

Formulation of Topical Microemulsion of Pregabalin for the Management of Neuropathic Pain

Halima Thwaib^{1,2}, Ibrahim Kayali¹, Numan Malkieh³, Muntaser S. Ahmad^{2,4,*}

¹ Department of Chemistry & Chemical Technology, College of Science & Technology, Al-Quds University, Jerusalem, Palestine.

² Department of Medical Imaging, Palestine Ahliya University, Bethlehem, Palestine.

³ Jerusalem Pharmaceuticals Co. Ltd. (Jepharm), Al Bireh-Ramallah, Palestine.

⁴ Department of Nuclear Medicine, Al-Ahli Hospital, Hebron, Palestine.

*Correspondence to: Muntaser S. Ahmad, Assistance Professor, Department of Medical Imaging, Faculty of Allied Medical Health, Palestine Ahliya University, Bethlehem, Palestine. Email: wmuntaser@gmail.com.

Abstract

Pregabalin, a medication with anticonvulsant properties, is used to manage epilepsy as well as alleviate neuropathic pain linked to diabetic peripheral neuropathy and post-herpetic neuralgia is commonly treated with pregabalin. Pfizer markets pregabalin under the brand name Lyrica® in various formulations including capsules, oral solution, and extended-release tablets. Although it is beneficial, it can have adverse consequences, particularly on kidney function. This study aims to address challenges associated with oral delivery by formulating a pregabalin microemulsion for topical application. Additionally, the study investigates the impact of the surfactant/cosurfactant ratio on the phase behavior of the microemulsion. The experimental focus was on constructing pseudo-ternary phase diagrams using aqueous titration. The formation of microemulsions was achieved by combining 0.1 M pregabalin at the aqueous phase, oleic acid, IPM, and R (+)-Limonene oil at the oily phase, which also acted as penetration enhancers, along with PG in different proportions. The formulation had different concentrations of Tween 80 and ethanol, which were used as surfactants and cosurfactants. The results indicated that microemulsion formulations had the potential to serve as a substitute for oral pregabalin. Increased surfactant concentrations resulted in a larger microemulsion area compared to the levels of cosurfactant. An isotropic zone was produced more effectively using a 2:1 ratio of surfactant to cosurfactant, as compared to a 1:1 ratio. Nevertheless, when the quantity of surfactant decreased, the surfactant/cosurfactant blend exhibited reduced efficacy.

Keywords: Pregabalin, neuropathic pain, microemulsion, topical drug delivery, penetration enhancer.

How to cite this article: Thwaib H, Kayali I, Malkieh N, Ahmad MS. Formulation of Topical Microemulsion of Pregabalin for the Management of Neuropathic Pain. *Int J Drug Deliv Technol.* 2026;16(6s): 569-577; DOI: 10.25258/ijddt.16.6s.82

Introduction

Oil, water, and surfactant, sometimes with a cosurfactant, combine to create isotropic, thermodynamically stable transparent microemulsions with droplets ranging in size from 20 to 200 nm. Their easy and cost-effective preparation and high bioavailability render them advantageous. The carrier facilitates the transdermal delivery of drugs, enhancing their absorption via the skin. Microemulsion-based skin formulations enhance the solubility, permeability, and skin penetration of medications. Microemulsion devices administered topically exhibit superior medication stabilization compared to conventional topical applications [1]–[9].

Neuropathic pain (NP) is caused by a primary injury or malfunction in the nervous system. This sensation is frequently characterized as a burning, tingling, or electric shocks. The condition is often characterized by persistence and/or chronicity, with the location being either peripheral or central depending on the specific lesion or dysfunction. Multiple investigations have demonstrated that pregabalin is a reliable and secure first treatment for neuropathic pain [10]–[12]

Systemic medicine frequently induces somnolence, vertigo, and weight increase. Individuals who have medical conditions or are advanced in age may have limitations in their ability to utilize neuropathic pain medications. Applying topical treatment helps to minimize the occurrence of systemic side effects and

Formulation of Topical Microemulsion of Pregabalin for the Management of Neuropathic Pain

drug interactions. Systemic medications need precise dose adjustment, but local administration makes it easier [13].

Figure 1 illustrates the global non-proprietary name for pregabalin, identified as (3S)-3-(aminomethyl)-5-methylhexanoic acid. Pregabalin is a derivative of the inhibitory neurotransmitter γ -aminobutyric acid (GABA) and is characterized by three substituents. Pregabalin, with the chemical formula $C_8H_{17}NO_2$, is a solid powder that is white to off-white in color. It has a highly crystalline structure and has low solubility in water. Pfizer markets Lyrica®, an anticonvulsant medication used for the treatment of epilepsy and neuropathic pain. Pregabalin is a very successful medication that has a wide range of therapeutic applications, which makes it a good candidate for future drug development. Simplified and efficient synthesis techniques are crucial research objectives for medicinal and organic chemists [14]–[16].

