Journal of Applied Pharmaceutical Science 01 (03); 2011: 57-61

Journal of Applied Pharmaceutical Science

Available online at www.japsonline.com

Received: 25-04-2011
Accepted: 03-05-2011

Using Algebraic Geometry to Describe Boundaries of Microemulsion Regions in Nonionic Systems

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ABSTRACT

This study aimed to propose an empirical polynomial function based on algebraic geometry which could represent microemulsion regions in nonionic systems. The systems composed of olive oil (OO), water (W) and various ratios of sorbitan monooleate (SMO) and polyoxyethylene 20 sorbitan monooleate (PSMO) mixtures were investigated for their microemulsion regions obtained on the phase diagrams. Concept of algebraic geometry in this study was that description of close-boundary shape was cross-sectioning of a 3D-geometrical object with a plane which could be explained by an empirical polynomial function of the {oil, water, surfactant mixture}. In-house *ad hoc* software was created according to the proposed concept. It was found that this method could describe boundaries of microemulsion regions in the studied systems. Although this method could not reduce time consumption since it required intensive computational powers, the software could automatically run. Moreover, the developed program could provide acceptable level of accuracy.

Key words: Microemulsions, Microemulsion region, Pseudoternary system, Algebraic geometry, Phase diagram

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INTRODUCTION

Microemulsions are defined as an isotropic dispersions of oil and water stabilized by an interfacial film of a surfactant and usually combined with a cosurfactant such as a polyhydroxy compound, a medium-chain alcohol or an another surfactant. They are of interest as carriers for many kinds of drugs such as dibucaine, lidocaine, tetracaine and their hydrochloride salts (Junyaprasert et al, 2007a, Junyaprasert et al, 2008), clindamycin phosphate (Junyaprasert et al, 2007b), and etc. In addition, they are of interest as cosmetic and cosmeceutical vehicles for skin, personal and hair products (Boonme, 2007; Boonme, 2009; Boonme et al., 2009; Boonme and Songkro, 2010; Boonme and Yotsawimonwat, 2011; Boonme et al., 2011). Microemulsions are widely used due to their several advantages, i.e., aesthetic appearance, thermodynamic stability, high solubilization power, ease of preparation and scaling up (Souto et al., 2011). Although microemulsions can be spontaneously formed by simply mixing the appropriate quantities of the components, the construction of a phase diagram is necessary since a diverse range of colloidal and coarse dispersions can be obtained from a system composed of oil, water, surfactant and cosurfactant. Types of the association structures formed in such systems are depended on ratios of the components (Eccleston, 1988; Lawrence and Rees, 2000). For simple microemulsions containing three basic components, i.e., oil, water and surfactant, the microemulsion regions can be investigated by constructing a ternary phase diagram on a triangular graph. However, in the case of pharmaceutical, cosmetic and cosmeceutical microemulsions, the systems always contain additional components such as a cosurfactant and/or an active compound and are known as quaternary or pseudoternary microemulsions (Eccleston, 1988). The phase behavior of a four-component mixture at fixed pressure and temperature can be exhibited using a tetrahedron (Alany

et al., 1999). A phase diagram can be constructed by two methods, i.e., titrating a mixture of two components with the third component and preparing a large number of samples of different ratios of components. If all mixtures reach equilibrium rapidly both methods give identical results. In contrast, if all mixtures do not reach equilibrium rapidly, the last method is recommended (Bhargava et al., 1987). However, full characterization is a tiresome work requiring a large number of experiments and consuming a lot of time. Abstraction of phase behavior of pseudoternary microemulsions with mathematical description is an alternative for data representation. Artificial neural network (ANN) model has been proved to be useful for representing microemulsion region (Alany et al., 1999; Djekic et al., 2008). Due to large scale network configuration, the conceptual diagram of the neural network is usually reported without showing the numerical details that could be used by other researchers. In order to exchange the detailed phase behavior of microemulsion systems, we proposed that to represent microemulsion region, partitioning the zone in the ternary plot with an empirical function would be a powerful alternative. In this study, algebraic geometry was applied for describing the microemulsion regions in pseudoternary systems composed of oil, water and two nonionic surfactants.

MATERIALS AND METHODS

Materials

Olive oil (OO), sorbitan monooleate (SMO) and polyoxyethylene 20 sorbitan monooleate (PSMO) were purchased from a local distributor, Thailand. Distilled water (W) was used throughout the experiments. All chemicals were of pharmaceutical grade and used as received without further purification.

Studies of phase behaviors of samples

The phase behavior of a four component mixture at constant pressure and temperature can be represented with a tetrahedron. In this study, five slices within a tetrahedron were selected at constant SMO:PSMO ratios of 2:1, 1.5:1, 1:1, 1:1.5 and 1:2 as illustrated in Figure 1.

