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Research Article

THE EFFECT OF SURFACTANT BLENDS ON THE PRODUCTION OF A NOVEL *SWIETENIA MACROPHYLLA* OIL SELF-NANOEMULSIFYING SYSTEM

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ABSTRACT

The growing demand of consumers and the advances in knowledge about production and stability of dispersed systems enable the development of differentiated vehicles such as nano-emulsions, which have been effectively used to increase the bioavailability and improve the stability of the active ingredients. Nowadays there is an intensely usage of natural bioactive materials as medicinal agent in pharmaceutical industries. *Swietenia macrophylla* is one of the most important plants of the family, Meliaceae. This plant has various types of medicinal values like antimalarial and antidiarrhoeal effects and it has been reported for its biological activities. Therefore, *Swietenia macrophylla* oil was used to select appropriate surfactants or blends of surfactants to study the ternary phase diagram behavior on the formulation of oral nano-emulsion as self-nanoemulsifying system. Nonionic surfactant blends of Tween 80, Labrafil, Cremophor EL, Waglinol and Capmul MCM series were screened based on their solubilization capacity with water for palm kernel oil esters. Five blends of Surfactants/co-surfactants were selected to study the phase diagram behavior of *Swietenia macrophylla* oil. The oil droplets size, size distribution, spreading time, appearance and viscosity were studied. Different oil/surfactants combinations showed different emulsification properties with relation to droplets size. It was found that the combinations which contain Tween 80 as one of the surfactants produced nano-size droplets. Therefore Tween 80 was considered as a good surfactant in producing self-emulsifying system. Self-nanoemulsifying formulations with different oil concentrations ranged from 20 to 50% was developed using Tween 80/Labrafil in the ratio of 2:1 and Cremophor EL/Waglinol in the ratio 1:2. Nanoemulsion was produced with droplets size below 200 nm formed upon gentile agitation with water with low polydispersity < 0.2. This study suggests that the phase diagram behavior of *Swietenia macrophylla* oil surfactant and co-surfactant is affected by the HLB value. The information gathered in this study is useful for researchers and manufacturers interested in using *Swietenia macrophylla* oil in pharmaceutical preparations.

Keywords: Phase diagram, *Swietenia macrophylla* oil, Nonionic surfactants, Nano-emulsion.

INTRODUCTION

The species *Swietenia macrophylla* (SM) is a member of the family *Meliaceae*[1]. S. *macrophylla* occurs mainly in open rain forest, semi-deciduous and deciduous forests (which lose their leaves in a partial way or total respectively, during the dry season)[2]. Its fruit seem to point upwards to the sky, therefore, it is commonly known as "sky fruit"[3]. It has been reported for its medicinal uses, as a treatment for hypertension, diabetes, malaria, cancer, amoebiasis, chest pains and intestinal parasitism[4]. Also as Anti-microbial[5], anti-nociceptive activity [6], and anti-diarrheal activity [7]. Nano-emulsions are a new class of emulsion which can be defined as an emulsion with uniform and extremely small droplet sizes, typically in the range of 20–200 nm[8,9]. The physical appearance of nano-emulsion is transparent or translucent because of their small droplets size which makes it kinetically stable against sedimentation or creaming for a long period of time[10,11]. The use of nano-emulsions in oral dosage forms, achieve promising results in increasing the effectiveness of the drug at the target site, as well as can increase drug bioavailability, enhanced permeability and therapeutic functions[12,13]. Self-nanoemulsifying system (SNES) is described as an isotropic mixture of natural or synthetic oil and surfactants or one or more hydrophilic surfactant and co-surfactants that have a unique ability of forming fine oil-in-water (O/W) nano-emulsions when mixed with aqueous media under mild agitation[14,15]. Spontaneous emulsification to produce fine oil-in-water emulsion under gentle agitation followed by dilution in aqueous media can occur in oil and surfactants mixture, if the entropy change favoring dispersion is larger than the energy required to increase the surface area of dispersion. Emulsification occurs spontaneously due to low and positive or negative free energy required to form the emulsion. The droplet size of emulsion is a critical factor in self-emulsifying system performance because it determines the rate and extent of drug release and absorption[16-19,20,21]. Therefore, for pharmaceutical formulation purposes, it is essential to identify such system, which is spontaneously emulsifying. The production of self-emulsifying formulation involves several combinations of oil and surfactant. The components used must be suitable for oral ingestion, such as medium chain triglyceride oils and nonionic surfactants. Factors that influencing the efficiency of self-emulsifying formulation are; HLB and surfactant concentration[22,23].

