Effects of components on and predictive modeling of microemulsion phase behavior in nonionic systems

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ABSTRACT

This study aimed to investigate phase behaviors, to study effects of cosolvent addition on size of microemulsion regions and to propose modified logistic regression which could describe microemulsion regions in nonionic systems. The systems composed of rice bran oil (RBO) or isopropyl palmitate (IPP), various ratios of sorbitan monooleate (SMO) and polyoxyethylene 20 sorbitan monooleate (PSMO) mixtures, water and isopropyl alcohol (IPA) or propylene glycol (PG) were studied for their microemulsion regions obtained on the phase diagrams. Concept of modified logistic regression was used to predict probability of microemulsion formation and size of microemulsion regions in the systems. It was found that both oil and cosolvent types affected on microemulsion formation. A system composed of IPP, 2:1 water:IPA, and 1:1 SMO:PSMO could provide the largest microemulsion region. However, the purposed modified logistic regression could be used consistently for only one system of the total four systems due to the faceted shape of microemulsion-zone.

INTRODUCTION

Microemulsions, one of well-known lipid-based colloidal formulations, have been recognized for their applications as drug delivery carriers and cosmetic vehicles. They are isotropic dispersions of oil and water stabilized by an interfacial film of a surfactant which can provide many advantages, i.e., good appearance, thermodynamic stability, high solubilization power, and ease of manufacture (Boonme, 2007; Souto *et al.,* 2011). However, microemulsions have usually composed of high concentration of a surfactant that might cause high risk of irritation. Hence, selection of microemulsion components should be carefully considered (Boonme, 2009). Nonionic surfactants are generally documented for lower toxicity and skin irritation potential than ionic ones (Ananthapadmanabhan *et al.,* 2009), and therefore they have been widely investigated as ingredients in skin microemulsions both for medicinal and cosmetic purposes (Junyaprasert *et al.,* 2007a; Boonme *et al.,* 2012).

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Additionally, a cosurfactant or a cosolvent has been reported that it can interact with the surfactant monolayer around microemulsion droplets, leading to increase the flexibility of the interfacial film and enlarge the size of microemulsion region (Alany *et al.,* 2000; Boonme *et al.,* 2006a; Boonme *et al.,* 2006b). Hence, it should be able an approach in reduction of surfactant concentration in a microemulsion formulation. Commonly, alcohols (e.g., ethanol, isopropyl alcohol) and polyhydroxy compounds (e.g., glycerin, propylene glycol) were recognized to act as a cosurfactant or a cosolvent (Boonme *et al.,* 2004; Azeem *et al.,* 2008).

Spontaneous formation of microemulsions results in ease of manufacture. They can be prepared by simple mixing of all components. No high energy input or specific instrument is required, leading to no problem in scaling up. However, finding suitable amount of each component in a microemulsion formulation consumes resources and times due to a phase diagram construction. In a system of oil, water and surfactant, microemulsions are only one form of among several association structures including emulsions, micellar and mesomorphic phases of various constructions such as lamellar, hexagonal, cubic, as well as various gels, and unstable dispersions (Eccleston, 1988; Lawrence and Rees, 2012).

Generally, a phase diagram can be constructed by two methods, i.e., preparation of various samples containing different ratios of components and titration of a mixture of two components (oil and surfactant) with the third component (water). If all mixtures reach equilibrium rapidly, there are no different results from both techniques. Nevertheless, if all mixtures do not reach equilibrium rapidly, the first method is recommended (Bhargava *et al.,* 1987). Mathematical descriptions are the alternatives for data representation of phase behavior of microemulsions such as artificial neural network (Alany *et al.,* 1999; Djekic *et al.,* 2008) and algebraic geometry (Boonme *et al.,* 2011).

This study aimed to investigate effects of components on microemulsion phase behavior in nonionic systems and to create novel predictive modeling equations of these systems.

MATERIALS AND METHODS

Materials

Polyethylene 20 sorbitan monooleate (PSMO), sobitan monooleate (SMO), and propylene glycol (PG) were purchased from P.C. Drug Center Co., Ltd. (Bangkok, Thailand). Isopropyl alcohol (IPA) was purchased from RCI Labscan Limited (Bangkok, Thailand). Rice bran oil (RBO) was purchased from Thai Edible Oil Co., Ltd. (Samut Prakan, Thailand). Isopropyl palmitate (IPP) was purchased from East Asiatic (Bangkok, Thailand). Distilled water was used throughout the experiments. All chemicals were of pharmaceutical grade and used as received without further purification.