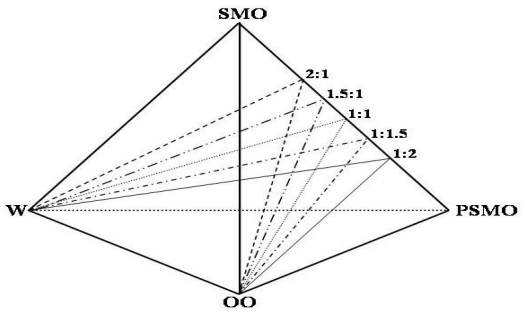

Fig 1. Four component tetrahedron demonstrating the position of the samples formulated at five different ratios of the studied surfactant mixtures. W: water; OO: olive oil; SMO: sorbitan monooleate; PSMO: polyoxyethylene 20 sorbitan monooleate.

For sample preparation, SMO and PSMO were mixed at a weight ratio of 2:1, 1.5:1, 1:1, 1:1.5 or 1:2 to obtain a surfactant mixture. Each surfactant mixture and OO were then mixed at the ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1. Calculated amount of W was added to give water concentrations in the range of 0-90% by weight at 10% intervals. The samples were prepared by adding an appropriate amounts of each component in the individual tubes, vigorously mixed and left for 24 hours to equilibrate. The obtained samples were classified as microemulsions when they appeared as clear isotropic liquids, as emulsions when they appeared as milky liquids and as gels when they did not show a change in the meniscus after tilting to an angle of 90° (Boonme et al., 2004; Suksawad et al., 2009).

The pseudoternary phase diagram of each system was constructed on a triangular graph to obtain microemulsion region. The first and second corners represented 100% of OO and W, respectively while the third corner referred to 100% of a binary mixture of SMO and PSMO. A cut-and-weigh method was used to determine the percentage of the total area of the phase diagram covered by the microemulsions (Junyaprasert et al, 2007b). No attempts were made to identify the regions of other association structures.

Algebraic geometry calculation

The microemulsion region is the area in two-dimension in the case of pseudoternary plots. However, closed-shape in two dimensions is difficult to describe with simple algebraic functions, but it is much easier to describe it with cross sectioning of two geometrical objects. For example, by intersecting a cone (three-dimension volume) with a plane (two-dimension surface), various cross sectional shapes could be obtained, i.e., circle, ellipse, hyperbola, or parabola in two-dimension surface. In this analogy, an intersection of asymmetrical geometrical objects could provide an asymmetrical boundary representing a ternary plot. This algebraic geometry was a more concise form of data representation.

RESULTS AND DISCUSSION

Phase behaviors of samples

The phase diagrams exhibited microemulsion regions originated in the studied systems were constructed as shown in Figure 2. The systems composed of SMO and PSMO at a weight ratio of 2:1, 1.5:1, 1:1, 1:1.5 and 1:2 possessed the percentage of the total area of the microemulsion region in the phase diagram of 3.71, 16.40, 14.33, 12.06 and 12.06, respectively. Besides microemulsions, other types of the association structures were found in the studied systems, i.e., emulsions and hazy gels crystals as illustrated in Figure 3.

For the ratios of SMO:PSMO at 2:1, 1.5:1, 1:1, 1:1.5 and 1:2, the maximum amounts of water that were able to be included in the microemulsions were around 4%, 18%, 16%, 14% and 13%, respectively. It could be noted that when ratio of SMO:PSMO was changed from 2:1 to 1.5:1, the maximum concentration of water was markedly increased from 4% to 18% due to the reduction of SMO, hydrophobic surfactant of the system. The 1.5:1 ratio could incorporate the highest amount of water and provide the largest microemulsion region. When the ratios of SMO were further decreased, both amounts of entrapped water and microemulsion regions were lower. The reason was unclear. However, the

