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Formulation and characterization of piroxicam-loaded water-in-oil microemulsions

Prapaporn Boonme[1*], Nattakit Molee[1], Thanakorn Kanchanaclod[1] and Hui Yang[1]
[1] *Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences & Drug Delivery System Excellence Center, Prince of Songkla University, Songkhla 90112, Thailand*
*E-mail: prapaporn@pharmacy.psu.ac.th

Abstract

This study aimed to investigate microemulsion (ME) formation of various non-ionic systems for seeking proper MEs to be incorporated with 0.5% w/w piroxicam. Characteristics of the obtained formulations were determined for appearance, ME type, stability tendency and *in vitro* drug release. ME regions in pseudoternary phase diagrams of twenty systems were constructed by the titration method. The studied oil phase was either isopropyl myristate (IPM) or oleic acid (OA). The investigated surfactant was either Cremophor RH 40 (RH40) or Tween 80 (T80). The examined cosurfactant was polyethylene glycol 400 (PEG400). The explored aqueous phase was either water (W) or 2:1 mixture of W and propylene glycol (2:1 W:PG). The results showed that the largest ME region was found in the system of IPM/3:1 T80:PEG400/2:1 W:PG. Six MEs (ME1 to ME6) were selected from the ME region of this system for evaluating the tendency of piroxicam solubility. ME5 and ME6 were found to provide desirable drug solubility. Finally, two 0.5% w/w piroxicam-loaded MEs, designated as ME5-P and ME6-P, were prepared to be further assessed. Both formulations were clear yellow liquids and water-in-oil (w/o) type. No changes in appearance and drug contents were observed after kept at room temperature for six weeks. However, ME5-P and ME6-P exhibited slower release rates and fewer amounts of the released drug than a commercial gel. The release limitation of the prepared piroxicam-loaded MEs may be possibly caused by a high affinity between piroxicam and ME components as well as entrapment of the drug molecules within the interfacial film.

Keywords: Drug release, Microemulsion, NSAIDs, Phase diagram, Piroxicam

1. Introduction

Piroxicam, one of the non-steroidal anti-inflammatory drugs (NSAIDs), is widely consumed due to its analgesic, anti-inflammatory and antipyretic properties. It is indicated for the treatment of inflammation in arthritis and other musculoskeletal disorders. Its mechanism of action is non-selective inhibition of cyclooxygenase (COX) enzymes, resulting in blocking the production of prostaglandins which are involved in inflammation. However, piroxicam causes severe side effects when orally administered such as gastrointestinal toxicity and hepatotoxicity (1). Hence, topical formulations of piroxicam with high effectiveness and ease of application are interesting. Nowadays, topical piroxicam has been commercially available in form of a gel, a semisolid dosage form, in many trade names. However, no liquid spray has been available since piroxicam is poorly water-soluble.

Microemulsion (ME) is one of the nanocarriers generally used for dermal drug delivery. It is a dispersed system consisting of oil and aqueous phases stabilized with the interfacial film of surfactant. Cosurfactant and cosolvent may be added to the systems for increasing ME formation. According to microstructure, ME is classified into three types, i.e., oil-in-water (o/w), bicontinuous and water-in-oil (w/o). ME is a single optically isotropic, thermodynamically stable and low viscous liquid, leading to be easily topically applied as spray. For formulation development, ME can offer solubility enhancement of both hydrophilic and hydrophobic drugs. Additionally, ME can spontaneously form when the system contains appropriate types and ratios of components, resulting in ease for scale-up production. Moreover, ME provides many pharmaceutical benefits such as enhancement of stability and skin penetration of the loaded drugs (2-5). Some formulations of piroxicam-loaded MEs have been previously reported as summarized in Table 1 (6-9). Various piroxicam-loaded o/w MEs were compared for skin permeation *via* Sprague-Dawley rat skin and the ME composed of 0.5% piroxicam, 10% Labrasol, 50% ethanol, 10% oleic