Studies of phase behaviors of samples

Phase behaviors of samples were studied in two steps, i.e., without and with a cosolvent (IPA or PG). Either RBO or IPP was an oil phase while either water or a mixture of water and a cosolvent was an aqueous phase. A blend of PSMO and SMO at various ratios was as a surfactant mixture.

In the first step (construction of phase diagrams of nonionic systems without a cosolvent), preparation of various samples containing different ratios of components was used as previously reported (Boonme *et al.,* 2004; Suksawad *et al.,* 2009; Boonme *et al.,* 2011). Briefly, all components at the determined accurate weight were put in glass bottles and vigorously mixed by a vortex mixer for 1 min. The samples were left at ambient temperature for overnight in order to let them to achieve equilibrium. Afterwards, the samples were observed for their appearance and classified as microemulsions, emulsions, unstable dispersions, or gels when they were clear isotropic liquids, milky liquids, separated liquids, or semisolids, respectively. The data were finally plotted on the triangular graphs.

In the second step (construction of phase diagrams of nonionic systems with a cosolvent), titration method was used since it was previously found that the sample appearances after mixing and overnight leaving were identical, implying that the investigated systems could fast equilibrate. In this method, a mixture of oil and surfactant mixture at weight ratios of 1:9, 2:8,

3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 was titrated dropwise with a 2:1 water:cosolvent mixture. When transparent liquid samples were occurred, points in the triangular graphs were marked. After phase diagram construction on the triangular graphs, size of microemulsion region of each system was evaluated by cut-and weight method (Junyaprasert *et al.,* 2007b).

Prediction via modified logistic regression

The amount of each component in units of percent (%) was shown in phase behaviors of the nonionic systems on the phase diagrams. From experiment, the critical percentage of aqueous phase could be obtained.

To describe mathematically, it was assumed that microemulsions could not form in systems with higher aqueous, but enabled in systems with lower aqueous phase. These criteria were used to generate more data sets with the same oil and surfactant by varying aqueous phase and labeled them as "microemulsion" or "no microemulsion". The new generated data sets were forwarded to modified logistic regression. Regression was performed by in-house software. The odd ratio was a function of independent variables including the amount of oil (o) and surfactant (s). Since aqueous phase could be determined from o and s, it was not regarded as an independent variable. Modified logistic regression method was used as described in previous study (Wongpoowarak *et al.,* 2011). The odd ratio has been described by function of independent variables as shown in Eq. (1).

$$\log (Odd) = f (o, s, r) \qquad (1)$$

The units of o, s and r were expressed in percent in regression analysis. The scanning radius, r, was temporary variable that assist in grouping frequency in order to calculate the odd ratio. After logistic regression, r is extrapolated to zero, this function would be independent from r.

The log (Odd) in Eq. (2) was described empirically with multivariate polynomial functions by regression analysis and extrapolate to $r = 0$ using function with extrapolatable form of r, i.e., computable at $r = 0$.

$$\log (Odd) = f (o, s) \qquad (2)$$

The function describes the relationship between amount of each component (oil and surfactant) and probability of microemulsion formation (P) as shown in Eq. (3).