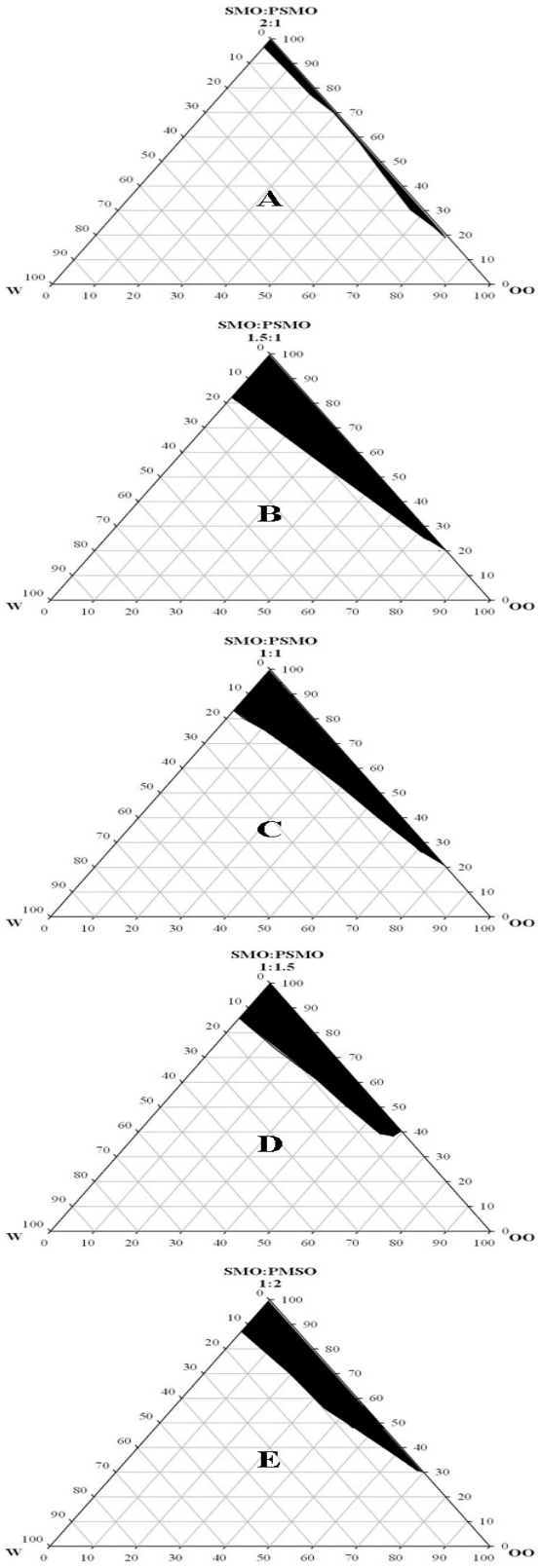

Fig 2. The pseudoternary phase diagram of OO, W and mixture of SMO:PMSO at ratios of (A) 2:1, (B) 1.5:1, (C) 1:1, (D) 1:1.5 and (E) 1:2. The shaded areas represented the microemulsion regions.

phenomenon might be explained that SMO:PSMO at the ratio of 1.5:1 may provide the optimum complex film at the OO and W interface.

Computational data

Close-boundary shape in two-dimension could be constructed by cross-sectioning of a 3D-geometrical object, described by an empirical polynomial function of the {oil, water, surfactant mixture}, with a plane.

Let q = function of (oil, water, surfactant mixture), where q is an empirical polynomial function and if $q>k_0$, microemulsion will be formed, where k_0 is an empirical value. If f is 3D-volume described by empirical polynomial function, to cross section it with a plane, k_0, a region containing all datasets in two-dimension would be created. Describing multiple zones is also possible if the proper form of q is used, i.e., a polynomial function with high degree.

Geometrical interpretations of this concept are (i) the compositions of such formulation would determine the microemulsion-forming capability designated as f, (ii) if f reaches a critical value, k_0, the microemulsion would be formed and (iii) q and the critical value is not real entity to be observed, it is only a mathematical abstraction of emulsificability. However, its accuracy of prediction was observable, for it can be adjusted in order to best represent the observed behavior. In this study, the predictor function had the following empirical forms.

$$q = k_1V_1^3 + k_2V_2^3 + k_3V_3^3 + k_4V_1^2 + k_5V_2^2 + k_6V_3^2 + k_7V_1 + k_8V_2 + k_9V_3 + k_{10}V_1V_2 + k_{11}V_2V_3 + k_{12}V_1V_3 + k_{13}V_1^2V_2 + k_{14}V_1^2V_3 + k_{15}V_2^2V1 + k_{16}V_2^2V_3 + k_{17}V_3^2V_1 + k_{18}V_3^2V_2 + k_{19}V_1V_2V_3 + k_{20}V_1^4 + k_{21}V_2^4 + k_{22}V_3^4 + k_{23}V_1^2V_2^2 + k_{24}V_2^2V_3^2 + k_{25}V_1^2V_3^2 + k_{26}\sin(0.001k_{27}(V_1V_3-V_2V_3)) + k_{28}\cos(0.001k_{29}(V_1V_2 - V_2V_3))$$

If $q>k_0$ then Microemulsion = YES otherwise Microemulsion = NO.

Fig 3. Examples of the association structures: (A) microemulsions, (B) emulsions and (C) gels, which could be formed when mixing of OO, W and 1:1 SMO:PSMO at different concentrations or at different areas in the phase diagram of Fig 2C.