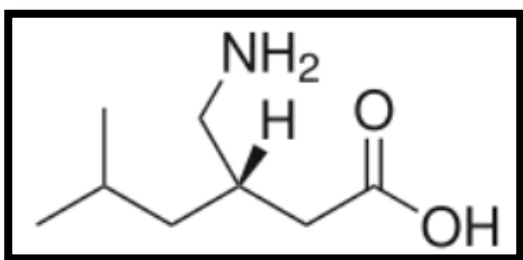


Figure 1. Chemical structure of Pregabalin [14].

Plaza-Villegas and colleagues (2012) conducted a study to explore the effects of topically administered pregabalin and diclofenac on neuropathic orofacial pain in rats induced by infraorbital nerve injury. The researchers discovered that the application of 10% pregabalin or 5% diclofenac topically resulted in a considerable reduction in pain. Specifically, the administration of pregabalin had a negative impact on motor coordination. Systemic treatment resulted in higher plasma drug levels in comparison to topical delivery. Both topical pregabalin and diclofenac were effective in relieving orofacial pain caused by nerve damage. However, the 10% pregabalin solution offered the greatest level of relief. This medication also had a favorable side effect profile, indicating that it may be effective and well-tolerated [17].

Systemic treatment of NP medication lowers the deleterious effects of pregabalin that are mediated centrally. The act of administering a substance through the mouth frequently leads to negative effects on the central nervous system (CNS), which in turn impede the

patient's ability to adhere to the treatment and tolerate it. Investigations into transdermal and topical administration methods might potentially address this issue. By employing alternative administration methods, these treatments can effectively bypass systemic circulation and mitigate adverse effects on the CNS [17]. Further investigation is required to comprehensively evaluate the effectiveness, safety, and practicality of transdermal and topical pregabalin formulations as therapies for neuropathic pain, despite initial positive outcomes and little adverse reactions.

This study aimed to develop microemulsion devices for the transdermal delivery of pregabalin as a substitute for oral treatment in order to mitigate its adverse effects. The microemulsions were prepared using penetration enhancers (PEs) such as oleic acid, IPM, and R (+)-Limonene oil. The aqueous phase had a concentration of 0.1 M pregabalin and different ratios of PG. Surfactants and cosurfactants, such as Tween 80 and ethanol, were employed in different quantities.

Materials and Methods

Chemicals

Pregabalin ($C_8H_{17}NO_2$, molecular weight=159.23g/mol, purity >98%) was purchased from Alembic Pharmaceuticals, India. R (+)-Limonene, isopropyl myristate (IPM) and n-octanol were purchased from Sigma-Aldrich, USA. Ethanol 99% and propylene glycol (PG) was purchased from Sigma-Aldrich, USA. Sorbitanmonooleate (Tween®80) were purchased from Kolb, Switzerland. Distilled and deionized water were used in all experiments.

Construction of Pregabalin ME Phase Diagrams

The water titration method was employed to construct pregabalin microemulsion (ME) phase diagrams, utilizing an aqueous phase. These diagrams were instrumental in delineating clear and single-phase areas, indicative of ME regions. These ME regions depicted a spectrum of potential concentrations for ME components (including oil, water, surfactant, and co-surfactant), conducive to forming single-phase MEs. A total of 18 phase diagrams were generated and categorized into three groups based on the choice of oil phase (oleic acid, IPM, R(+)-Limonene), as detailed in Table 1. Mixtures of oils and surfactant/co-surfactant were prepared at various weight ratios ranging from 1:9 to 9:1, respectively. To construct each phase diagram, a blend of oil and surfactant/co-surfactant was titrated with the aqueous phase dropwise under magnetic stirring. The

Formulation of Topical Microemulsion of Pregabalin for the Management of Neuropathic Pain

titration proceeded until the solution reached a cloudy endpoint, determined visually. Transparent mixtures were characterized as macroemulsion. Temperature regulation was maintained at $25\pm 1^\circ\text{C}$ using a temperature-controlled bath throughout the process. Additionally, the pH of the formulations was assessed at ambient temperature using a pH meter (Hash Company, USA). Finally, Pregabalin ME phase diagrams were

plotted using Origin Pro 8.0 software (Originlab Corporation, Massachusetts, USA). In vitro drug release studies were then conducted on MEs which provided clear and single-phase ME with the least surfactant/co-surfactant concentration and the highest oil concentration.

Table 1. Composition of pregabalin ME formulations.