MATERIALS AND METHODS

Swietenia macrophylla (SM) oil was gifted by Nawa Pharma Sdn Bhd (Kuala Lumpur, Malaysia). Cremophor EL (Ethoxylated castor oil), Capmul MCM (Glyceryl monocaprylocaprate) were gifts from Abitec Corporation (Columbus, Ohio) and BASF corporation (Mount Olive NJ), respectively. Tween 80 (polyoxyethylene sorbitan monooleate) from Sigma-Aldrich (USA). Waglinol 9238 (Caprylic Capric triglycerides) and Labrafil M-1944CS (Oleyl polyoxylglycerides) were gifts from Lasemul corporation.

Formulation of self-emulsifying system

Series of formulations comprising various combinations of *Swietenia macrophylla* oil with surfactant and co-surfactant were prepared. A ternary phase diagram was constructed based on five different types of surfactants combinations with *Swietenia macrophylla* oil at a constant temperature, which will produce SNEDDS and SMEDDS. Formulation A contained mixture of oil, Tween 80/Labrafil (2:1) and Cremophor EL/Waglinol (1:2) while formulation B consists of oil, Cremophor EL and Capmul MCM. Formulation C contained combination of oil, Labrafil M-1944CS and Cremophor EL. Formulation D contained combination of oil, Tween 80 and Waglinol. Formulation E contained combination of oil, Tween 80 and Capmul MCM. The mixtures were then used to distinguish the effect of such parameters on the emulsification of the oil.

Series of formulations were weighed based on pseudo ternary automatic diagram. Analytical balance (Meller Tolledo) was used to measure the weight of each formulation. The sample was mixed by vortex for two minutes to mix the compounds in the formulation. An amount of 50 mg of the sample was dissolved in 100 ml of distilled water. The resultant formulation was observed and the droplet size of the produced emulsion was then measured by Malvern Mastersizer 2000 laser diffraction particle analyzer (Malvern instruments, UK) in order to find the efficiencies region of emulsification. All experiments were carried out at room temperature of about 25 °C. The formulations that contained in non-emulsified phases were not shown in the phase diagrams because they are out of study scope. According to the ternary phase diagrams, nano-emulsion region was marked to indicate the transparent and fine droplets, whereas micro-emulsion region was marked due to more whitening and isotropic solutions that might contain micelle solutions and coarse emulsion was the region of visibly cloudy dispersions even by visual observation.

Droplet size and size distribution analysis

Droplets size and size distribution of self-emulsifying system were determined using Malvern Mastersizer 2000 laser diffraction particle analyzer (Malvern instruments, UK). Photon correlation spectroscopy or dynamic light scattering, which is specialized in analysis of particle size of submicron, is a valuable technique which analyses changes in light intensity fluctuations initiated by Brownian motion. The temperature needs to be stable otherwise convection currents in the sample will cause non-random movements which will ruin correct size interpretation.

To observe the droplet size and size distribution, 250 µl of an oil/surfactant was added to 300 ml of distilled water in a 500 ml beaker. A glass rod was used to induce gentle agitation in the mixture. The droplet size and size distributions of resultant emulsion were examined by using Malvern Mastersizer 2000 laser diffraction particle analyzer. This step was conducted for screening study of ternary phase diagram. Mean size and size distributions measurements were performed in triplicates.