$$P = Odd/ (1+Odd) \qquad (3)$$

The microemulsion region in percent of total area of each phase diagram could be determined according to the following procedure. First, the varying amount of each component (i.e., oil, surfactant, water and cosolvent) was simulated randomly within the range 0 and 100 and the total sum must be 100. Such combination will be computed to check for emulsificability. By randomly repeated this process several times (N = 10,000,000 times), the probability of microemulsibility in the triangular diagram for could be known.
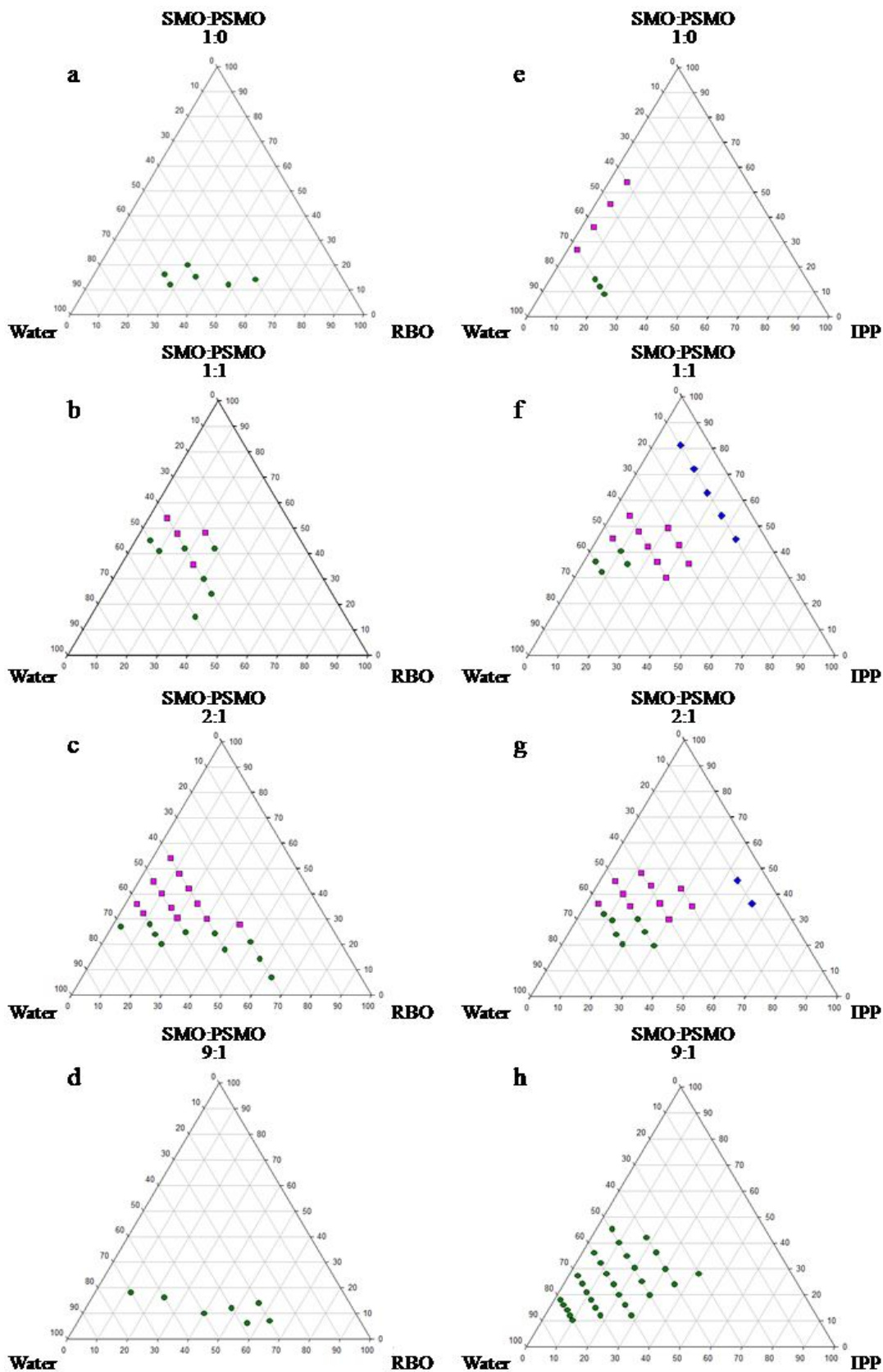
Fig. 1: Phase diagrams of the investigated nonionic systems containing RBO or IPP as an oil, SMO:PSMO at various ratios as a surfactant mixture, and water as an aqueous phase (circle: emulsion, square: gel, diamond: microemulsion, and white area: unstable dispersion)
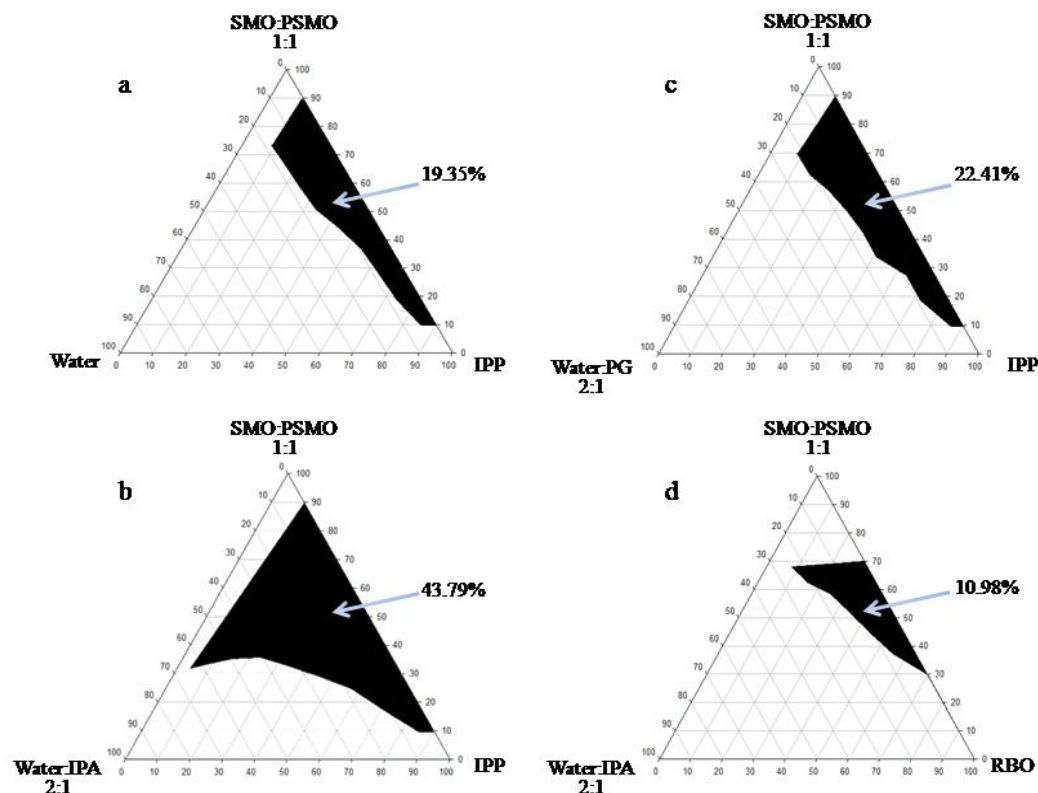
Fig. 2: Microemulsion regions reported as % of total area in phase diagrams of systems of (a) SMO:PSMO(1:1)/IPP/water, (b) SMO:PSMO(1:1)/IPP/water:IPA(2:1), (c) SMO:PSMO(1:1)/IPP/water:PG(2:1), and (d) SMO:PSMO(1:1)/RBO/water:IPA(2:1).