Group	System	Surfactant/co-surfactant	Oil phase	Aqueous phase
1	A	Tween 80	Oleic acid	0.1M pregabalin
	B	Tween 80: Ethanol (2:1)	Oleic acid	0.1M pregabalin
	C	Tween 80: Ethanol (1:1)	Oleic acid	0.1M pregabalin
	D	Tween 80	Oleic acid	0.1M pregabalin: PG *(1:1)
	E	Tween 80: Ethanol (2:1)	Oleic acid	0.1M pregabalin: PG (1:1)
	F	Tween 80: Ethanol (1:1)	Oleic acid	0.1M pregabalin: PG (1:1)
2	G	Tween 80	IPM**	0.1M pregabalin
	H	Tween 80: Ethanol (2:1)	IPM	0.1M pregabalin
	I	Tween 80: Ethanol (1:1)	IPM	0.1M pregabalin
	J	Tween 80	IPM	0.1M pregabalin: PG (1:1)
	K	Tween 80: Ethanol (2:1)	IPM	0.1M pregabalin: PG (1:1)
	L	Tween 80: Ethanol (1:1)	IPM	0.1M pregabalin: PG (1:1)
3	M	Tween 80	R (+)-Limonene	0.1M pregabalin
	N	Tween 80: Ethanol (2:1)	R (+)-Limonene	0.1M pregabalin
	O	Tween 80: Ethanol (1:1)	R (+)-Limonene	0.1M pregabalin
	P	Tween 80	R (+)-Limonene	0.1M pregabalin: PG (1:1)
	Q	Tween 80: Ethanol (2:1)	R (+)-Limonene	0.1M pregabalin: PG (1:1)
	R	Tween 80: Ethanol (1:1)	R (+)-Limonene	0.1M pregabalin: PG (1:1)

* PG: propylene glycol; ** IPM: isopropyl myristate

Results

The phase behavior of pregabalin microemulsion was examined by employing ternary or pseudo-ternary phase diagrams. The points on the phase diagram indicated the weight percentages required for achieving clear, transparent, and isotropic solutions of the aqueous phase, surfactant, and oil. A demarcation was established between these locations, where the right side signifies a completely monophasic microemulsion and the left side denotes a cloudy dispersion or multi-phase region. The AT% was determined by dividing the monophasic area by the triangular phase diagram area in order to quantify microemulsion generation. Previous research has employed this metric to determine the ratio of monophasic and isotropic microemulsion area, encompassing oil-continuous, bi-continuous, and water-continuous structures. The study did not examine the transition between the three pregabalin microemulsions based on the amount of aqueous phase content since it

was not within the scope of the investigation. The area occupied by the formed microemulsion within each system is determined relative to the total area of the pseudo-ternary phase diagrams utilizing the ZWCAD program

1. Pseudo-ternary phase diagrams of Group

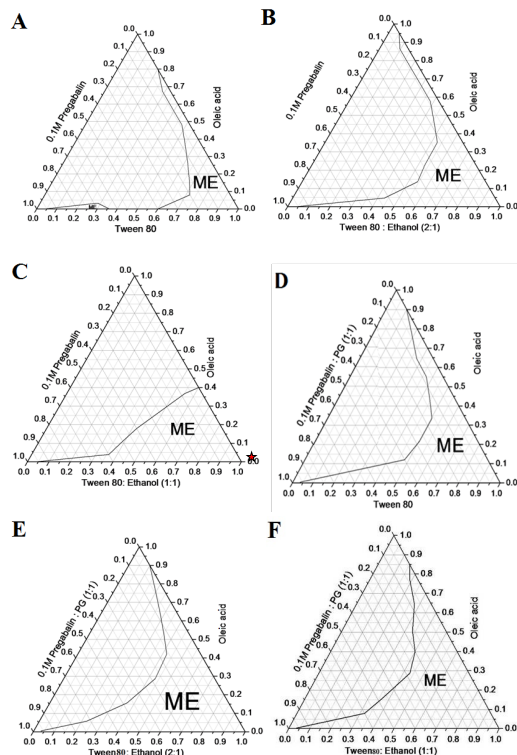
1

Figure 2 displays the composition of the microemulsion system in the form of a pseudo-ternary phase diagram. The oil phase consists of oleic acid, whereas the surfactant used is Tween 80. The ratios between the surfactant and cosurfactant might vary. The aqueous phase includes 0.1 M pregabalin with varying propylene glycol (PG) concentrations. Ethanol and propylene glycol alter the characteristics of their physical states. Therefore, pseudo-ternary phase diagrams were generated by altering the ethanol concentration both individually and in combination with PG.

Figure 2. Pseudo-ternary phase diagrams of Oleic acid, 0.1 M pregabalin, Tween 80: Ethanol ratio (A) 1:0,

Formulation of Topical Microemulsion of Pregabalin for the Management of Neuropathic Pain

(B) 2:1, (C) 1:1 and Oleic acid, 0.1M pregabalin: PG (1:1), Tween 80: Ethanol ratio (D) 1:0, (E) 2:1, (F) 1:1



System A (as depicted in Fig. 2.A) exemplifies the fundamental phase diagram within group 1. It comprises oleic acid as the oil phase, Tween 80 as the surfactant, and 0.1M pregabalin as the aqueous phase. This system delineated two microemulsion (ME) regions, with each region occupying 17.0% of the total phase diagram area.

System B (Fig. 2.B), utilizing a mixture of 2:1 Tween 80/ethanol, exhibited a microemulsion area (AT%) of 31.0%, surpassing that of system A. At 1:0, the area of the microemulsion reduced, as seen in Figure 2.A. At a ratio of 1:1 (Fig. 2.C), the AT% was 22.5%, which was lower than that of system B (Fig. 2.B).