acid (OA) and 29.5% water was determined as the optimal formulation (6). The o/w ME containing 55.0% ethanol, 26.5% Tween 80 (T80), 7.5% castor oil and 11.0% phosphate buffer could enhance piroxicam solubility due to its hydrophobic composition and lipophilic tail of surfactant (7). Pre-microemulsions composed of T80, propylene glycol (PG) and OA could be incorporated with piroxicam and then they could form o/w ME *in situ* upon water dilution (8). It can be noted that most investigations focused on o/w MEs and comparison of release characteristics between the investigated piroxicam-loaded o/w MEs versus a commercial product was not assessed (6-8). Nevertheless, w/o MEs may be conveniently applied on the skin together with massage because of the lubricant effect. A report about piroxicam-loaded w/o MEs was previously presented; however, its drug content was only 0.3% w/w which was lower than the usual concentration of 0.5% w/w due to the low solubility of the drug in the formulation. Besides, the amount of released piroxicam from this 0.3% piroxicam-loaded w/o ME was less than that from 0.5% piroxicam marketed gel (9). Therefore, the development of w/o ME systems with high solution capacity and with desirable drug release for piroxicam is challenging. Additionally, ME components should be selected according to their generally recognized as safe (GRAS) status.

Table 1 Overview of previous reports about piroxicam-loaded MEs

Drug content (% w/w)	ME Component			Type	Ref.
	Oil phase	Surfactant, Cosurfactant	Aqueous phase		
0.5	Oleic acid (OA)	Labrasol, Ethanol	Water (W)	o/w	(6)
1.0	Castor oil	Tween 80 (T80), Ethanol	Phosphate buffer	o/w	(7)
0.5	OA	T80, Propylene glycol (PG)	W	o/w	(8)
0.3	Isopropyl palmitate	T80, Span 80	W, Isopropyl alcohol	w/o	(9)

This study aimed to investigate the phase behavior of non-ionic systems for finding suitable w/o MEs to be used as topical vehicles of piroxicam. Basic properties and *in vitro* drug release *via* the dialysis membrane of the obtained piroxicam-loaded w/o MEs were also evaluated.

2. Materials and Experiment

2.1 Materials

Piroxicam and Tween 80 (T80, polyoxyethylene 20 sorbitan monooleate) were purchased from PC Drug Center (Bangkok, Thailand). Cremophor RH 40 (RH40, polyoxyl 40 hydrogenated castor oil), isopropyl myristate (IPM), oleic acid (OA), polyethylene glycol 400 (PEG 400) and propylene glycol (PG) were purchased from JKK Chemical LP (Bangkok, Thailand). Ethanol, methanol and hydrochloric acid (HCl) were purchased from RCI Labscan Asia (Bangkok, Thailand). Sodium chloride, anhydrous disodium hydrogen orthophosphate and potassium dihydrogen orthophosphate were purchased from Univar Australia Pty Ltd. (New South Wales, Australia). All chemicals were pharmaceutical or analytical grade and used without modification. The 0.1 M methanolic HCl, isotonic phosphate buffer solution pH 7.4 (PBS) and distilled water (W) were prepared in-house. A 0.5% w/w piroxicam commercial gel was bought from a drug store in Hat-Yai, Songkhla, Thailand.

2.2 Construction of pseudoternary phase diagrams

The effects of various types and ratios of components on ME formation were elucidated. The studied oil phase was either IPM or OA. The investigated surfactant was either RH40 or T80. The examined cosurfactant was PEG400. The explored cosolvent in the aqueous phase was PG. These components were in GRAS status and widely used in pharmaceutical products. Furthermore, the solubility of piroxicam in IPM and OA was high as 2.52 ± 0.29 and 4.20 ± 0.25 mg/g, respectively (6). It is generally known that non-ionic surfactants, e.g., RH40 and T80, can act as skin penetration enhancers with a low risk of skin irritation (10). PEG400 was reported for its capability to form stable MEs with RH40 (11) and with T80 (12). The addition of PG in the aqueous phase was indicated for its ability to enlarge ME regions of the systems containing palm oil as oil phase and blend of Span 80 and T80 as surfactant mixture (13). In this study, twenty systems were investigated as shown in Table 2. Pseudoternary phase diagram construction was performed by the titration method. Briefly, oil was mixed with a surfactant or with a mixture of surfactant and cosurfactant at weight ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1. Afterward, each obtained mixture was titrated drop-by-drop with W or with 2:1 W:PG under vigorous agitation. The component amounts providing clear MEs were recorded, calculated in terms of % w/w and plotted on a triangular graph to obtain ME region in pseudoternary phase diagram of each system (13).

