

Physico-chemical evaluation of a biocompatible microemulsion system containing IPM/Tween80/Isobutanol

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Abstract

A biocompatible microemulsion system comprising of isopropyl myristate (IPM) as oil, tween 80 as a non-ionic surfactant and isobutanol as co-surfactant, was studied experimentally at 298.15 K. The pseudo-ternary phase diagram for the microemulsion system has been delineated at different surfactant to co-surfactant mass ratio of 1:1, 2.4:1 and 4:1. Some physico-chemical properties such as density, viscosity, refractive index, conductivity and pH, for a typical surfactant to co-surfactant mass ratio of 2.4:1 were determined precisely. It is verified that the transition point of viscosity, conductivity, refractive index and density occurs at about 30 wt% of water. The transition point could be attributed to either the change in the shape of droplets or the transition from o/w microemulsion phase to bicontinuous phase.

Keywords: Microemulsion vehicles; phase diagram; viscosity; density; conductivity.

Introduction

Microemulsions are thermodynamically stable and isotropic clear dispersions of oil, water and surfactant (and/or co-surfactant) mixtures, which have high stability, low viscosity and transparency [1,2]. These systems which have nanometer-sized droplets have been used in various fields, such as pharmaceuticals, cosmetics, nanoparticle synthesis, nanocomposites, biotechnology and food industry [3-7]. Because of the presence of hydrophobic and hydrophilic components as parts of the structure, microemulsion systems may serve as vehicles for drugs of different solubility. To study the drug-delivery potential of microemulsion vehicles, it is necessary to characterize

the microstructure of pure microemulsion systems.

The microemulsion region is usually characterized by a ternary-phase diagram. It is worth mentioning that phase study helps to determine different phases that exist in the region depending on the composition ratios, so that both water-in-oil (w/o) and oil-in-water (o/w) microemulsions may be formed [8,9]. Water-in-oil microemulsion consist of nanometer-sized domains of water, stabilized by a monolayer of the surfactant, dispersed in the continuous oil phase and topologically is similar to reverse micelles. Oil-in-water microemulsion can be formed when oil droplets are dispersed in the continuous aqueous phase.

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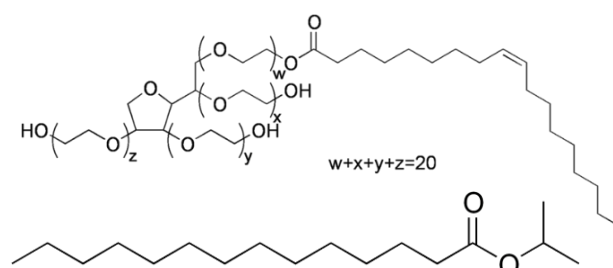
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Physico-chemical and electrochemical characterization of microemulsion are currently receiving considerable attention due to their potential implications in chemical, electrochemical and biochemical processes. In this sense, extensive reviews on the physico-chemical and general pattern of the phase behavior, properties, microstructure of microemulsions are available [10]. Evaluation of microemulsions is generally related to the phase transitions from o/w to w/o through bicontinuous phase. Different experimental approaches can be monitored to study the individual microemulsion phases and phase transitions. The changes in the internal structure of a microemulsion or nanoemulsion system can be monitored by analyzing some physico-chemical properties such as conductivity, viscosity, density and refractive index [11-15].

In order to construct a pharmaceutically accepted

microemulsion system, one has to know its physico-chemical properties [16]. In this study, a pharmaceutically useful non-ionic microemulsion system composed of tween 80 (Polyoxyethylene (80) sorbitan monooleate), isobutanol, isopropylmyristate (IPM) and pure water has been investigated. Tween 80, as illustrated in scheme 1 (a), was selected as a non-ionic surfactant in this formulation, due to the fact that it was less affected by pH and ionic strength changes and can also enhance the permeability into cell membrane [17]. Isobutanol was chosen as co-surfactant due to its ability to form transparent and stable microemulsion. In principle, a co-surfactant with very low HLB and a surfactant with a high HLB are used together to change the general HLB of the system [18]. Short to medium chain length alcohols (C3-C8) are commonly added as co-surfactants which further reduce the interfacial tension and increase the fluidity of the interface.



Scheme 1. Chemical structure of (a) Tween 80 and (b) IPM

The used oil is the IPM, a liquid with low viscosity that is practically colorless and odorless and decomposed at 208 °C. IPM, as illustrated in scheme 1 (b), is a very useful oil in cosmetics and topical medicinal preparation as emollients and lubricant [19]. After construction of pseudo-ternary phase diagram, some physico-chemical properties such as density, viscosity, refractive index, conductivity and pH for the mentioned

microemulsion system were precisely determined at 298.15 K.