Figure 2.D illustrates the impact of solubilization enhancers on the phase behavior and dilatibility of pregabalin microemulsion in System D was investigated. This involved substituting 0.1 M pregabalin with a mixture of 0.1 M pregabalin/PG in a 1:1 ratio resulted in an augmentation of pregabalin microemulsion synthesis using the same surfactant. System D, as shown in Figure 2.D, exhibited an AT% of 36.0%, which represents a 112.0% increase compared to the AT% of 0.1 M pregabalin alone, as shown in Figure 2.A. According to Figure 2.D, the microemulsion that consists of 0.1 M pregabalin /PG may be completely diluted with the aqueous phase without becoming cloudy when the weight ratio of surfactant to oleic acid is 9:1. The presence of the "red asterisk" on the oleic acid-surfactant arm signifies that the boundary line of the microemulsion reached the corner of the 100.0% 0.1M pregabalin/PG phase diagram without any breaks.

In group 1, System E and F (Fig. 2.E and 2.F) exhibited the largest microemulsion regions, occupying 45.0% and 44.0% of the phase diagram area, respectively. System E (Fig. 2.E) exhibited a larger microemulsion area compared to D. System E in group 1 exhibited the most favorable phase diagram, characterized by the largest microemulsion area as shown in Figure 2.E.

2. Pseudo-ternary phase diagram of Group 2

The pseudo-ternary phase diagram depicts the microemulsion system, comprising isopropyl myristate (IPM) as the oil phase, Tween 80 as the surfactant, and various ratios of surfactant-to-cosurfactant. The aqueous phase consists of a solution with a concentration of 0.1 M pregabalin, along with different amounts of propylene glycol. Alcohol or propylene glycol (PG) can influence phase dynamics. Therefore, pseudo-ternary phase

Formulation of Topical Microemulsion of Pregabalin for the Management of Neuropathic Pain

diagrams were generated by manipulating ethanol concentrations both independently and in combination with PG.

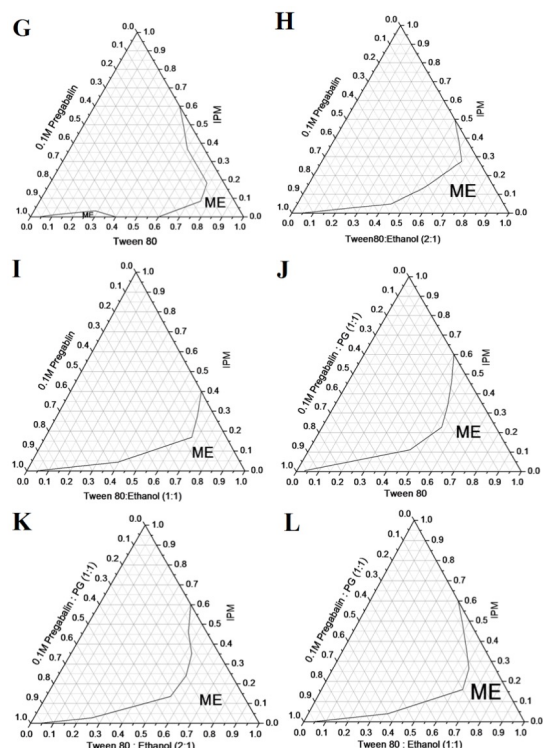


Figure 3. Pseudo-ternary phase diagrams of IPM, 0.1 M pregabalin, Tween 80: Ethanol ratio (G) 1:0, (H) 2:1, (I) 1:1 and IPM, 0.1M pregabalin: PG (1:1), Tween 80: Ethanol ratio (J) 1:0, (K) 2:1, (L) 1:1

Group 2 systems exhibit phase behavior that is analogous to that of group 1. Group 2 consists of System G, as shown in Figure 3.G, which has the most basic phase diagram. The oil phase is IPM, the surfactant is Tween 80, and the aqueous phase is 0.1 M pregabalin. This technique delineated two distinct regions on the phase diagram, specifically microemulsion (ME) zones, each occupying 13.0% of the total area. In group 2 (H, I, J, K, and L), it had the smallest microemulsion area.

When ethanol was added as a cosurfactant in system H (as shown in Figure 3.H) at a ratio of 2:1, the AT% increased from 13.0% to 21.2%. This is a significant 63.1% increase compared to the formulation without a cosurfactant. On the other hand, when the surfactant/cosurfactant ratio was adjusted to 1:1 in system I (as shown in Figure 3.I), the percentage of microemulsion area decreased from 21.2% to 18.4%, indicating that a ratio of 2:1 was the most optimal.

System J (Fig. 3.J) imitated system D (Fig. 3.D) by including PG as solubilization enhancers and transitioning from 0.1 M pregabalin to a 1:1 mixture of 0.1 M pregabalin and PG. System J (Fig. 3.J) exhibited

an AT% of 31.0%, which is a 138.5% increase compared to the AT% of 0.1 M pregabalin alone (Fig. 3.G).

The ME zone in System K (as shown in Figure 3.K) accounted for 28.3% of the phase diagram. The inclusion of ethanol as a cosurfactant, propylene glycol (PG), and a 0.1 M concentration of pregabalin in the aqueous phase resulted in a modification of the phase behavior. Within system L (as shown in Figure 3.L), adjusting the ratio of surfactant to cosurfactant to 1:1 resulted in a decrease in AT% from 28.3% to 22.5%, hence proving the validity of the 2:1 ratio. In group 2, J and K exhibited the largest microemulsion areas, surpassing those of G, H, I, and L.