2.3 Preparation and characterization of piroxicam-loaded MEs

After ME regions of the studied twenty systems were obtained, six expected w/o MEs with higher ratios of oil phase than those of aqueous phase were selected from the system with the largest ME region. They were then mixed with 1% w/w of

piroxicam powder (two folds of required content) to observe solubility tendency. MEs providing high solubility tendency of piroxicam which could be seen as clear appearance were subsequently used to prepare 0.5% w/w piroxicam-loaded MEs. The formulated MEs were characterized for visual appearance. Their type was confirmed by the drop dilution test. Briefly, each sample was dropped into a brilliant blue aqueous solution. If the sample was miscible with the water-soluble dye solution, it was defined as o/w ME. In contrast, if the immiscibility was observed, the sample was defined as w/o ME (14). The samples were kept in tight containers for six weeks at room temperature. Subsequently, they were observed for appearance changing in terms of clarity, phase separation, drug precipitation and discoloration. Drug remaining amounts were also chemically analyzed comparing with the initial drug contents. Briefly, piroxicam was extracted from the prepared MEs with 0.1 M methanolic HCl and then analyzed by UV spectrophotometry technique (9, 15). All experiments were performed in triplicate.

Table 2 Types and ratios of components for phase behavior study

System	Component				
	Oil phase	**Surfactant (S)**	**Cosurfactant (CoS)**	**S:CoS ratio**	**Aqueous phase**
#1	IPM	RH40	PEG400	1:1	W
#2	IPM	RH40	PEG400	2:1	W
#3	IPM	RH40	-	-	W
#4	OA	RH40	PEG400	1:1	W
#5	OA	RH40	PEG400	2:1	W
#6	OA	RH40	-	-	W
#7	IPM	T80	PEG400	1:1	W
#8	IPM	T80	PEG400	2:1	W
#9	IPM	T80	-	-	W
#10	OA	T80	PEG400	1:1	W
#11	OA	T80	PEG400	2:1	W
#12	OA	T80	-	-	W
#13	IPM	T80	PEG400	2:1	2:1 W:PG
#14	IPM	T80	PEG400	1:1	2:1 W:PG
#15	OA	T80	PEG400	1:1	2:1 W:PG
#16	OA	T80	PEG400	2:1	2:1 W:PG
#17	OA	RH40	PEG400	1:1	2:1 W:PG
#18	OA	RH40	PEG400	2:1	2:1 W:PG
#19	OA	T80	PEG400	3:1	2:1 W:PG
#20	IPM	T80	PEG400	3:1	2:1 W:PG

2.4 *In vitro* drug release study

In vitro drug release of the prepared piroxicam-loaded MEs and a piroxicam commercial gel through dialysis membrane with molecular weight cut-off (MWCO) 3500 Dalton (Spectra/Por®3, Spectrum Laboratories, Inc., USA) was evaluated using modified Franz diffusion cells (Hanson Model 57-6 M, Hanson Research Corporation, USA). The membrane was cut into appropriate size and soaked in the receptor fluid for 30 min before placed between donor and receptor chambers of each diffusion cell with an effective release area of 1.77 cm^2 (14). A 3:1 mixture of PBS and ethanol was used as receptor fluid (16). The receptor chamber was filled with 12 mL of degassed receptor fluid and continuously stirred at a speed of 200 rpm by a magnetic bar. The diffusion cells were connected to a circulating water bath thermostated at 37 ± 0.5°C. Afterward, 1 g of each sample was placed onto the dialysis membrane in the donor chamber. At defined time intervals (0, 0.5, 1, 2, 3, 4, 5 and 6 h), 1 mL of receptor fluid was taken from each receptor chamber and immediately replaced with an equal volume of fresh receptor fluid. Each withdrawn receptor fluid was diluted with an appropriate amount of 0.1 M methanolic HCl and quantitatively analyzed using UV spectrophotometry technique (9, 15). Cumulative amounts of released piroxicam were calculated in terms of % of applied dose per area and eventually plotted against time to obtain release profiles. All experiments were carried out in triplicate.

