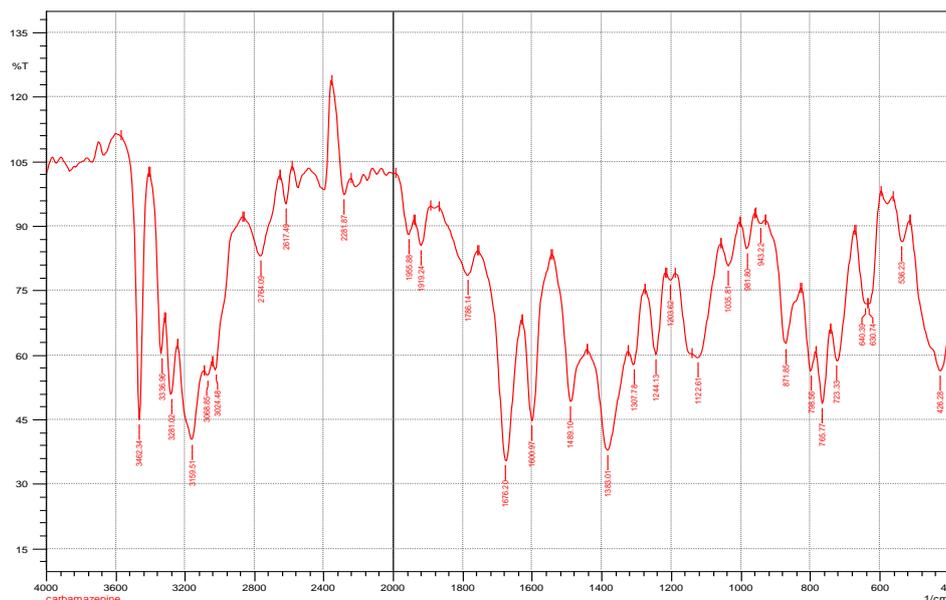


Figure 2: IR Spectrum of Carbamazepine.

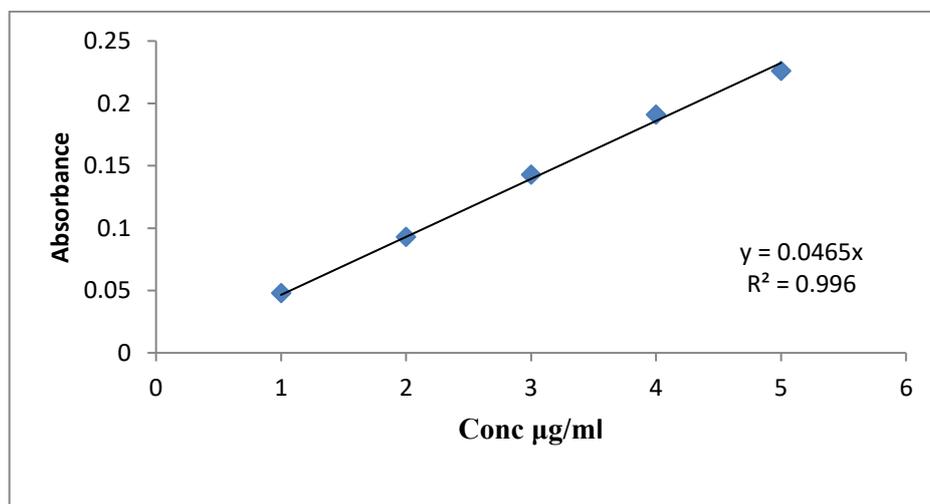


Figure 3: Calibration curve of Carbamazepine in pH 7.4 phosphate buffer.