Experimental

General

The non-ionic surfactant tween 80 (Polyoxyethylene (80) sorbitan monooleate), isobutanol and IPM were obtained from Merck. All chemicals were used as received. The microemulsion systems were prepared with Milli-Q purified water.

The electric conductivity measurements were carried out to show the effect of water dilution on microemulsion structure. The electric conductivity (σ) was measured by means of Metrohm712 digital conductivity meter with precision of $\pm 10^{-3}$ μs . The constant of the conductivity cell was calibrated using standard KCl solutions. The electrode was dipped in the microemulsion sample until equilibrium was reached and reading becomes stable.

Viscosities (η) were measured using a rotational type programmable viscometer (LV DV-II+ Brookfield, Inc., USA) with a small sample adapter. The adapter consisted of a cylindrical sample holder, a water jacket and spindle. The viscometer drives the spindle immersed into the sample holder containing the test fluid sample. A wide range of spindle speeds are available in this viscometer (0–200 RPM). The spindle type and speed combinations will produce satisfactory results when the applied torque is between 10% and 100%; therefore spindle types and speeds are selected in such a way that the torque values lie in this prescribed range. The temperature of the test sample is monitored by a temperature sensor embedded into the sample holder. The viscometer is connected to a computer which records the data automatically. The data collection is done by software (Wingather) which collects spindle RPM, torque, viscosity, shear stress, shear rate, temperature and time. The model has a specified accuracy of $\pm 1\%$.

The densities (ρ) of the various IPM/tween 80/isobutanol/water microemulsion solutions were measured using a Mettler Toledo densimeter

(DE51) with precision of $\pm 1 \times 10^{-5}$ g/cm^3 . The temperature of the vibrating tube in the densimeter was controlled to within ± 0.01 K. The densimeter was calibrated before each set of density measurement using the density of air and pure water.

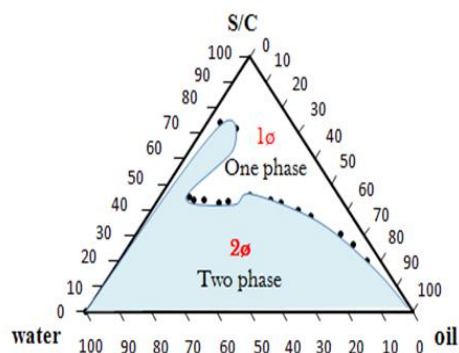
Refractive index (n_D) of the microemulsion samples was measured by Mettler Toledo refractometer with temperature control (RE50). The precision of the refractive index determination was $\pm 10^{-5}$. The refractometer was calibrated using the refractive index of pure water. pH of the all microemulsion samples was determined by Metrohm 691 pH meter.

General procedure for Microemulsion formulation and phase diagram preparation

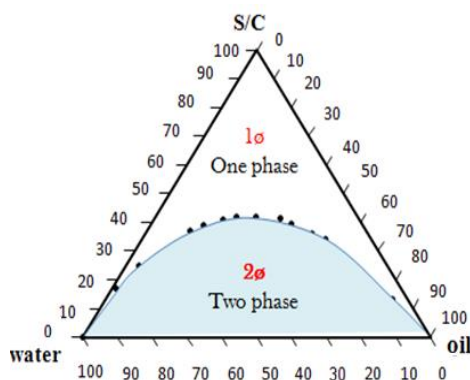
The pseudo-ternary phase diagram was mapped using IPM as oil, tween 80 (with HLB = 15) as surfactant and isobutanol as co-surfactant. A microemulsion phase was identified as the area in the phase diagram where a clear and transparent formulation was produced based on visual inspection of many samples. Combination of IPM and distilled water as aqueous phase were used at different volume ratios in different glass vials. Each combination of oil and water was titrated with surfactant/co-surfactant mixtures, with magnetic stirring at room temperature till transparency persisted. The volume ratios of surfactant to co-surfactant were fixed at 1:1, 2.4:1 and 4:1.

Results and discussion

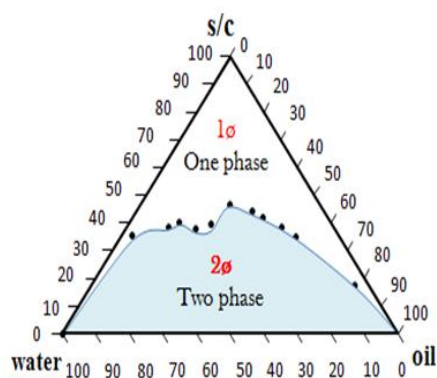
Pseudo-ternary phase diagrams were constructed at 298.15 K to obtain the appropriate components and their concentration ranges of the microemulsion existing zone.