2.5 Analysis of piroxicam

Drug analysis was performed by the previously reported UV spectrophotometry technique with some modifications (9, 15). Briefly, the samples were measured for the absorbance values at the wavelength of 334 nm by UV spectrophotometer (Spectronic Genesys 5, Milton Roy, USA) and 0.1 M methanolic HCl was used as the blank for zero settings. The drug amounts in the samples were finally calculated with the linear equation of the calibration curve. Before sample analysis, the calibration curve between absorbance values versus concentrations of piroxicam standard

solutions at 2, 4, 6, 8 and 10 μg/mL was validated for linearity with regression (r^2), slope and intercept of 0.999, 0.082 and 0.010, respectively. All experiments were done in triplicate.

3. Results and Discussion

3.1 Pseudoternary phase diagrams and ME regions

The ME regions in pseudopternary phase diagrams of the investigated systems were illustrated in Figure 1. It was found that ME formation could originate in all studied systems. It could be seen in Figure 1 that among the studied systems, the largest ME region was found in System #20 composed of IPM, 3:1 T80:PEG400 and 2:1 W:PG. The 3:1 T80:PEG400 and 2:1 W:PG could generate flexible curvature of the interfacial film between oil and aqueous phases. When compared between two investigated oils, IPM ($C_{17}H_{34}O_2$) could provide a larger ME region than OA ($C_{18}H_{34}O_2$) since its smaller molecules could easier penetrate in hydrophobic part of the interfacial film. These results were in good agreement with the previous works reported that both types and weight ratios of components affected ME formation according to curvature of the interfacial film and penetration of oil molecules in the lipophilic portion of the interfacial film (13, 14).

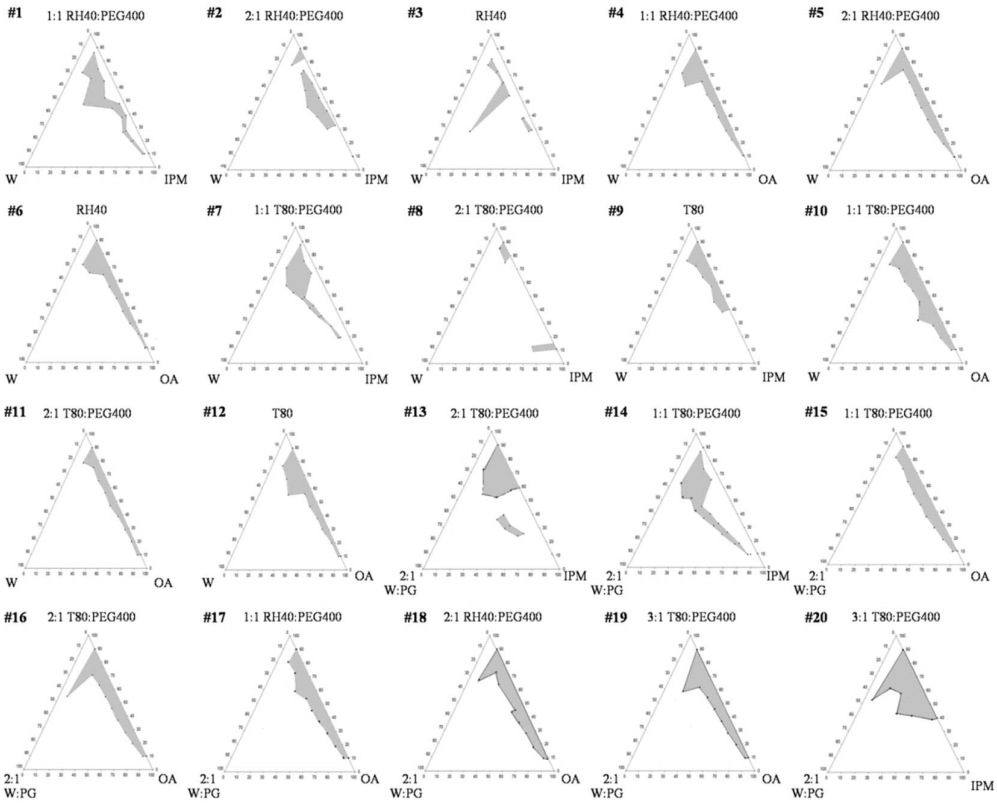

Figure 1 Pseudoternary phase diagrams showing ME regions (shaded areas) of twenty studied systems according to Table 2