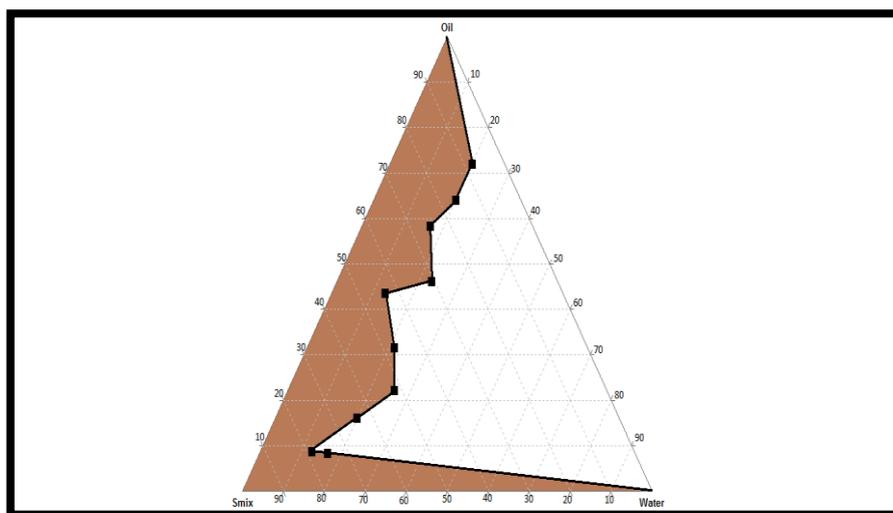


Figure 4: Pseudo-ternary phase diagram showing microemulsion region of oil, water and Smix (Tween-80: transcutol, 1:1).

The oil concentration should be sufficient to solubilise the

Table 4: Evaluation parameter for microemulsion.

Code	Appearance and Clarity	pH	Percent drug Content (%)	Percent Transmittance (%)	Particle Size (nm)
M1	+++	6	92.9	89.4	27.53
M2	+++	6.5	89.6	94.5	30.34

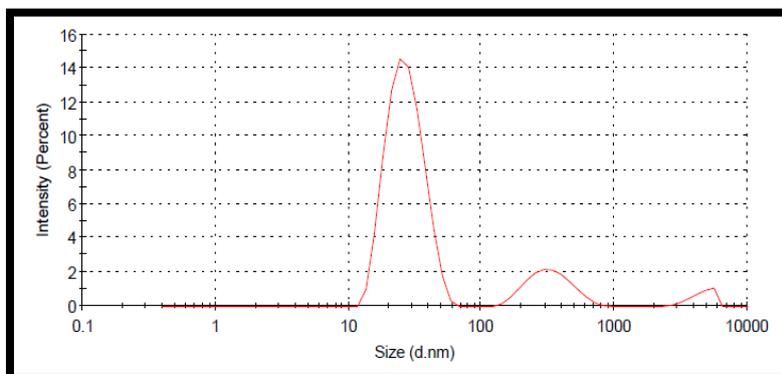


Figure 5: Particle size of batch M1.

Table 5: Viscosity of microemulsion.

Code	Viscosity of microemulsion at different rpm (cps)	
	50	100
M1	210	180
M2	120	109

Table 6: Evaluation of microemulsion based gel.

Formulation	pH	Spreadability gm cm/sec	Percent drug content
FG1	6.5	21.42	94.6
FG2	6.8	15	93.5
FG3	6.5	18.75	93.9
FG4	7.2	12.93	90.2
FG5	7.2	16.66	90.5
FG6	6.2	20.83	94.3
FG7	6.5	14.65	93.4
FG8	6.2	20.34	93.8
FG9	7.4	16.78	89.5
FG10	7.4	21.21	89.9

Table 7: Comparison of microemulsion based gel, propylene glycol solution and topical gel (1%) by cumulative permeation (flux).

Formulations	Cumulative permeation (µg/cm ² /min)
Microemulsion based gel(FG1)	0.0888
Propylene glycol solution	0.0994
Topical gel	0.0094

Selection of formulation from Pseudo-ternary Phase diagram

Two compositions of oil, Smix and water were selected for microemulsion formulation on the basis of following criteria:

drug equivalent to dose (1gm/100gm of microemulsion) considering the solubility of the drug in the selected oil. Optimum quantity of water and Smix should be used so as to form homogenous, clear, transparent microemulsion for the selected quantity of oil.

Preparation of Microemulsion

A series of microemulsion formulations were prepared using following procedure:

Drug was dissolved in oil. Surfactant and co-surfactant were accurately weighed and mixed and mixture, Smix (Tween-80 + Transcutol) (1:1) was added to oil phase. The mixture was mixed by vortexing until the drug was completely dissolved. The mixture was stored at room temperature until further use. Table 1, shows different microemulsion formulations using Capryol 90 as oil phase. While formulating microemulsion, Transcutol was selected as co-surfactant. Transcutol has low viscosity as compared to PEG-400 and the selected surfactant (Tween-80) is also highly viscous. Therefore, in order to avoid the problem of precipitation of microemulsion the co-suractant with lower viscosity (Transcutol) was selected.