Visual observation

To observe the progress of emulsion droplets as well as the tendency for the formulation to emulsify spontaneously, 250 µl of an oil/surfactant mix was added to 300 ml of distilled water in a 500 ml beaker. A rod glass was used to induce gentle agitation in the mixture. The emulsion was considered as good when the droplets can spread easily in water and produce fine milky emulsion. Meanwhile, the emulsion was classified as moderate when longer time required in emulsifying and producing milky emulsion. The emulsion was considered as bad when there was poor or no formation of emulsion and immediate coalescence of oil droplets when gentle agitation was stopped. In this study, the ease of dispersion and emulsion formation in terms of its ability to spread and mix the water were observed and the emulsification time was expressed in terms of the time taken for emulsion to be emulsified.

Viscosity of the self-nanoemulsifying formulations

Viscosity measurements were carried out using a Brookfield Viscometer (Wingather 2.1 software) at 25 ± 1 °C. Spindle size 31s was applied. The speed of spindle was set starting from 40, 50, 60, 70, 80, 90, 100 and 120 rpm at one minute time interval. The viscosity, in centipoises (cP), could be obtained by multiplying the resulting value with sample density.

RESULTS AND DISCUSSION

Effect of different surfactants combination on the formulation of self-nanoemulsion system A variety of isotropic mixtures were investigated for their ability to self-emulsify in water under gentle agitation. The ternary phase diagrams of *Swietenia macrophylla* oil with different mixtures of surfactant and co-surfactant were presented in figures (1-5). The ternary phase diagrams represent five types of formulation for *Swietenia macrophylla* oil that were developed to obtain the optimum condition of SNEDDS. It was observed that there were different areas division in each diagram such as transparent emulsion, isotropic emulsion, coarse emulsion and separation emulsion. The nano-emulsion (NE) indicated that the droplet size was measured in nano range (<1000 nm). Meanwhile, micro-emulsion (ME) represent the droplet size in micron range (<20 µm) and coarse emulsion (CE) showed the droplet size which was more than 20 µm. Separation emulsion (SE) indicated the separation of oil.

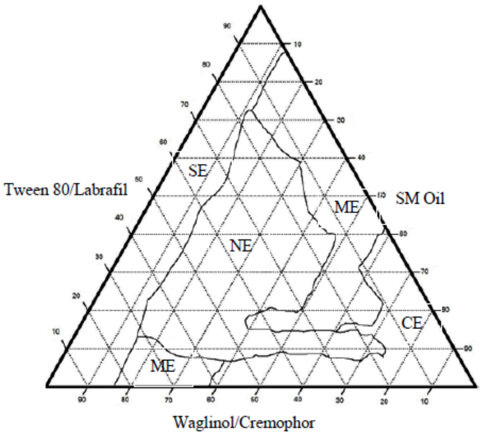

Fig. 1: System A; SM oil, T80/Labrafil (2:1) and Cremophor EL/Waglinol (1:2)