(a)



(b)



(c)

Figure 1. Pseudo-ternary phase diagrams of microemulsion systems containing IPM/tween80/isobutanol with different tween80/isobutanol ratios: (a) 1:1, (b) 2.4:1 and (c) 4:1

Three different surfactant/co-surfactant ratios of 1:1, 2.1:1 and 4:1 were chosen and phase diagrams constructed as shown in Figure 1. In these diagrams the stable microemulsion

one phase region (1ϕ) has been separated from two-phase region (2ϕ) by a phase boundary curve. The microemulsion existing region for 2.4:1 ratio (Figure 1. b) was comparatively

larger than 1:1 and 4:1 ratios (Figure 1. a and c); hence microemulsion system with 2.4:1 ratio of surfactant to co-surfactant was selected for more study.

In order to determine the physico-chemical properties of microemulsion systems, six points (A to F) were chosen into the stable region of the phase diagram as shown in Figure 2.

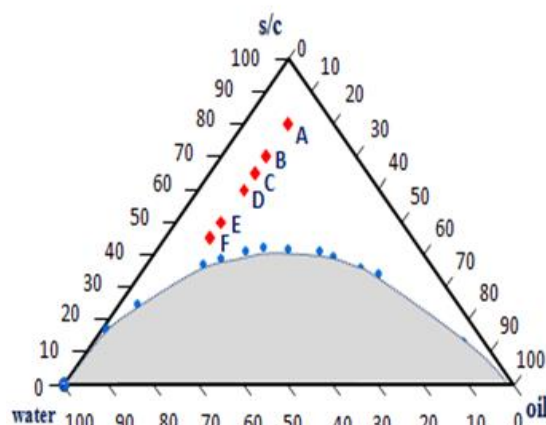


Figure 2. Showing the position of the investigated microemulsion systems in the phase diagram

The composition of the chosen formulations (shown as A-F in Figure 2) has been collected in Table 1, as weight

percent. All points are in microemulsion stable region at constant oil percent.

Table 1. Composition of six formulations for IPM/tween80/isobutanol microemulsion systems was indicated in Figure 2.

Sample	Water (wt%)	S/C (wt%)	Oil (wt%)
A	10	80	10
B	20	70	10
C	25	65	10
D	30	60	10
E	40	50	10
F	45	45	10

For the selected microemulsion systems, electrical conductivity, viscosity, density, refractive index and pH were precisely measured and reported in Table 2. The experimental results of conductivity, viscosity, density and refractive index are plotted against weight percent of water in Figure 3.

Electrical conductivity results

Electrical conductivity data provide a simple and inexpensive technique for

microemulsion characterization. The conductivity measurement technique can be used to determine the type of microemulsion, and to estimate phase boundaries resulting from changes in composition or temperature [20]. As can be seen from conductivity data reported in Table II and plotted in Figure 3 (a), the conductivity is initially low (point A) and a small increase is observed with increasing water content up to point D (30 wt% of water). With increasing water content more than 30 wt%, the

electrical conductivity is increased rapidly. Obviously, the low conductivity data indicate limited water mobility. The great changes in conductivity (break in the slope of conductivity curve at 30 wt% of water) with water dilution can be attributed to onset of phase inversion from direct micelles (w/o) to bicontinuous structure. In principle, the

change in the internal structure could be due to either the change in the shape of droplets or the transition from o/w or w/o microemulsion to bicontinuous phase [21]. The transition point of conductivity data was observed at around 30% weight fraction of water in microemulsion system.

Table 2. Experimental values of conductivity, viscosity, density, refractive index and pH of the microemulsion systems were indicated in Figure 2.

Sample	Conductivity ($\mu\text{s}/\text{cm}$)	Viscosity (cp)	Density (gr/cm^3)	Refractive index	pH
A	2.7	88.6	0.97463	1.43955	7.4
B	6.3	94.6	0.97811	1.42997	6.9
C	9.4	100.9	0.98059	1.42574	6.6
D	14.2	124.7	0.98523	1.42199	6.2
E	30.2	98.9	0.98631	1.41160	6.1
F	40.0	196.1	0.98683	1.39070	6.0

Dynamic viscosity results

The viscosity of a solution is sensitive to interactions forces and it is a kind of technique to study molecular interactions in the systems of known structure. The change in viscosity with the increase in water content should be correlated to compositional and structural effects from the microemulsion. As can be seen from Figure 3 (b), at water content below 30 wt %, the viscosity of microemulsion systems was slowly increased. For water contents between 30 wt % and 40 wt %, the viscosity of the microemulsion systems was decreased and above 40 wt % of water content a sharp decrease in the viscosity can be observed. The increase in the dynamic viscosity for water contents below 30 wt % indicates an increase in the degree of hydration of the hydrophilic head groups of tween 80 and also to the presence of isobutanol, which increases the hydrophilicity of the tween 80. With major dilution, between 30 wt% and 40 wt%, first a decrease and

then a sharp increase in the viscosity can be seen. This behavior may be related to gradually transition of the microemulsion structure from w/o to bicontinuous phase and then to o/w.

