Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Suppl 3, 2013

Research Article

A NOVEL *SWIETENIA MACROPHYLLA* OIL SELF-NANOEMULSIFYING SYSTEM: DEVELOPMENT AND EVALUATION

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Received: 18 Jun 2013, Revised and Accepted: 09 July 2013

ABSTRACT

The improvement in emulsion production has been shown with the discovery of nanoemulsion. 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 self-emulsifying systems, which gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. 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 medicinal values like antimicrobial, anti-inflammatory and anticancer activities. Therefore, the aim of this study was to use *Swietenia macrophylla* oil blends surfactants to prepare self-nanoemulsifying systems. Self-nanoemulsifying systems for *Swietenia macrophylla* oil were prepared, by constructing five different ternary phase diagrams containing nonionic surfactants Tween 20, Labrafil, Labrasol, and Capmul MCM to and studying their behavior on the formulations. The oil droplets size, size distribution, spreading time, appearance and viscosity were studied for the optimum formulations which showed droplets size below 200 nm. Different oil/surfactants combinations showed different emulsification properties with relation to droplets size. It was found that the combinations which contain Tween 20 as one of the surfactants produced nano-size droplets. Therefore Tween 20 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 20/Labrafil in the ratio of 2:1 and Labrasol/Capmul in the ratio 1:2. Nanoemulsion was produced with droplets size below 200 nm formed upon gentile agitation with water with low polydispersity < 0.3. 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: Self-nanoemulsifying system; *Swietenia macrophylla* oil; Tween 20; Labrasol; Labrafil; Capmul.

INTRODUCTION

Recently, nanoemulsion has been the subject of interest for researches as they carry many advantages. Nanoemulsion are known as an isotropic dispersed system with droplets size in the size range of 20–200 nm [1,2]. Due to their size characteristic, it is stable against sedimentation or creaming and also has high kinetic stability and optical transparency [3,4]. Self-emulsifying drug delivery systems (SEDDS) have been noted as a promising strategy to overcome low oral bioavailability of poorly water soluble drugs [5,6]. Self-nanoemulsifying system (SNES) is an isotropic mixture of natural or synthetic oil and surfactants, that have a unique ability to form nanoemulsions when mixed with aqueous media under gentle agitation [7,8]. The droplet size of emulsion is a critical factor in the performance of self-emulsifying system, because it determines the rate and extent of drug release and absorption [9-14]. Therefore, for pharmaceutical formulation purposes, it is essential to identify such system, which is spontaneously emulsifying. The mechanism behind the spontaneous emulsification of self-emulsifying system and producing emulsion under mild agitation in aqueous media of gastrointestinal fluid, occur when 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 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. Self-emulsifying formulations can be influenced by surfactants concentration and their hydrophilic lipophilic balance [15,16].

Swietenia macrophylla species is one of the most important plants of the family *Meliaceae* [17]. It is planted widely in Southern Asia and Pacific region. It was located in more than 40 countries [17-19]. Its fruit commonly known as sky fruit, that's because it seems to point upwards to the sky [19]. *S. macrophylla* has various types of medicinal values, such as in the treatment of diabetes, hypertension, malaria, cancer, amoebiasis, chest pains and intestinal parasitism [20]. Also as Anti-microbial [21], anti-nociceptive [22], anti-diarrheal [23], antibacterial and antifungal activities [24].

MATERIALS AND METHODS

Materials

Swietenia macrophylla oil was obtained from Nawa Pharma Sdn Bhd (Kuala Lumpur, Malaysia). Labrasol (Caprylocaproyl macrogol-8 glycerides), Labrafil M1944CS (Oleoyl macrogol-6 glycerides) were obtained from Gattefosse SAS (France). Capmul MCM C8 (Glyceryl Monocaprylate) obtained from Abitec corporation (USA) and Tween 20 (polyoxyethylenesorbitan monolaurate) from Sigma-Aldrich (USA).

Methods

Formulation of self-nanoemulsifying system

Self-emulsifying formulations were prepared by comprising various combinations of *Swietenia macrophylla* oil with surfactant and co-surfactant. Pseudo ternary phase diagram was constructed based on five different surfactants mixtures with *Swietenia macrophylla* oil at a constant temperature, which helped in obtaining the self-nanoemulsifying formulations. Combination A consists of a mixture of oil, Tween 20/Labrafil (2:1) and Labrasol/Labrafil (1:2), while B consists of oil, Tween 20 and Capmul. Combination C consists of oil, Tween 20 and Labrafil. Combination D consists of oil, Labrasol and Capmul. Finally combination E consists of a mixture of oil, Tween 20 and Capmul. The mixtures were then used to distinguish the effect of different parameters on the emulsification of the oil.