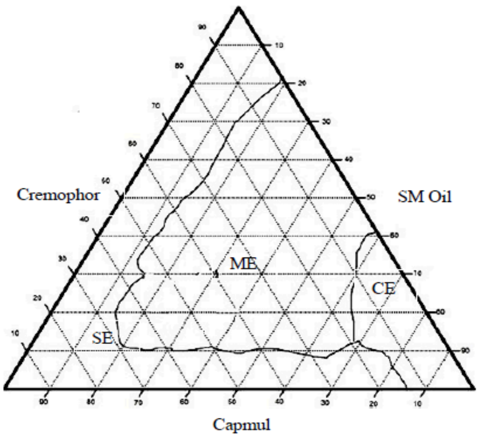

Fig. 2: System B; SM oil, Cremophor EL and Capmul MCM

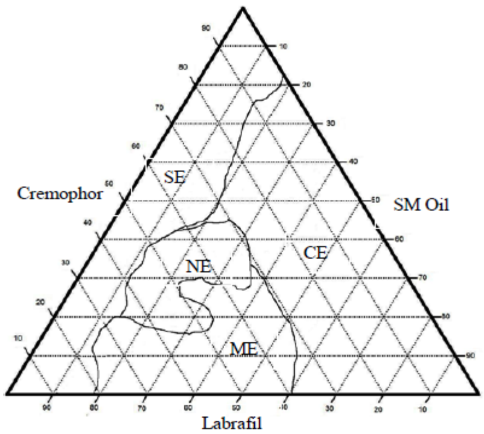

Fig. 3: System C; SM oil, Labrafil and Cremophor EL

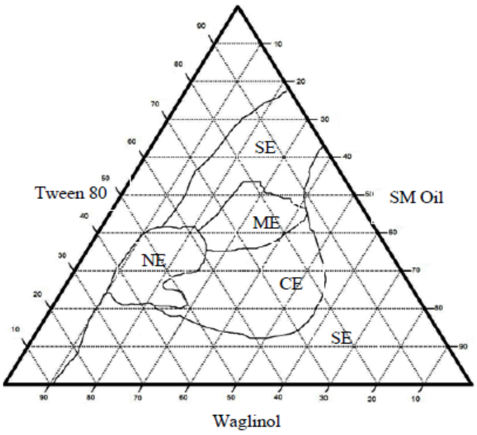

Fig. 4: System D; SM oil, T80 and Waglinol

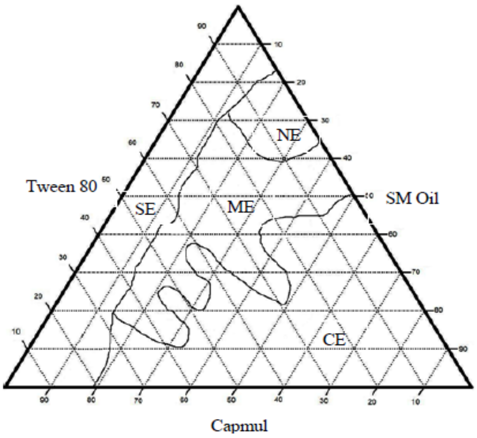

Fig. 5: System E; SM oil, T80 and Capmul MCM

According to figures 1 the ternary phase diagram of system A comprised three combinations of non-ionic surfactant and one co-surfactant. The combination of different types of surfactants produced larger region of nano-emulsion compared to other systems. This is because of the presence of many series of formulations which enhance the formation of nano-emulsion area with higher stability. On the other hand, the ternary phase diagrams of system B and system C in figures 2 and 3 showed bad properties of nano-emulsion that's because most of the formulations produced micro-emulsion. However, in figures 4 and 5, the ternary phase diagram D and E showed moderate properties of emulsification because they have few formulations produced nano-emulsion but these formulations are not so stable after left overnight.

It is clear from the comparison between different ternary phase diagrams, the ternary phase diagram system A showed the field of interest in forming nano-emulsion, which managed to produce range of different concentrations of oil with nano range below 200 nm and around 20, 35 and 50% of oil mixed with different concentrations of Tween 80/Labrafil M 1994 CS at ratio 2:1 and Waglinol/Cremophor EL at ratio 2:1, therefore, mixing different surfactants will help in producing better self-nanoemulsifying system. The combination of various types of surfactants contributed to more accurate results compared to single surfactant used. The nano-emulsion region was greatly increased in the phase diagram, also the oil concentrations were broader that allow different amounts of oil in the formulation. Pouton[24], reported that in the development of self-emulsified formulation, it is important for the formation of micro-emulsion to choose the right surfactants which have a blend of high and low HLB (hydrophile lipophile balance). Surfactants with high HLB values showed the ability of rapid self emulsifying formation with excellent spreading properties. On another hand, surfactants with low HLB values displayed poor self-emulsifying properties and long time consuming for emulsion formation also slowed poor spreading characteristics.