Method of preparation of microemulsion based gel

The poloxamer 407 and Carbopol-974 were used to construct the microemulsion- based gel for improving the viscosity of microemulsion for topical administration. The polaxmer 407 (20%, 18%, 19% w/w) was dispersed in water and then kept in freezer for 24 hr. Carbopol-974(1%, 3% w/w) was dispersed in water and was kept at room temperature. Then, the poloxamer 407 and carbopol-974 solution was mixed with Microemulsion under stirring. Carbopol-974 gel was neutralized with triethanolamine. As the microemulsion was added to the solution of poloxamer, the viscosity of microemulsion based gel increased. The gel was then subjected to physicochemical evaluation and stability studies, and was further evaluated on the basis of diffusion studies.

Evaluation of microemulsion

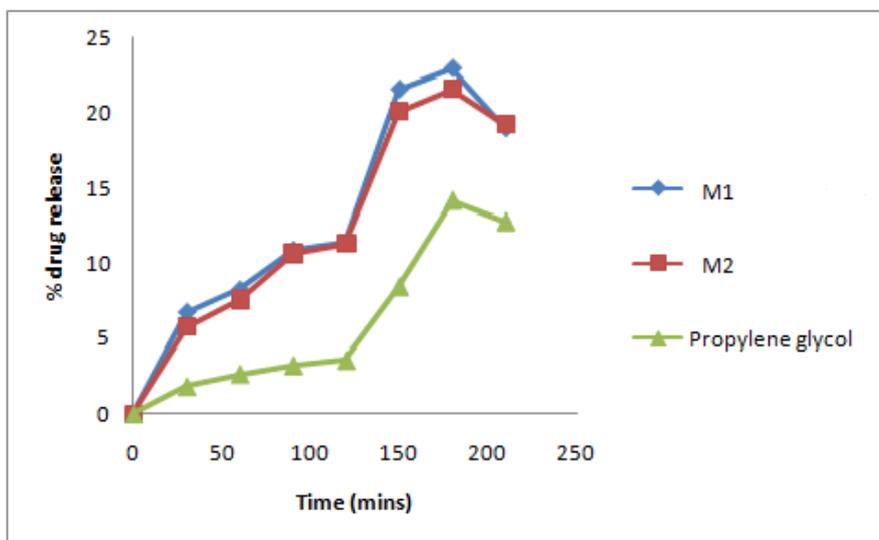


Figure 6: In-vitro diffusion

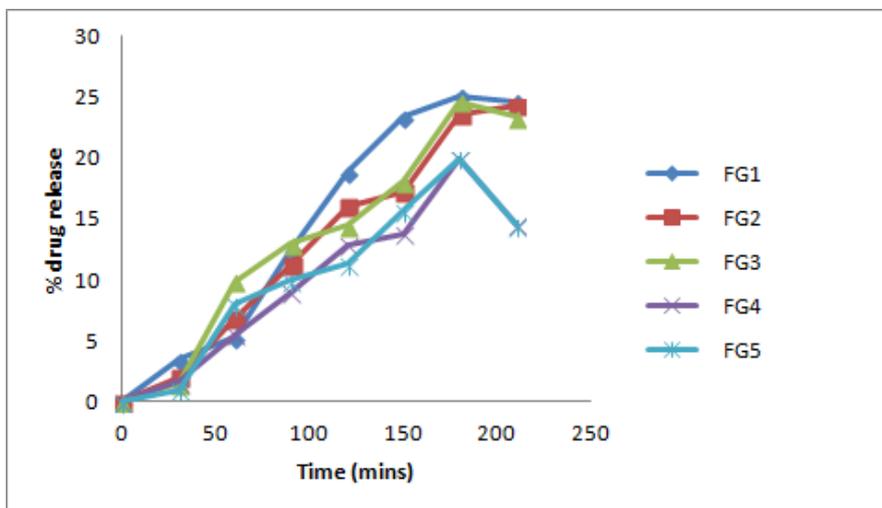


Figure 7: Invitro drug diffusion from batch FG1-FG5

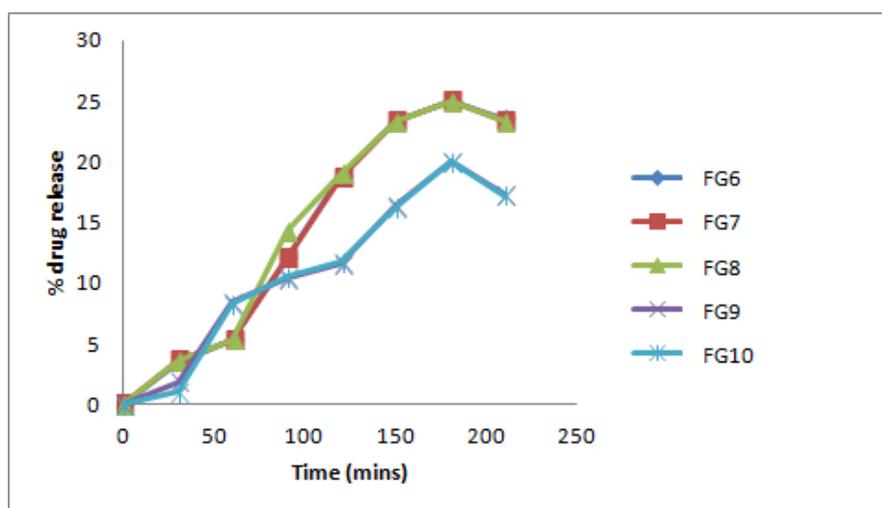


Figure 8: Invitro drug diffusion from batch FG6-FG10

pH

The pH of formulations was determined by using pH meter.

Viscosity

The viscosity of the solution was determined using programmable viscometer (Brookfield RVDV II) with

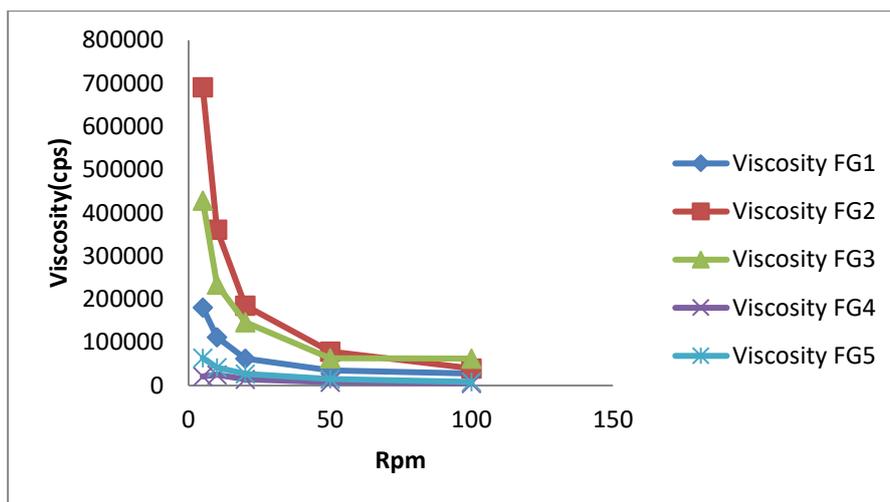


Figure 9: viscosities of various Microemulsion based gel formulation batch FG1-FG5.

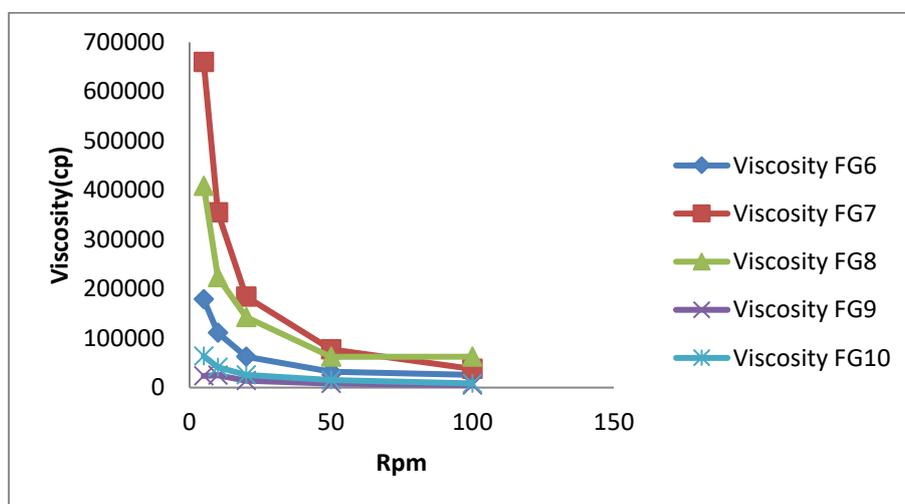


Figure 10: viscosities of various Microemulsion based gel formulation batch FG6-FG10.