3. Pseudo-ternary phase diagram of Group 3

Figure 4 illustrates the pseudo-ternary phase diagram delineating a microemulsion system. This system comprises R (+)-Limonene as the oil phase, Tween 80 as the surfactant with diverse surfactant to cosurfactant ratios, and 0.1 M pregabalin as the aqueous phase featuring varied PG to pregabalin ratios. The phase dynamics undergo alterations when ethanol and/or PG are introduced. Therefore, pseudo-ternary phase diagrams were generated by progressively increasing ethanol concentrations, both with and without the presence of PG.

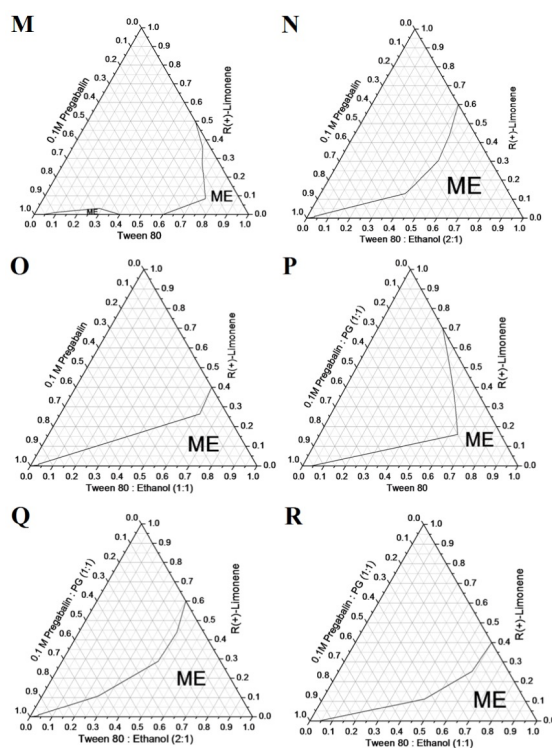


Figure 4. Pseudo-ternary phase diagrams of R (+)-Limonene, 0.1 M pregabalin, Tween 80: Ethanol ratio (M) 1:0, (N) 2:1, (O) 1:1 and R (+)-Limonene, 0.1M pregabalin: PG (1:1) Tween 80: Ethanol ratio (P) 1:0, (Q) 2:1, (R) 1:1

Formulation of Topical Microemulsion of Pregabalin for the Management of Neuropathic Pain

Group 3 systems exhibit phase characteristics akin to those observed in groups 1 and 2. System M (illustrated in Fig. 4.M) epitomizes the most straightforward phase diagram within group 3. This system employs R (+)-Limonene as the oil phase, Tween 80 as the surfactant, and 0.1 M pregabalin as the aqueous phase. This system delineated two microemulsion (ME) areas occupying 13.1% of its total area. However, group 3 systems N, O, P, Q, and R exhibited larger microemulsion areas compared to system M.

Introducing ethanol as a cosurfactant in a 2:1 ratio increased the AT% of system N from 13.1% to 41.0%, marking a notable 213.0% increase over system M (Fig. 4.M). In contrast, modifying the surfactant/cosurfactant ratio to 1:1 in system O (depicted in Fig. 4.O) decreased the AT% from 41.0% to 31.2%, suggesting that the 2:1 ratio was optimal.

In system P (Fig. 4.P), incorporating PG as solubilization enhancers and transitioning from 0.1 M pregabalin to a 0.1 M pregabalin/PG (1:1) mixture mirrored the phase behavior observed in systems D (Fig. 2.D) and J (Fig. 3.J). System P (Fig. 4.P) demonstrated an AT% of 30.0%, representing a 129.0% increase over 0.1 M pregabalin alone.

Among the five systems in group 3, system Q (Fig. 4.Q) exhibited the largest microemulsion area (AT%) at 42.2%. The alteration in phase behavior was attributed to the addition of ethanol as a cosurfactant and PG in conjunction with 0.1 M pregabalin as the aqueous phase. Nevertheless, modifying the surfactant/cosurfactant ratio to 1:1 in system R (as shown in Fig. 4.R) resulted in a reduction of the microemulsion area percentage from 42.2% to 27.0%, thereby confirming the superiority of the 2:1 ratio for these systems.

The effect of surfactant /cosurfactant ratio on the phase behavior.

Upon scrutinizing the phase behavior across all systems within groups 1, 2, and 3, it becomes apparent that the area occupied by the microemulsion was significantly larger when a higher quantity of surfactant was present compared to cosurfactant. Specifically, a surfactant/cosurfactant ratio of 2:1 demonstrated greater efficacy in promoting the formation of the isotropic region than a ratio of 1:1. This effectiveness of the surfactant/cosurfactant blend diminished as the amount of surfactant decreased, as clearly illustrated in Table 2.