Density results

Density values for points A to F, reported in Table II, show increase with increasing the weight fraction of water at constant oil content. However, the increasing rate of the density data from A to D is more than D to F. It means that at about 30 wt% of water content (point D), the microemulsion structure is changed as confirmed with conductivity and viscosity data. The change of structure could be attributed to incorporation of internal droplets to form the interfacial monolayer with increasing water¹⁴. This interesting trend of density data is shown in Figure 3 (c).

Refractive index results

Essentially the refractive index of a solution is dependent on the internal

structure of the microemulsion system. As can be seen from experimental refractive index data reported in Table II and shown in Figure 3 (d) the gradual increase of the water content leads to two readily distinguishable linear

dependencies. As mentioned above, this behavior may be related to transition of different microemulsion structures at water contents between 30 wt% and 40 wt%.

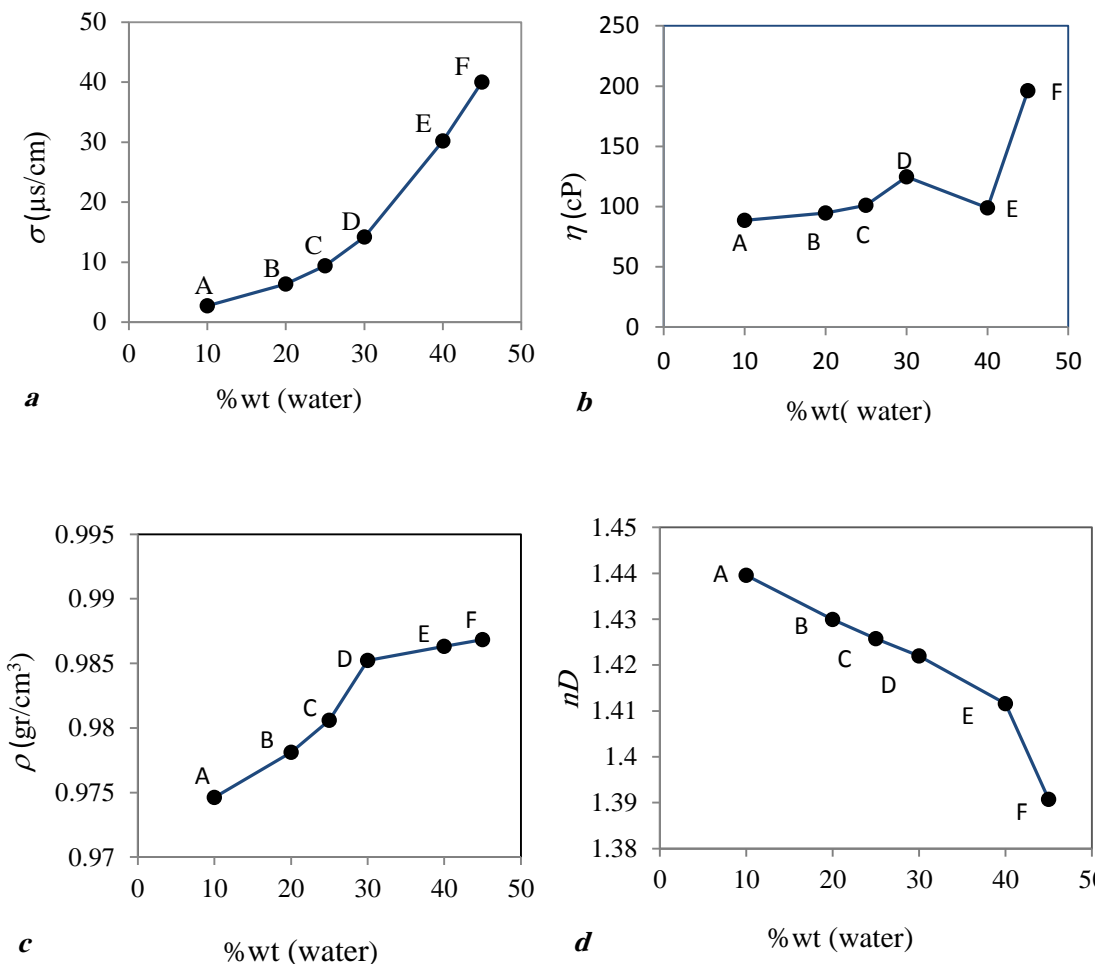


Figure 3. Variation of electrical conductivity (a), dynamic viscosity (b), density (c) and refractive index (d) of the microemulsion systems