The last two terms introduced trigonometric expressions in order to increase the nonlinearity into the overall expressions. This strategy could avoid very high degree polynomial terms and

reduce the parameters to within 30 terms with satisfactory results. The values of *k*'s (unknown parameters) were varied arbitrarily until the above relationship could best describe all data sets (criterion 1) and maximize the microemulsion-forming region simultaneously (criterion 2). The values of simulated *k*'s which were obtained in this study are exhibited in Table 1.

Table 1. Values of simulated *k*'s used in the proposed equation

k	value
k_0	-635.9693332
k_1	-753.3093465
k_2	875.6350438
k_3	1585.212594
k_4	203.4937459
k_5	2405.660081
k_6	550.3989015
k_7	179.8718875
k_8	-710.9784309
k_9	-83.93805389
k_{10}	1991.134995
k_{11}	983.7563625
k_{12}	1287.906159
k_{13}	707.3354752
k_{14}	1573.478681
k_{15}	1671.536936
k_{16}	-976.6816511
k_{17}	-520.3435945
k_{18}	2231.078796
k_{19}	2930.947274
k_{20}	-510.2901524
k_{21}	288.5566438
k_{22}	-2712.589814
k_{23}	-732.5222727
k_{24}	2155.803698
k_{25}	-2195.906253
k_{26}	217.16629
k_{27}	716.660029
k_{28}	-1349.062461
k_{29}	-175.3116916

The process of finding all *k*'s was very slow and computation-intensive. Fast numerical search algorithm could speed up this process. Heuristic random optimization algorithm (Li and Rhinehart, 1998) was modified and implemented in an in-house *ad hoc* software in order to find all the unknown parameters that satisfy both predefined criteria, i.e., best fit to the dataset and maximize the microemulsion-forming region. After obtaining all the unknown parameters, the areas of the microemulsion-forming regions were computed by Monte Carlo integration method.

The concept of Monte Carlo integration method in one-variable graph was that if the average height of any curve could be found, the area under the curve was the average height multiplies with the base width. Random samplings at arbitrary positions could provide average height. This method could be extended to multivariable integration due to the ease of implementation and acceptable accuracy by similar analogy. The area fraction of the region in the ternary plot was equal to the probability that the microemulsion would be formed by randomly varying the content of oil, water, and surfactant mixture. By simulating a formulation randomly, we could use the aforementioned function to predict if the microemulsion could be formed or not. Perform these procedures repeatedly and the probability of microemulsion forming could be computed directly from its mathematical function. This probability has the same meaning as fraction of the total area of the microemulsion forming regions in the phase diagrams.

Confidence interval of the calculated area fraction

It was found that the proposed function could provide correct description of microemulsion regions in the investigated systems when compared with the experimental data as presented in Table 2. The best soluble capability was 0.11166. The proposed function provided the best description for the system composed of 1:1 SMO:PSMO (%correction = 97.0%). The percentage of correction in description of microemulsion regions via the proposed function was lower when the ratios of SMO:PSMO were different from 1:1. However, the percentages of correction for all studied systems were more than 90%, resulting in desirable description. Therefore, large amount of the experimental data in phase diagram construction for finding the microemulsion regions could be encapsulated in an empirical polynomial function of the {oil, water, surfactant mixture}.

Table 2. Percentage of correction in description of microemulsion regions via the proposed function

SMO:PSMO	%Correction
2:1	92.3
1.5:1	94.0
1:1	97.0
1:1.5	90.2
1:2	90.9

One could prove that the accuracy of such numerical integration method varies inversely with square root of simulation sizes. Let *p* is the probability to obtain microemulsion zone and *N* is the sampling size. Since the standard error of *p* could be described by binomial distribution, i.e.,

$$SE(p) = \sqrt{\frac{p(1-p)}{N}}$$

where *SE*(p) is the standard error of *p*. Since *p*(1-*p*) always less than 0.25 for all *p* between 0 and 1, the 95 % confidence interval for *p* in this process could be approximated by

$$1.96\sqrt{0.25}/\sqrt{N} \text{ or } 0.98/\sqrt{N}$$

For example, with 10^6 simulations the reliability should be approximately 3 significant digits. This simulation size was affordable and the level of accuracy was acceptable for practical purpose.

CONCLUSION

Full characterization in construction of a phase diagram to find a microemulsion region is a tedious work requiring a large number of experiments and consuming a lot of time. Describing all data sets with algebraic geometry concept proposed in this study could be analyzed by an in-house *ad hoc* software to present geometrical boundaries of microemulsion regions in the investigated nonionic systems with acceptable level of accuracy. The main disadvantage of this method was the requirement of intensive computational powers. However, with fast improvement in computer speed, this method is potentially useful method for representing massive database with a more concise mathematical form.

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