Table 2. A comparison between the percentage of the monophasic area relative to the total area of the triangle phase diagram (AT %) for the whole eighteenth systems.

Group	System	Surfactant/cosurfactant ratio	A _T %
1	A	1:0	17.0
	B	2:1	31.0
	C	1:1	22.5
	D	1:0	36.0
	E	2:1	45.0
	F	1:1	44.0
2	G	1:0	13.0
	H	2:1	21.2
	I	1:1	18.4
	J	1:0	31.0
	K	2:1	28.3
	L	1:1	22.5
3	M	1:0	13.1
	N	2:1	41.0
	O	1:1	31.2
	P	1:0	30.0
	Q	2:1	42.2
	R	1:1	27.0

Table 2 highlights that while cosurfactants contribute to the formation of microemulsions, their presence surpassing the requisite amounts tends to affect interfacial parameters adversely, thereby diminishing the solubilization capacity of surfactant molecules. Furthermore, the AT% values presented in Table 2 for each system in group 1 are notably higher compared to their counterparts in groups 2 and 3. This observation suggests that microemulsions containing oleic acid as the oil phase exhibit superior phase behavior compared to those utilizing IPM and R (+)-Limonene as the oil phase.

pH of pregabalin ME formulations

All pH values of pregabalin ME formulations are within the acceptable physiologic pH range for dermal preparations (pH = 4.0–7.0).

Discussion

According to the pseudo-ternary phase diagrams for groups 1, 2, and 3, system A (Fig. 2.A), system G (Fig. 3.G), and system M (Fig. 4.M) were all prepared using an oil phase, Tween 80 as the surfactant, and 0.1 M pregabalin as the aqueous phase. The sole distinction between these systems is in the oil phase.

Formulation of Topical Microemulsion of Pregabalin for the Management of Neuropathic Pain

Nevertheless, each of the three systems exhibits phase diagrams containing two microemulsion (ME) zones that encompass 13.0%–17.0% of the overall region.

Figures 2.A, 3.G, and 4.M demonstrate the formation of a turbid zone when the concentration of pregabalin at 0.1 M fluctuates between 40% and 60%. This turbid zone acts as a barrier, separating the two zones of ME. Turbidity in this range is caused by inadequate hydration of polyoxyethylene groups that are essential for expanding the surfactant chain. When the concentration of pregabalin reaches 0.1 M and goes above 60%, the larger distance between the polyoxyethylene groups causes the turbid structure to become unstable, resulting in the formation of another area (AT%) with a concentration of 2.0%.

Oleic acid exhibited the highest microemulsion area when compared to IPM and R (+)-Limonene, as shown in Table 2. This is seen in Figure 2.A for Oleic acid, Figure 3.G for IPM, and Figure 4.M for R (+)-Limonene. However, in 2017, Dr. Sisak and his colleagues discovered that using IPM as the oil phase was more effective in creating a bigger microemulsion region with a greater concentration of water. This also resulted in a shift from a water-in-oil (w/o) phase to an oil-in-water phase [18].

The impact of the surfactant/cosurfactant ratio is seen in Figures 2 A-C, 3 G-I, and 4 M-O. The absence of ethanol resulted in a reduction in microemulsion regions at a ratio of 1:0, as shown in Figure 2A, 3G, and 4M. Ethanol acts as a cosurfactant, decreasing the interfacial tension between oil and water in microemulsions, hence enhancing the flexibility of stacking. Cosurfactants facilitate the dispersion of surfactants across both the aqueous and oil phases, hence modifying their hydrophilic and lipophilic properties. When comparing systems B, H, and N to systems C, I, and O (as shown in Figure 2C, Figure 3I, and Figure 4O), the AT% fell at a ratio of 1:1. This decrease can be attributed to the reduced proportion of surfactant.

The surfactant/cosurfactant ratio used in this study yielded comparable outcomes to those seen in prior experiments. In 2014, Dr. Agubata and his colleagues conducted an analysis of the phase behavior as well as the concentrations of oil, surfactant, and cosurfactant. In 2017, Dr. Elfiyani and her colleagues conducted an experiment to examine the impact of a mixture of Tween 80 and ethanol on the synthesis and mechanical strength of microemulsions that included antibacterial eucalyptus oil [19]. In conclusion, the ratio of 2:1 emerged as the

optimal surfactant to cosurfactant ratio, as it resulted in the highest microemulsion area.

Figures 2.D, 3.J, and 4.P, which represent System D, J, and P respectively, illustrate the impact of solubilization enhancers on the phase behavior and expansibility of pregabalin microemulsion. By substituting the aqueous phase from 0.1 M pregabalin to 0.1 M pregabalin /PG in a 1:1 ratio, the production of pregabalin microemulsion was enhanced. Certain surfactant molecules exhibit self-assembly in polar organic solvents such as PG. These solvents, similar to water, have the ability to form hydrogen bonds and possess high dielectric constants. As a result, they are unable to mix with hydrocarbon solvents. As these solvents replace water, they decrease or remove the LC phase areas at the surfactant interface. System D (Fig. 2.D) exhibited an AT% of 36.0%, which is a significant increase of 112.0% compared to formulations containing only 0.1 M pregabalin. It is worth mentioning that microemulsions that have a concentration of 0.1 M pregabalin /PG may be completely mixed with the water phase without becoming cloudy, even when the weight ratio of surfactant to oleic acid is 9:1. In Figure 2.D, the boundary line of the microemulsion extends without any breaks to the corner of the 100.0% 0.1 M pregabalin/PG phase diagram. PG, a molecule containing a "diol" group, may arrange itself at the interface between oleic acid and a solution containing 0.1 M pregabalin. This arrangement, together with the presence of a surfactant, enhances the flexibility of the interfacial layer and reduces its tension. This behavior induces a decrease in the natural curvature of the film, resulting in a negative value. This hinders the formation of the gel phase and encourages the synthesis of microemulsions.