Comparison of Topical gel and propylene glycol solution and microemulsion based gel (1%).E

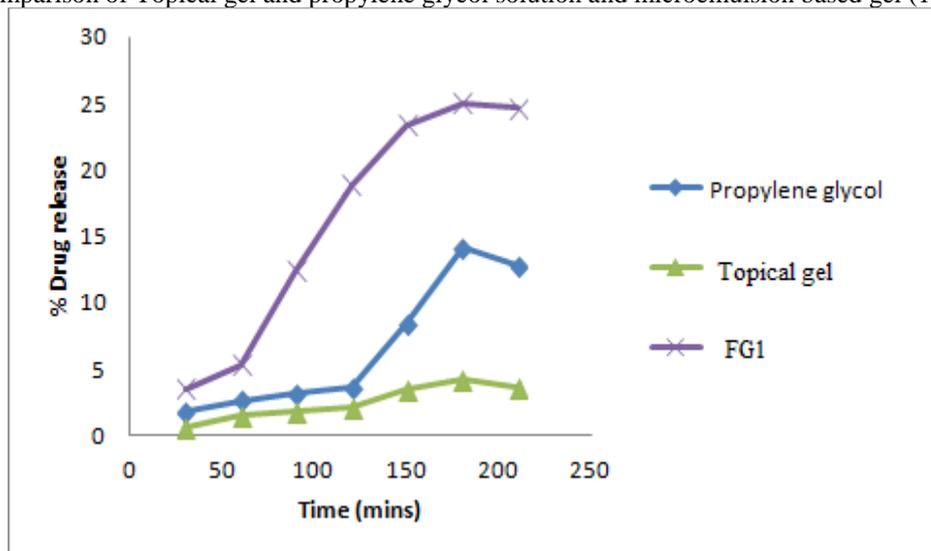


Figure 11: Comparison study of topical gel, Propylene glycol solution and Microemulsion based gel (1%).E

small sample volume adaptor⁹ and it was operated under following conditions:

7 ml of prepared microemulsion was transferred in sample cell which was placed carefully within the adaptor. The

guard leg was placed around the adaptor and the volume of sample was stirred slowly using a motor driven stirring element. The viscosity values were recorded from the display window at 50 and 100 rpm.

Percent Transmittance

The percent transmittance of formulation was analyzed directly by UV spectrophotometer (UV 1700 Shimadzu) at 600 nm.

Percent Drug Content

The microemulsion formulation (equivalent to 30 mg of Carbamazepine) was dissolved in 100 ml of methanol. From this solution, 1 ml samples were withdrawn and diluted to 10 ml with methanol. The Carbamazepine content in methanol was analyzed by UV spectrophotometer at 284 nm using methanol as blank. The concentration of Carbamazepine in each sample was determined from standard curve in methanol.

Droplet size measurements

Size analysis of microemulsion was carried out by dynamic light scattering experiments. The polydispersity index of the formulation was determined by the Malvern instrument (Zetasizer ver 7.12).

Centrifugation

It included centrifugation of microemulsion formulation for 3 min at 3000 rpm and formulations were observed for instability by evaluating them for change in phase separation and optical clarity.

In vitro diffusion study

The study was performed using Franz diffusion cells with available diffusional area of 2.759 cm² and with 41 ml volume. 1 ml of Carbamazepine loaded microemulsion was placed in the donor compartment and the receptor compartment was filled with mixture of phosphate buffer solution (pH 7.4), maintained at 37±1°C and stirred by using magnetic stirrer bar (300 rpm). For *in-vitro* release studies, artificial dialysis membrane was soaked in the same buffer solution for 24 hr before mounting on the diffusion cells. At 30, 60, 90, 120, 150, 180, 210 min, 1 ml of sample was withdrawn and for ensuring “sink conditions”, 1 ml of fresh phosphate buffer pH 7.4 was added. Then the carbamazepine concentration was assayed by UV spectrophotometric method at 284 nm.

Characterization of microemulsion based gel

pH

The pH of formulations was determined by using pH meter.

Viscosity

The viscosity of formulation was determined by using Brookfield viscometer. Spindle S-94 was used for the measurement of viscosity of gel.