RESULTS AND DISCUSSION

Phase behaviors of samples

Phase diagrams of systems of RBO and water at various ratios of SMO:PSMO mixtures (1:0, 1:1, 2:1 and 9:1) in Fig 1(a-d) exhibited that association structures (i.e., emulsions, unstable dispersions, and gels) could form but microemulsions could not form in these systems. RBO contains high amount of linoleic acid in 20-42% of the total fat (Nicolosi *et al.,* 1992). This long chain and *cis* double-bond fatty acid might be too large to penetrate into the hydrocarbon portion of the rigid interfacial films of these 4 studied systems. When the oil phase was changed to IPP, some microemulsion points could be found as shown in Fig 1(e-h). However, they were not enough for further formulations of medicinal and cosmetic products. Hence, in the next step, a cosolvent (IPA or PG) was used for preparation of 2:1 water:cosovent mixture to act as an aqueous phase in the system containing IPP as an oil phase. The surface tension and dielectric constant of this phase was expected to be decreased and a large microemulsion region might be found. It could be obviously seen in Fig 2(b,c) that the systems with cosolvent addition gave larger microemulsion region than their cosurfactant-free counterpart in Fig 2(a) as anticipated. Type of cosolvent also affected size of the obtained microemulsion region. IPA could provide larger microemulsion region than PG. This phenomenon could be interpreted that IPA (C_3H_7OH) has lower oxygen content, dielectric constant, and surface tension than that of PG ($C_3H_8O_2$)

which was in consistence with the previous research (Alany *et al.,* 2000; Boonme *et al.,* 2004). When RBO was used instead of IPP in the system with the largest microemulsion region, formation of microemulsions could be observed but in lesser size of microemulsion region as shown in Fig 2(d) since a cosolvent could enhance flexibility of the interfacial film (Alany *et al.,* 2000; Boonme *et al.,* 2006a; Boonme *et al.,* 2006b).