Within their respective groups, System E, K, and Q exhibited significant microemulsion zones, as seen in Figures 2-4. The phase behavior was altered by the addition of ethanol as a cosurfactant and PG with a concentration of 0.1 M pregabalin as the aqueous phase. The addition of ethanol modifies the interfacial film, increasing the size of the single-phase region. Figure 2.E displayed a greater microemulsion area compared to both system D (Figure 2.D) and system F (Figure 2.F) due to the presence of a cosurfactant ratio of ethanol in a 2:1 proportion. Microemulsions have undergone substantial development for the purpose of administering topical medications, owing to their numerous advantages. This study proposes that the use of microemulsions might enhance the effectiveness of topical administration of

Formulation of Topical Microemulsion of Pregabalin for the Management of Neuropathic Pain

pregabalin. Pregabalin is used orally in tablet, pill, and solution formulations, with less attention dedicated to topical preparations to facilitate oral delivery.

In 2014, Dr. Fukasawa and his colleagues conducted a study to explore the potential of a transdermal solution containing pregabalin as a treatment for neuropathic pain (NP) in animal models. The primary focus of their research was on Pregabalin's capacity to increase pain thresholds in animal models when subjected to mechanical stimulation across several types of nerves. One limitation of their investigation was the lack of penetration enhancers, which could potentially augment pregabalin's penetration capability and enhance pain threshold elevation [20]. In contrast, our study formulated several microemulsion systems with various penetration enhancers, including oleic acid in group 1, IPM in group 2, and R (+)-limonene in group 3. Additionally, ethanol and PG were utilized with different ratios in each group, both of which can play a role in enhancing penetration.

Dr. Bhatia and colleagues created the initial transdermal pregabalin patch for neuropathic pain in 2012. Every transdermal patch requires the use of liner, medication, adhesive, membrane, backing, permeation enhancer, and matrix filler. Transdermal patches should be evaluated for their thickness, weight variation, capacity to withstand folding, tensile strength, ability to absorb moisture, and moisture content [21]. Nevertheless, in this study, the formulation of pregabalin microemulsion for the treatment of NP offers advantages such as ease of preparation, low cost, and thermodynamic stability.

Conclusion

The foregoing results indicate that under mentioned conditions, topical pregabalin microemulsion can be successfully formulated using Generally Recognized as Safe (GRAS) and topically acceptable surfactants, co-surfactants and oily phase. The results provide a basis for the successful design of pregabalin microemulsion resulting in improved penetration through the skin which may be used as a feasible alternative to conventional formulations of pregabalin.

References

- [1] I. Pathan and C. Setty, "Chemical Penetration Enhancers for Transdermal Drug Delivery Systems," *Trop. J. Pharm. Res.*, vol. 8, no. 2, pp. 173–179, Jul. 2009, doi: 10.4314/tjpr.v8i2.44527.
- [2] D. Ramadon, M. T. C. McCrudden, A. J. Courtenay, and R. F. Donnelly, "Enhancement strategies for transdermal drug delivery systems: current trends and applications," *Drug Deliv. Transl. Res.*, vol. 12, no. 4, pp. 758–791, Apr. 2022, doi: 10.1007/s13346-021-00909-6.
- [3] A. Kogan and N. Garti, "Microemulsions as transdermal drug delivery vehicles.," *Adv. Colloid Interface Sci.*, vol. 123–126, pp. 369–385, Nov. 2006, doi: 10.1016/j.cis.2006.05.014.
- [4] J. S. Yuan, M. Ansari, M. Samaan, and E. J. Acosta, "Linker-based lecithin microemulsions for transdermal delivery of lidocaine," *Int. J. Pharm.*, vol. 349, no. 1–2, pp. 130–143, Feb. 2008, doi: 10.1016/j.ijpharm.2007.07.047.
- [5] G. Sahu, H. Sharma, A. Gupta, and C. Kaur, "Advancements in Microemulsion Based Drug Delivery Systems for Better Therapeutic Effects," *Int. J. Pharm. Sci. Dev. Res.*, vol. 1, no. 1, pp. 008–015, Aug. 2015, doi: 10.17352/ijpsdr.000003.
- [6] S. Talegaonkar, A. Azeem, F. Ahmad, R. Khar, S. Pathan, and Z. Khan, "Microemulsions: A Novel Approach to Enhanced Drug Delivery," *Recent Pat. Drug Deliv. Formul.*, vol. 2, no. 3, pp. 238–257, Nov. 2008, doi: 10.2174/187221108786241679.
- [7] S. P. Callender, J. A. Mathews, K. Kobernyk, and S. D. Wettig, "Microemulsion utility in pharmaceuticals: Implications for multi-drug delivery," *Int. J. Pharm.*, vol. 526, no. 1–2, pp. 425–442, Jun. 2017, doi: 10.1016/j.ijpharm.2017.05.005.
- [8] J. Malakar, S. O. Sen, A. K. Nayak, and K. K. Sen, "Development and evaluation of microemulsions for transdermal delivery of insulin.," *ISRN Pharm.*, vol. 2011, p. 780150, 2011, doi: 10.5402/2011/780150.
- [9] R. Arora, "MICROEMULSION SYSTEM IN ROLE OF EXPEDIENT VEHICLE FOR DERMAL APPLICATION," *J. Drug Deliv. Ther.*, vol. 2, no. 4, pp. 23–28, Jul. 2012, doi: 10.22270/jddt.v2i4.196.
- [10] S. Mackey and S. Feinberg, "Pharmacologic therapies for complex regional pain syndrome," *Curr. Pain Headache Rep.*, vol. 11, no. 1, pp. 38–43, Mar. 2007, doi: 10.1007/s11916-007-0020-z.
- [11] J. L. M. Jongen, G. Hans, H. T. Benzion, F. Huygen, and C. T. Hartrick, "Neuropathic Pain and Pharmacological Treatment," *Pain Pract.*,