Conclusion

A microemulsion system with pharmaceutical used for drug encapsulation and delivery has been developed and characterized by physico-chemical methods. The pseudo-ternary phase diagram for IPM/tween/isobutanol/water microemulsion system, at different surfactant to co-surfactant mass ratio of 1:1, 2.4:1 and 4:1, was constructed. The

variation of dynamic viscosity, conductivity, refractive index and density with water content for some stable microemulsion systems was studied. As an interesting result, the transition points of viscosity, conductivity, refractive index and density occur at about 30 wt% of water. The break in the slope of the physico-chemical properties against water content is possibly due to the change in

the microstructure of the microemulsion system. The change in the internal structure could be due to either the change in the shape of droplets or to the transition from o/w microemulsion to bicontinuous phase.

Acknowledgements

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References

- [1] J. Eastoe, In: T. Cosgrove (editor) *Colloid science: principles, methods and applications*, Blackwell Publishing; **2005**, P. 77.
- [2] J. Eccleston, In: J. Swarbrick, J.C. Boylan (editors). *Encyclopedia of Pharmaceutical Technology*. vol. 9. New York, NY, Marcel Dekker, **1994**, P. 375.
- [3] N. Grampurohit, P. Ravikumar, R. Mallya, *Ind. J. Pharm. Edu. Res.*, **2011**, 45, 100-107.
- [4] A. Salabat, F. Dehghani Sanij, *Bull. Korean Chem. Soc.*, **2012**, 33, 3387-3390.
- [5] S.P. Moulik, A.K. Rakshit, *J. Surface Sci. Technol.*, **2006**, 22, 159-186.
- [6] A. Salabat, H. Saydi, *Polym. Composite*, **2014**, 35, 2023-2028.
- [7] G. Shishu, A. Prabhleen, K. Neeraj, P. Ashana, *AAPS PharmSciTech*, **2014**, 15, 810-821.
- [8] T. Schmidts, P. Nocker, G. Lavi, J. Kuhlmann, P. Czermak, F. Runkel, *Colloid Surf. A: Physicochem. Eng. Aspects*, **2009**, 340, 187-192.
- [9] A. Salabat, J. Eastoe, K. J. Mutch, R. F. Tabor, *J. Colloid Interf. Sci.*, **2008**, 318, 244-251.
- [10] R. Sripriya, K. Muthu Raja, G. Santhosh, M. Chandrasekaran, M. Noel, *J. Colloid Interf. Sci.*, **2007**, 314, 712-717.
- [11] A. Kajbafvala, A. Salabat, A. Salimi, *Pharm. Dev. Technol.*, in press; doi.org/10.1080/10837450.2016.1263995.
- [12] S.K. Mehta, G. Kaur, K.K. Bhasin, *Colloid Surf. B: Biointerfaces*, **2007**, 60, 95-104.
- [13] S. Hickey, S.A. Hagan, E. Kudryashova, V. Buckina, *Int. J. Pharm.*, **2010**, 388, 213-222.
- [14] X. Dong, X. Ke1, Z. Liao, *Drug Dev. Ind. Pharm.*, **2011**, 37, 894-900.
- [15] C.A. Ayannides, G. Ktistis, *J. Cosmet. Sci.*, **1999**, 50, 1-7.
- [16] S.K. Mehta, G. Kaur, K.K. Bhasin, *Pharm. Research*, **2007**, 25, 227-236.
- [17] X. Fua, F. Feng, B. Huang, *Inter. J. Pharm.*, **2006**, 321, 171-175.
- [18] A.S. Narang, D. Delmarre, D. Gao, *Inter. J. Pharm.*, **2007**, 345, 9-25.
- [19] M. Fanun, W.S. Al-Diyn, *Colloid Surf. A: Physicochem. Eng. Aspects*, **2006**, 277, 83-89.
- [20] D.P. Acharya, P.G. Hartley, *Curr. Opin. Colloid Interf. Sci.*, **2012**, 17, 274-280.
- [21] A. Kogan, A. Aserin, N. Garti, *J. Colloid Interf. Sci.*, **2007**, 315, 637-647.