First *S. macrophylla* oil and surfactants were weighed based on pseudo ternary phase diagram using analytical balance (Meller Tolledo) to prepare each formulation. The formulation containing the oil and surfactants was mixed by vortex mixer for two minutes. Then 50 mg of the formulation 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 particle size 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 macro-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, size distribution and zeta potential analysis

Droplets size and size distribution of self-emulsifying system were determined using Malvern Mastersizer 2000 particle size 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 using Malvern Mastersizer 2000 particle size analyzer. This step was conducted for screening study of ternary phase diagram. Mean size and size distributions measurements were performed in triplicates. The zeta potential was carried out for those formulations with droplets size below 200 nm using Malvern Nano Zetasizer.

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 glass rod 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

In the present study, the self emulsifying system of various combinations of surfactants and *S. macrophylla* oil were prepared using simple mixing method. A variety of isotropic mixtures were investigated for their ability to self-emulsify in water under gentle agitation and forming self-nanoemulsifying system. Figures (1-5) showed ternary phase diagrams of *S. macrophylla* oil with different mixtures of surfactant and co-surfactant. The ternary phase diagrams represented different types of *S. macrophylla* oil and surfactants combinations 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, macro-emulsion (ME) represent the droplet size in micron range (<10 µm) and coarse emulsion (CE) showed the droplet size which was more than 10 µm.

According to figures 1, ternary phase diagram of system A consists of different surfactants and one co-surfactants combinations. The combination of different types of surfactants produced larger region of nano-emulsion compared to other systems. This is because of the presence of different surfactants and co-surfactants which help in preparing 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 moderate properties of emulsification because they have few formulations produced nano-emulsion but these formulations are not so stable after left overnight. However, in figures 4 and 5, the ternary phase diagram D and E showed bad properties of nano-emulsion that's because most of the formulations produced macro-emulsion.

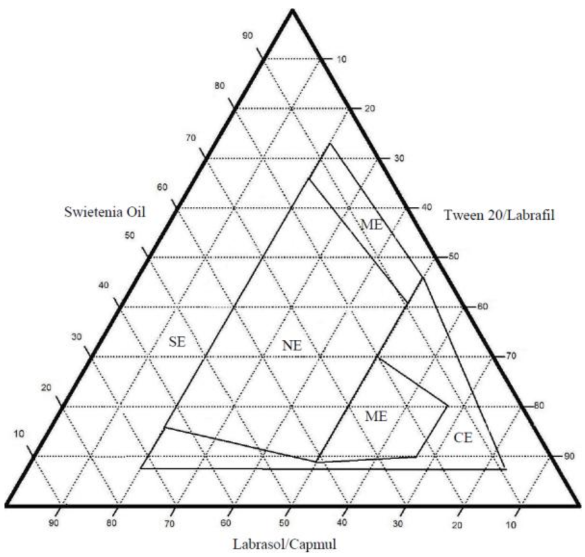

Fig. 1: System A; *Swietenia* oil, Tween 20/Labrafil (2:1) and Labrasol/Capmul (1:2)