Formulation of Topical Microemulsion of Pregabalin for the Management of Neuropathic Pain

- vol. 14, no. 3, pp. 283–295, Mar. 2014, doi: 10.1111/papr.12085.
- [12] R. Baron, A. Binder, and G. Wasner, “Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment,” *Lancet Neurol.*, vol. 9, no. 8, pp. 807–819, Aug. 2010, doi: 10.1016/S1474-4422(10)70143-5.
- [13] M. L. Haanpää *et al.*, “Treatment Considerations for Patients With Neuropathic Pain and Other Medical Comorbidities,” *Mayo Clin. Proc.*, vol. 85, no. 3, pp. S15–S25, Mar. 2010, doi: 10.4065/mcp.2009.0645.
- [14] G. Martinotti *et al.*, “Pregabalin versus naltrexone in alcohol dependence: a randomised, double-blind, comparison trial,” *J. Psychopharmacol.*, vol. 24, no. 9, pp. 1367–1374, Sep. 2010, doi: 10.1177/0269881109102623.
- [15] N. M. Gajraj, “Pregabalin: its pharmacology and use in pain management,” *Anesth. Analg.*, vol. 105, no. 6, pp. 1805–1815, Dec. 2007, doi: 10.1213/01.ane.0000287643.13410.5e.
- [16] H. N. Jang and T. J. Oh, “Pharmacological and Nonpharmacological Treatments for Painful Diabetic Peripheral Neuropathy,” *Diabetes Metab. J.*, vol. 47, no. 6, pp. 743–756, Nov. 2023, doi: 10.4093/dmj.2023.0018.
- [17] F. Plaza-Villegas *et al.*, “Topical pregabalin and diclofenac for the treatment of neuropathic orofacial pain in rats,” *Oral Surg. Oral Med. Oral Pathol. Oral Radiol.*, vol. 114, no. 4, pp. 449–456, Oct. 2012, doi: 10.1016/j.oooo.2012.05.002.
- [18] M. A. Abd Sisak, R. Daik, and S. Ramli, “Study On the Effect of Oil Phase and Co-Surfactant on Microemulsion Systems,” *Malaysian J. Anal. Sci.*, vol. 21, no. 6, pp. 1409–1416, Dec. 2017, doi: 10.17576/mjas-2017-2106-23.
- [19] R. Elfiyani, A. Amalia, and S. Y. Pratama, “Effect of Using the Combination of Tween 80 and Ethanol on the Forming and Physical Stability of Microemulsion of Eucalyptus Oil as Antibacterial,” *J. Young Pharm.*, vol. 9, no. 1s, pp. s1–s4, Mar. 2017, doi: 10.5530/jyp.2017.1s.1.
- [20] H. Fukasawa, H. Muratake, M. Nagae, K. Sugiyama, and K. Shudo, “Transdermal administration of aqueous pregabalin solution as a potential treatment option for patients with neuropathic pain to avoid central nervous system-mediated side effects.,” *Biol. Pharm. Bull.*, vol. 37, no. 11, pp. 1816–1819, 2014, doi: 10.1248/bpb.b14-00278.
- [21] A. Kulkarni, D. P. Chaudhari, and D. P. Uttekar, “DEVELOPMENT AND EVALUATION OF PREGABALIN TRANSDERMAL PATCH FOR THE TREATMENT OF NEUROPATHETIC PAIN.,” *Int. J. Adv. Res.*, vol. 4, no. 7, pp. 163–169, Jul. 2016, doi: 10.21474/IJAR01/1050.