3.2 Formulation and characteristics of blank MEs and piroxicam-loaded MEs

From the data in Figure 1, the largest ME region was observed in System #20 which is composed of IPM as oil phase, 3:1 T80:PEG400 as surfactant mixture and 2:1 W:PG as the aqueous phase. Hence, six points were chosen from the ME region of this system to prepare six blank MEs designated as ME1 to ME6. All blank MEs could be easily prepared by simply mixing due to spontaneous formation property (2-5). The obtained blank MEs were clear yellow liquids. Their composition and solubility tendency for incorporation with piroxicam was exhibited in Table 3. It was found that ME5 and ME6 can dissolve 1% w/w piroxicam while other MEs (ME1-ME4) cannot. It could be explained that ME5 and ME6 contained high ratio of T80, providing high solubility of piroxicam (9). Hence, the results indicated that the solubilization power of MEs depended on the formulation components.

Afterward, ME5 and ME6 were selected to prepare 0.5% w/w piroxicam-loaded MEs by dissolving 0.5% w/w of piroxicam into 99.5% w/w of each ME. The obtained piroxicam-loaded MEs were designated as ME5-P and ME6-P, respectively. Characteristics of the prepared ME5-P and ME6-P were shown in Table 4. Incorporation of 0.5% w/w piroxicam into ME5 and ME6 did not affect appearance. ME5-P and ME6-P were clear yellow liquids like their blank counterparts. Although the hydrophilic-lipophilic balance (HLB) value of T80 is high, ME5-P and ME6-P were w/o MEs due to more ratio of oil phase than that of aqueous phase (17). Both ME5-P and ME6-P had a stability tendency during the studied period since no change in appearance was found and percentages of drug remaining were higher than 90% after being stored at room temperature for six weeks (14).

Table 3 Components and piroxicam solubility tendency of the chosen blank MEs

Formulation	Component (% w/w)			Appearance after mixed with 1% w/w piroxicam (two folds of required content)
	IPM	3:1 T80:PEG400	2:1 W:PG	
ME1	55.15	40.35	4.50	Turbid with non-dissolved drug
ME2	49.38	40.92	9.70	Turbid with non-dissolved drug
ME3	44.87	49.58	5.55	Turbid with non-dissolved drug
ME4	34.37	49.95	15.18	Turbid with non-dissolved drug
ME5	40.07	55.54	4.39	Clear
ME6	33.59	55.15	11.26	Clear

Table 4 Characteristics of ME5-P and ME6-P

Formulation	After preparation		After kept for six weeks	
	Appearance	Dilution with brilliant blue solution	Appearance compared with initial	% Drug remaining
ME5-P	Clear yellow liquid	Immiscible	No change	99.7 ± 0.2
ME6-P	Clear yellow liquid	Immiscible	No change	99.5 ± 0.2

3.3 *In vitro* release of piroxicam from MEs and commercial gel

Figure 2 exhibited release profiles of two formulated 0.5% w/w piroxicam-loaded MEs (ME5-P and ME6-P) compared with that of a 0.5% w/w piroxicam commercial gel. It could be noted that amounts of released piroxicam followed the order of commercial gel > ME6-P > ME5-P. Additionally, a lag time of 0.5 h was observed in the release profiles of ME5-P and ME6-P.