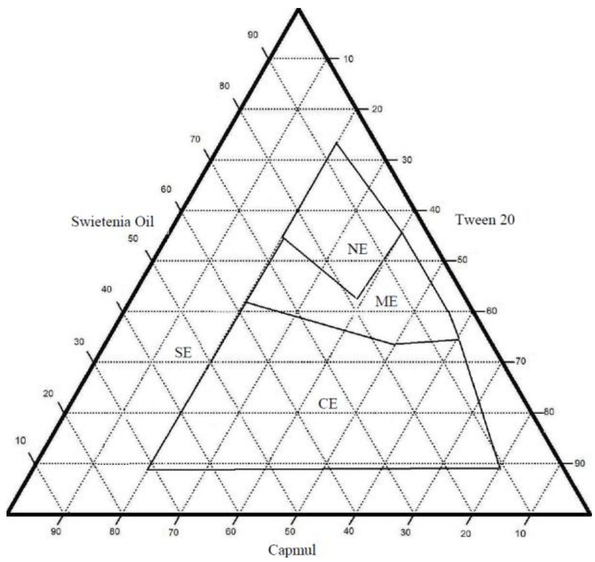

Fig. 2: System B; *Swietenia* oil, Tween 20 and Capmul MCM

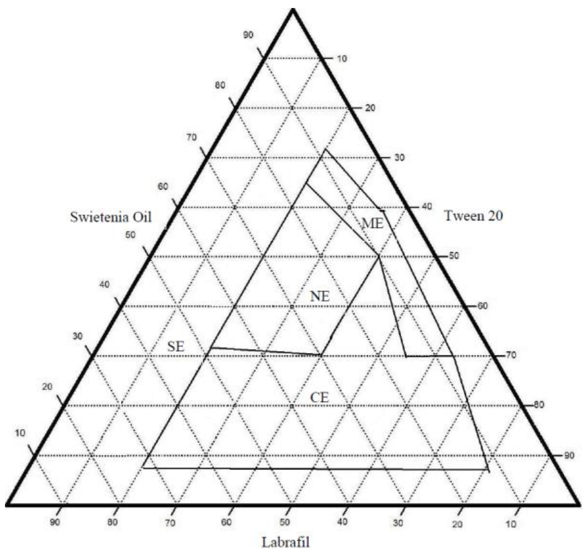

Fig. 3: System C; _Swietenia_ oil, Tween 20 and Labrafil

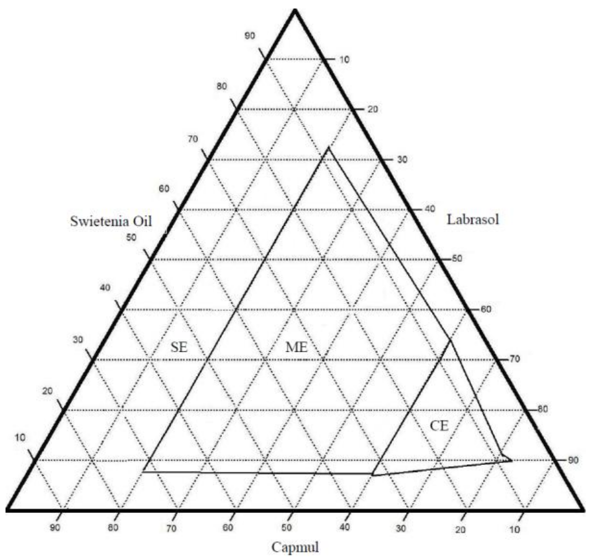

Fig. 4: System D; _Swietenia_ oil, Labrasol and Capmul

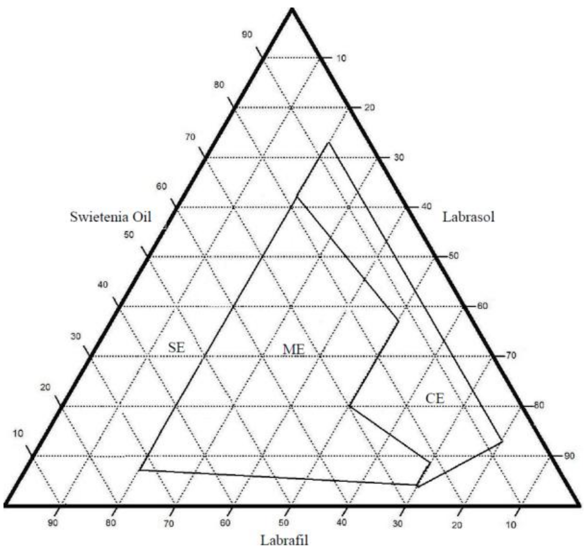

Fig. 5: System E; _Swietenia_ oil, Labrasol and Labrafil

It is clear from the comparison between different ternary phase diagrams, that the ternary phase diagram system A showed the field of interest in forming nano-emulsion, which managed to produce range of different oil concentrations between 20 to 50% when mixed with different concentrations of Tween 20/Labrafil at ratio 2:1 and Labrasol/Capmul at ratio 2:1. This could justify the minimum surfactants concentration of and maximum oil concentration. Therefore, mixing different surfactants will help in producing better self-nanoemulsifying system with a range of nano-size below 200 nm. 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 [25], 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/surfactants mixture. In system A, Tween 20 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 20 (HLB 16) and Labrafil (HLB 4) at ratio 2:1 can influence the self-emulsifying properties, because Tween 20 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 was added to influence the self-emulsifying properties making the system more stable. Also the combination containing Labrasol (HLB 14) and Capmul (HLB 5-6) at ratio 2:1 helped solubilizing hydrophobic oil components and produced stabilized self-emulsifying system. While in system D with a combination of Labrasol and Capmul and system E with a combination of Labrasol and Labrafil showed a high region of macro-emulsion and no nano-emulsion region, which indicate that those combinations are not suitable to produce nano-emulsion, but good in producing self-macro-emulsion system. These findings are in agreement with Gao & Morozowich [26], 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 B with a combination of Tween 20 and Capmul, and system C, with a combination of Tween 20 and Labrafil, showed a capability of producing nanoemulsion. Therefore, Tween 20 is a good non-ionic surfactant and solubility properties that is suitable for producing self-nanoemulsion system. Without Tween 20 the system become poor that was prove based on system B and C. However the surfactants with high HLB value like Labrasol used to prepare self-emulsifying system was worse without Tween 20. Only the right blends of surfactant and co-surfactant will produce well performed self-nanoemulsion system. Same finding was reported by Mahdi *et al*. [27], 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 20 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, size distribution (uniformity) and zeta potential.