The results suggested that incorporation of a cosolvent in aqueous phase could promote microemulsion formation; however, size of microemulsion region depended on both cosolvent and oil types (Boonthongchuay *et al.,* 2013).

Computational data

The microemulsion region (dark area in 4 systems in Fig 2) could be described by modified logistic regression model. Probability of microemulsion forming zone (*P*) was calculated from the Eq. (3). The odd ratio of microemulsificability was fit with regression analysis by using in-house software by one of the authors, the simplified results after extrapolation to $r = 0$ are as follows:

(I)   SMO:PSMO(1:1)/IPP/water system
Odd =   EXP(-7.555141 + 8.289037*X + 13.17805*Y + 6.724813*X^2 + 5.149009*Y^2 + 0.0122807*X*Y + (-4.640447)*X^3 + (-7.54514)*Y^3)

(II)   SMO:PSMO(1:1)/IPP/water:IPA(2:1) system
Odd = EXP(-3.989452 + (-6.415338)*X* + 10.09107*Y* + 19.60377*X*^2 + 13.23021*Y*^2 + 16.51494*X**Y + (-13.01325)*X*^3 + (-19.70038)*Y*^3)

(III)   SMO:PSMO(1:1)/IPP/water:PG(2:1) system
Odd = EXP(-6.311316 + 2.350736*X* + (-10.38001)*Y* + 11.53621*X*^2 + 34.51663*Y*^2 + 11.22662*X**Y + (-9.524601)*X*^3 + (-23.63385)*Y*^3 + 5.987874*Y*^(1/2))

(IV)   SMO:PSMO(1:1)/RBO/water:IPA(2:1) system
Odd = EXP(-12.10035 + 13.2768*X* + 14.94932*Y* + (-9.363487) *X*^2 + 0.1579124*Y*^2 + 8.125074*X**Y + 1.978377*X*^3 + (-5.46505)*Y*^3)

where: *X* = fraction of oil and *Y* = fraction of surfactant mixture.

The fraction area of microemulsion region was calculated as shown in Table 1. Microemulsions could form if calculated probability is higher than an arbitrary cut-off value. This cut-off value could be obtained from the average of calculated probability of microemulsifable group and non-microemulsificable group. This cut-off value should provide the lowest-as-possible prediction error. However, it was found that the actual size of microemulsion region in Fig 2 and the predicted one in Table 1 were different. The empirical polynomial function of modified logistic regression could desirably explain the size of microemulsion region of SMO:PSMO(1:1)/IPP/water:PG(2:1) system with the error less than 4% while more than 25% of error prediction was found in other studied systems. The main reason may be due to the faceted shape of microemulsion-zone which could not be described by a continuous function. The purposed function could explain well in case that water content microemulsion region was quite constant like in SMO:PSMO(1:1)/IPP/water:PG(2:1) system as illustrated in Fig 2(c).

Table. 1: Probability of microemulsion formation (*P*) and size of microemulsion region (% ME region) predicted via modified logistic regression.

Systems	*P*	% ME region
SMO:PSMO(1:1)/IPP/water	> 0.950	14.48
SMO:PSMO(1:1)/IPP/water:IPA(2:1)	> 0.660	61.46
SMO:PSMO(1:1)/IPP/water:PG(2:1)	> 0.756	23.28
SMO:PSMO(1:1)/RBO/water:IPA(2:1)	> 0.211	19.97

CONCLUSIONS

Many parameters could influence on microemulsion formation such as oil and cosolvent types. In this study, IPP could provide larger microemulsion region than RBO due to component structure for penetration in the interfacial film. IPA and PG could provide larger microemulsion area than cosolvent-free system, respectively.

Among investigated systems, a system composed of IPP, 2:1 water:IPA, and 1:1 SMO:PSMO could offer the largest microemulsion region which the optimal microemulsions might be able to be used in medicinal and cosmetic preparations. Describing all data sets with modified logistic regression proposed here could reduce the resource and time consumption. However, the attempt to describe all data sets with modified logistic regression could not be used consistently since the faceted shape of microemulsion-zone could not be described by a continuous function. The empirical polynomial function was not compatible with all actual geometries found in the study. This limits the applicability of this method.

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