Self-emulsifying systems are very sensitive to the ratio of oil/surfactant mixture. In system A, Tween 80 with high HLB value was chosen as a non-ionic surfactant because it produces better self-emulsifying formulations with faster emulsification time and smaller oil in water droplets. In System A the combination of Tween 80 (HLB 15) and Labrafil (HLB 4) at ratio 2:1 can influence the self-emulsifying properties, because Tween 80 which is a hydrophilic surfactant produces an immiscible oil/surfactant mixture resulting in poor self-emulsifying properties if the oils are very hydrophobic, therefore, Labrafil M 1944 CS can influence the self-emulsifying properties making the system more stable. Also the combination containing Cremophor EL (HLB 12-14) and Waglinol at ratio 2:1 helped solubilizing hydrophobic oil components and produced stabilized self-emulsifying system. While in system B with a combination of Cremophor EL and Campul MCM (HLB 5) and system C with a combination of Cremophor El and Labrafil M 1944 CS showed a high region of micro-emulsion and no nano-emulsion formulation, which indicate that those combinations are not suitable to produce nano-emulsion, but good in producing self-micro-emulsion system. These findings are in agreement with Gao & Morozowich[25], who stated that, nonionic surfactants with high HLB values used in formulation of self-emulsifying drug delivery system showed an immediate formation of O/W droplets and rapid spreading of the formulation in the aqueous media with high stability. In contrast, system D with a combination of Tween 80 and Waglinol, and system E, with a combination of Tween 80 and Capmul MCM, showed a capability of producing nanoemulsion and micro-emulsion. Therefore, Tween 80 is a good non-ionic surfactant that is suitable for producing self-nanoemulsion system. Without Tween 80 the system become poor that will prove based on system B and C. However the surfactants with high HLB value like Cremophor EL used to prepare self-emulsifying system is worse without Tween 80. Only the right blends of surfactant and co-surfactant will produce well performed self-nanoemulsion system. Same finding was reported by Mahdi *et al.*[26], on blends of Tween and Tween/Span, as non-ionic surfactants, which screened based on their solubilization capacity with water for palm kernel oil esters. It showed that Tween 80 has high solubilizing capacity compared to other surfactants and high HLB blends of surfactant and co-surfactant showing better solubilization capacity compared to lower HLB values.

The behavior of *Swietenia macrophylla* oil and surfactants combinations on droplets size and size distribution (uniformity)

The oil and surfactants combinations were studied for their droplets size and uniformity to identify the region of emulsion formation. In according to the ternary phase diagrams showed in the above figures, the droplets size are totally different when different combination of surfactants were used. Ternary phase diagram A showed the smallest droplets size compared to the ternary phase diagram B, C, D and E. The smallest droplet size of SM oil preconcentrate was 111 nm with 0.195 uniformity compared with system B was 1.11 µm with 1.262 uniformity and system C was 1.103 µm with 0.547 uniformity. On the other hand, system D and E showed better droplets size and uniformity compared with system B and C but still not as good as system A, system D droplet size was 178 nm with uniformity 0.349 and system E droplet size was 165 nm with 0.289 uniformity.

The composition of selected self-nanoemulsifying formulations from system A with their droplets size and uniformity were shown in table 1. The formulations droplet size and uniformity were measured by MasterSizer Malvern Instrument during the preliminary investigation because this instrument allows the measurement over a range of droplets size from nm to µm sample. The selection of the nano-size formulation was based on its droplet size, which is below 200 nm. Formulations with good droplets size and uniformity were shown in table 1 with different oil concentrations ranged from 20 to 50%. Among those combinations formulations B, C and D showed the best droplets size and uniformity when compared to other formulations having same oil concentration. Therefore, it could be concluded that these formulations are the best to prepare self-nanoemulsifying formulation.