Spreadability study

It consists of wooden block, which was provided by a pulley at one end. By this method spreadability was measured on the basis of “slip” and “drag” characteristics of gels. To determine the spreadability, 1 g of microemulsion based gel was placed within circle of 1 cm diameter pre-marked on a glass slide, over which second slide was placed. A weight of 100 gm was allowed to rest on the upper glass plate for 5 min. Spreadability is expressed by measuring time in seconds taken by two

slides to slip off from microemulsion based gel. It is calculated by using the formula.

$$S = M \cdot L / T \dots\dots\dots 1$$

Where, M = weight tied to upper slide

L = length of glass slides

T = time taken to separate the slides

Percent Drug Content

The microemulsion formulation (equivalent to 30 mg of Carbamazepine) was dissolved in 100 ml of methanol. From this solution, 1 ml samples were withdrawn and diluted to 10 ml with methanol. The Carbamazepine content in methanol was analyzed by UV spectrophotometrically at 284 nm using methanol as blank. The concentration of Carbamazepine in each sample was determined from standard curve in methanol.

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RESULTS AND DISCUSSION

Melting Point

The melting point was found to be 191.8°C. The reported melting point for carbamazepine is between 189°C to 193°C, hence the experimental finding was in good compliance with the reported value.

FTIR Spectrum Interpretation

The FTIR spectrum of drug sample was taken. An IR spectrum of carbamazepine is shown in figure 2 and its interpretation is shown in table 3. Major peaks are similar to reported IR¹⁰.

UV-Visible Spectrophotometry

The λ_{max} value was determined in pH 7.4 phosphate buffer. Both in water and pH 7.4 phosphate buffer, wavelength of maximum absorbance (λ_{max}) was 284 nm. Figure 3 shows standard curve obtained in phosphate buffer pH 7.4. The graph of absorbance v/s concentration of Carbamazepine was found to be linear in the concentration range of 1-5 μg/ml. Thus, the standard curve obeys Beer-Lamberts' law.

Saturation solubility of carbamazepine in oils, surfactant and co-surfactant

Solubility of Carbamazepine is reported in oils, surfactants and co-surfactants. So on basis of reported solubility Capryol-90 (oil), Tween-80 (surfactant), and Transcutol (co-surfactant) were selected to prepare microemulsion.

Construction of pseudoternary phase diagram

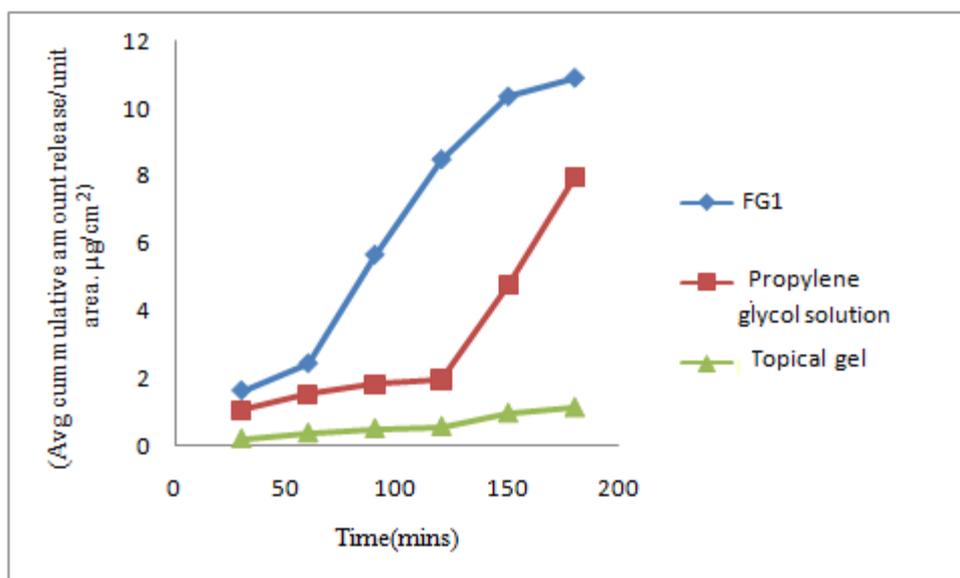


Figure 12: Comparison of microemulsion based gel, propylene glycol solution and topical gel (1%) using flux.