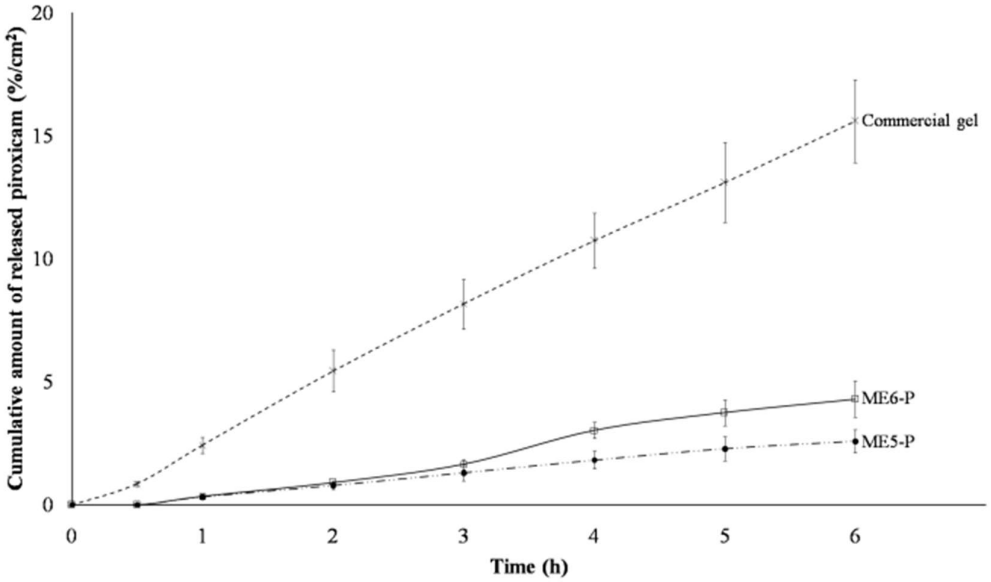

Figure 2 Release profiles of the investigated samples through the dialysis membrane

This phenomenon could be explained by the high affinity between drug and vehicle retarded the drug release (18). The commercial gel was hydrophilic, leading to low affinity with hydrophobic piroxicam. ME5-P was composed of a larger amount of oil phase than ME6-P. Hence, ME5-P provided higher affinity with hydrophobic piroxicam than ME6-P, resulting in lower drug release. The findings were in agreement with the previous study reported that increasing ratios of oil phase in MEs resulted in slow release of itraconazole, a hydrophobic antifungal drug, from the formulations (19). Moreover, location of the drug in ME microstructure could influence drug release. Due to its hydrophobicity, piroxicam was expected to be located in bulk of the external oil phase or entrapped with long hydrophobic tail of the surfactant arranging outward into external oil phase. Low and slow release of piroxicam from the prepared w/o MEs indicated that the drug location was possible near interface rather than in external phase. In addition, piroxicam was previously reported for its location in the palisade layer of interfacial film of T80-based ME system when measured by fluorescence spectra analysis (7). The o/w MEs prepared from 19% w/w OA, 13% w/w buffer, 24% w/w T80 and 44% w/w ethanol provided release of various antitubercular drugs to be sequenced in the order of isoniazid > pyrazinamide > rifampicin due to different location of each drug in ME microstructure, i.e., in external phase, near the interface and internal phase, respectively (20). The release of ibuprofen from MEs was reported to be less than that from hydrogel since the drug molecules were probably entrapped at the interface film of MEs (21). Although the release profiles inferred that both ME5-P and ME6-P were not proper to be used for pain relief, the obtained data revealed that the composition and microstructure of MEs may cause the adverse release of the loaded drug.

4. Conclusions

Our findings indicated that among twenty studied systems, the system of IPM/3:1 T80:PEG400/2:1 W:PG could provide the largest ME region. Six blank MEs obtained from this system showed the different capacity for solubilizing piroxicam due to the intrinsic solubilization power of the composition. Two prepared 0.5% w/w piroxicam MEs, i.e., ME5-P and ME6-P, were w/o MEs and clear yellow liquids. The stability tendency of ME5-P and ME6-P was implied by no changes in appearance and drug contents after kept at room temperature for the studied period of six weeks. Hindrance in drug release from the studied MEs was observed when compared with a commercial gel.

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Declaration of conflicting interests

The authors declared that they have no conflicts of interest in the research, authorship, and this article's publication.

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