Table 1: Selected nano-size formulations for SM oil from system A

Formulation	Tween80/Labrafil M1994CS (%)	Waglinol 9238/ Cremophor EL (%)	SM oil (%)	Droplet size (nm) ± SD	Uniformity ± SD
A	32.0	48.0	20.0	138 ± 1.2	0.197 ± 0.004
B	40.0	40.0	20	111 ± 0.7	0.195 ± 0.005
C	32.0	32.0	36.0	133 ± 1.3	0.207 ± 0.002
D	25.0	25.0	50.0	150 ± 2.1	0.215 ± 0.005
E	48.0	32.0	20.0	128 ± 2.5	0.260 ± 0.003
F	38.4	25.6	36.0	146 ± 1.8	0.255 ± 0.006
G	56.0	24.0	20.0	126 ± 1.1	0.339 ± 0.005
H	44.8	19.2	36.0	151 ± 1.9	0.487 ± 0.001
I	35.0	15.0	50.0	163 ± 0.6	0.477 ± 0.004
J	64.0	16.0	20.0	149 ± 1.2	0.535 ± 0.003

All data are presented as mean ± SD, (n= 3).

It was observed from the ternary phase diagrams that when the oils content in the formulations increased their droplets size were increased also and their ability to self emulsifying become more faster. However due to the big droplets size, separation of oil will occur few minutes later, which means when the oil content increased the droplets size increased and the system will not be stable after self-emulsification. This can be attributed to the decrease in surfactants content availability for adsorption and forming film at the oil–water interface. Thereby unstable system will be formed, which is not enough to support the self-emulsification process when the oils content increased. Same finding was reported by Zhao *et al.*[27], on Zedoary essential oil prepared as SNEDDS for oral delivery, he found that the droplet size decreased from 180 nm to 38 nm when surfactants content increased from 30% to 75% and such decrease in droplet size is due to the presence of more surfactant at the oil–water interface, thereby providing stabilized emulsion with nano-size droplet.

The behavior of *Swietenia macrophylla* oil and surfactants combinations on time of emulsification and appearance of self-nanoemulsifying formulations

Based on visual observation, the nano-emulsion formulations were transparent and yellowish in color. The increase in oil content would cause the color of emulsion to become more yellowish. Zhao *et al.*[27], described that emulsification time increased from 1 to 5 minutes with an increase in the surfactant concentration from 30 to 75%. Same findings also were reported by Gao *et al.*[28], who demonstrated that an increase in the surfactant and co-surfactant concentration increased the emulsification time.

Thus, the self-emulsifying properties required to produce formulation in nano range droplet size can be affected by the ratio of oil and surfactants. But the emulsification time is reversely affected by the effect of surfactant and co-surfactant. These results are supported by previous studies that have reported similar relationships between the emulsification time and particle size for range of oil/surfactant mixtures. Buyukozturk *et al.*[29], declared that a strong interaction influences the mean droplet size of emulsion with the change in the oil/surfactant ratio and the HLB value of the surfactants. Bachynsky *et al.*[30], stated that the presence of little oil in the emulsion could reflect the self-emulsification properties of the emulsion. In addition, it was also mentioned that the good self-emulsifying properties was significantly affected by the oil which has good spreading characteristics and ability to form cloud within 60 seconds.

On the other side, self-emulsifying process becomes difficult when the proportion of surfactant and co-surfactant increased. The increase in surfactant content would increase the viscosity of the formulation. Hence, lead to longer time of emulsification. System A showed moderate emulsification time with around 20 to 120 seconds then system B and C have an emulsification time around 15 to 100 seconds and lastly system D and E showed an emulsification time around 25 to 120 seconds. Tables 2 represented the results of visual examination for self-nanoemulsifying formulations for *Swietenia macrophylla* oil, all formulations showed good spreading with different emulsification time. For both oil formulations A, B, E, G and J showed the longest emulsification time between 45 to 57 seconds. While, self-nanoemulsifying formulations with moderate emulsification time around 30 to 37 seconds were C, F and H. On the other hand, formulations D and I showed the best emulsification time between 22 to 26 seconds. Emulsification time basically depends on the oil chemical structure and the proportion of oil, surfactant and co-surfactant in the mixture. Both oils showed that the emulsification time was reversely affected by surfactant and co-surfactant mixture concentration. When oil was increased from 20 to 50% the emulsification time was increased from 20 to 57 seconds, which shows that the emulsification time was increased with the decrease of surfactant and co-surfactant mixture. Overall, the emulsification time for all formulations was good because all of the formulations form cloud within less than 60 seconds.