The pseudoternary phase diagram was constructed in order to obtain the concentration range of components for the existence range of microemulsions using “TRIPLLOT” software version 4.1.2. The phase diagram of Capryol 90(oil), Tween-80+ Transcutol (Smix1:1) and water is shown in fig 5. The transparent o/w microemulsion area was presented as a shaded region in the phase diagrams. After the Microemulsion region in the phase diagram was identified, the Microemulsion formulations were selected at different component ratios as described in Table 1. The microemulsions containing excess amount of drug were prepared and evaluated. The effect of amount of surfactant:co-surfactant and oil phase on globule size of drug loaded microemulsions were investigated. Formulations in which the oil content was 3% and surfactant-co-surfactant (ratio 1:1) were 27%, 40% and for water 70% and 57% respectively, were investigated for drug loading.

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).

Estimation of Carbamazepine content in microemulsion formulation was carried out by the UV spectrophotometric method at 284 nm. The content of carbamazepine in various microemulsion was found to be in range of 90-100%.

Percent transmittance in microemulsion formulation was carried out by UV spectrophotometric method at 630 nm. The percentage transmittance of Carbamazepine microemulsion formulations was found to be in the range, 89-95%.

Droplet size of microemulsion formulation is critical parameter. Smaller the droplet size, the larger will be interfacial surface area provided for drug permeation. The average droplet size of the selected formulation M1&M2 were found to be less than 100 nm.

Viscosity values are given in table no. 6. Viscosity of M2 is relatively less because of higher content of Smix.

It was observed that maximum drug release from microemulsion was achieved within 3 hrs. In release

profile of microemulsion, formulation M1 showed maximum drug release (22.95%) through dialysis membrane in three hours.

Evaluation parameter for microemulsion based gel

Table 6 gives evaluation of microemulsion based gels.

The pH of all the microemulsion based gel formulations were found to be in the range of 6.2-7.4. These pH values were considered to be acceptable since the skin pH ranges between 4-7.

Good spreadability is because of the loose gel matrix nature of Microemulsion based gel due to presence of oil globules as compared to the conventional cream formulation. Although good spreadability was observed for all the formulations, the formulation gelled with poloxamer - 407 showed better spreadability in range of 14- 30. The greater the viscosity the longer will be the time taken for spreading.

The drug content in the carbamazepine loaded microemulsion based gel is as shown in table 6 and was well within the limits

Diffusion study

It was observed that maximum drug release from microemulsion was achieved within in 3 hrs. In release profile of microemulsion, formulation FG1& FG6 show maximum drug release through dialysis membrane. Typical diffusion profiles showed reduction in cumulative diffusion after 180 min. This could not be explained as there is no saturation of receptor medium (pH 7.4 buffer) at that concentration.

Viscosity of Microemulsion based gel

Viscosities of microemulsion based gels are given in fig 10 and fig 11.

As compared to Propylene glycol solution and Topical gel; microemulsion based gel showed higher drug release. Due to presence of oil, the penetration of drug into the skin increases and the drug release will be more as compare to propylene glycol solution and topical gel. Also as compared to topical gel, propylene glycol solution and microemulsion based gel showed less lag time.

Drug solution in propylene glycol showed the highest flux (0.0994 $\mu\text{g}/\text{cm}^2/\text{min}$) followed by microemulsion gel (0.0888 $\mu\text{g}/\text{cm}^2/\text{min}$). Topical gel showed lowest flux (0.0094 $\mu\text{g}/\text{cm}^2/\text{min}$). As compared to drug solution and topical gel; microemulsion based gel showed the less lag time for diffusion, so microemulsion based gel is suitable dosage form for carbamazepine.

DISCUSSION

While formulating clear formulation of microemulsion of Carbamazepine, various problems like turbidity and drug precipitation occurred due to low solubility of carbamazepine in water. When carbopol was added to prepared microemulsion drug precipitation was observed. Hence the drug with oil and Smix was prepared separately and aqueous gel phase was prepared separately. The drug solution in oil and Smix was added to the aqueous gel phase to give the clear and stable gel. Among the two gelling agents, poloxamer-407 gave stable gel.

CONCLUSION

An optimized carbamazepine loaded formulation consisting of Capryol-90 (3%), Smix (Tween-80 and Transcutol) (1:1) gave the advantage of good clarity systems at high oil content and thus offered good solubilization of carbamazepine. Microemulsion based gel can be used as a possible alternative to conventional topical formulation of carbamazepine.

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