Viscosity of the Self-Nanoemulsifying Formulations

The viscosity of the self-nanoemulsifying formulations which consists of oil, surfactants and co-surfactants could be observed from table 3. These formulations were discovered to be viscous at ambient temperature. The viscosity values fall within the range of 105 to 145 cP. The most viscous formulation was formulation J which has 145 cP, followed by formulation G which has 140 cP. Formulation A has the lowest viscosity compared to other formulations which was 105 cP.

Table 2: Visual characteristics of SM oil SNEDDS formulations

Formulation	Spread	Time (s) ± 0.5	Appearance
A	Yes	50	transparent emulsion
B	Yes	48	transparent emulsion
C	Yes	32	transparent emulsion
D	Yes	22	transparent (yellowish) emulsion
E	Yes	45	transparent emulsion
F	Yes	30	transparent emulsion
G	Yes	55	transparent emulsion
H	Yes	35	transparent emulsion
I	Yes	25	transparent (yellowish) emulsion
J	Yes	56	transparent emulsion

(n= 3).

Table 3: Viscosity values of self-nanoemulsifying formulations for SM oil

Formulation	Tween80/Labrafil M1994CS (%)	Waglinol 9238/ Cremophor EL (%)	SM oil (%)	Viscosity (cP)
A	32.0	48.0	20.0	140.7 ± 4.0
B	40.0	40.0	20.0	143.5 ± 4.5
C	32.0	32.0	36.0	126.4 ± 3.7
D	25.0	25.0	50.0	105.0 ± 4.1
E	48.0	32.0	20.0	138.1 ± 2.4
F	38.4	25.6	36.0	119.8 ± 2.8
G	56.0	24.0	20.0	140.9 ± 4.3
H	44.8	19.2	36.0	127.5 ± 4.4
I	35.0	15.0	50.0	110.7 ± 2.9
J	64.0	16.0	20.0	145.0 ± 2.6

All data are presented as mean ± SD, (n= 3).

It appears that different formulations showed different viscosity values. The concentrations of oil, surfactant and co-surfactant have an effect on the flow properties. This can be seen with different concentrations of surfactant and co-surfactant. High concentration of oil would result in low viscosity values. The increase in viscosity might require greater shear forces for dispersion and longer time to perform emulsification. In this experiment, all formulations could still undergo self-emulsification by gentle agitation with fast time emulsification and small droplet size.

CONCLUSION

In conclusion, self-nanoemulsifying formulations containing *Swietenia macrophylla* were successfully prepared by mixing the oil with various types of surfactant and co-surfactants. The self-nanoemulsifying system properties were sensitive to the ratio of the oil/surfactant/co-surfactant and the nature of the surfactant/co-surfactant phase. The use of surfactant/co-surfactant blend help to reduce the oil droplet size when compare to the use of a single surfactant. Also the self-nanoemulsifying formulations were greatly improved and showed better self-nanoemulsifying properties with the use of Tween 80 in the surfactants mixture. In general, the size of the oil droplets was reduced when the concentration of Tween 80 as hydrophilic surfactant was increased from 20 to 50%. The increase in the hydrophilic surfactant in the formulation increased the emulsification time that is due to the high viscosity of the hydrophilic surfactant. In the other hand, the emulsification time was very fast when the oil content in the formulation increased, but this lead to poor self-nanoemulsifying system properties with an increase in the oil droplets size and separation of the oil occur after few minutes. All the formulation which has good properties of self-nanoemulsifying system produce transparent nano-emulsion and the emulsification time was below 1 minute.

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