To identify the region of emulsion formation *S. macrophylla* oil and surfactants combinations were studied for their droplets size and uniformity. 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 *S. macrophylla* oil was 111 nm with 0.177 uniformity compared with system B which showed 231 nm with 1.02 uniformity and system C was 189 nm with 0.469 uniformity. On the other hand, system D and E showed larger droplets size and uniformity compared with system A, B and C. System D droplet size was 1.07 µm with uniformity 1.632 and system E droplet size was 1.103 µm with 0.547 uniformity.

The composition of selected self-nanoemulsifying formulations from system A with their droplets size and uniformity were shown in table 1. The formulations droplets size and uniformity were measured by Malvern Mastersizer 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 should be below 200 nm. Formulations with small droplets size and uniformity were shown in table 1 with different oil concentrations ranged from 20 to 50%. Among those combinations formulations A, B and E were one of the best formulations to produce small droplets size and uniformity when compared to other formulations having same oil concentration 20%. Also formulation I showed small droplets size 116 nm with the smallest uniformity 0.117 in the presence of high oil concentration (50%) compared to other formulations. Therefore, it could be concluded that this formulation is the best to prepare self-nanoemulsifying formulation.

Table 1: *S. macrophylla* oil self-nanoemulsifying formulations from system A

Formulation	Tween 20/Labrafil (%)	Labrasol/ Capmul (%)	*S. macrophylla* oil (%)	Droplet size (nm) ± SD	Uniformity ± SD	Zeta-Potential (mV)
A	32.0	48.0	20.0	118 ± 1.7	0.283 ± 0.007	-26.3
B	40.0	40.0	20.0	119 ± 1.6	0.267 ± 0.004	-28.6
C	32.0	32.0	36.0	133 ± 1.9	0.371 ± 0.009	-26.4
D	40.0	10.0	50.0	184 ± 1.1	0.293 ± 0.006	-23.3
E	48.0	32.0	20.0	111 ± 1.4	0.260 ± 0.008	-28.9
F	38.4	25.6	36.0	146 ± 1.2	0.255 ± 0.005	-28.2
G	56.0	24.0	20.0	126 ± 1.7	0.339 ± 0.009	-21.8
H	44.8	19.2	36.0	151 ± 1.3	0.387 ± 0.004	-23.3
I	35.0	15.0	50.0	116 ± 1.6	0.177 ± 0.007	-34.4
J	64.0	16.0	20.0	169 ± 1.8	0.335 ± 0.005	-33.0

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

In general, 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*. [28], 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 zeta potential for the optimum formulations was measured by Malvern Zetasizer. In general, the limit to differentiate stable from unstable emulsion is -30 mV or +30 mV. Emulsions with potential more positive or negative than 30 mV are considered stable [28]. Zeta potential is a potential existing between the droplet surface and the dispersing liquid that will vary accordingly with the distance of the ion from the droplet surface. The zeta potential for the formulations was between -21.8 to -34.4. Formulation I showed the best zeta potential -34.4 which indicates its good stability compared to other formulations.

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

The visual observation of self-nanoemulsifying formulations was transparent and yellowish in color. The increase in oil content would cause the color of self-nanoemulsifying formulations to become more yellowish. Zhao *et al*. [29], found an increase in the emulsification time from 1 to 5 minutes when the surfactant concentration increased from 30 to 75%. Similar findings were also reported by Gao *et al*. [30], who confirmed that an increase in the surfactant and co-surfactant concentration will increase the emulsification time.

Therefore, the self-emulsifying properties required to produce formulation in nano range droplets size can be affected by the ratio of oil and surfactants. On the other hand, surfactant and co-surfactant concentrations were reversely affected the emulsification time. These finding were supported by previous studies that showed similar relationships between the emulsification time and the range of oil/surfactant mixtures. Buyukozturk *et al*. [31], discovered a strong interaction which influenced the mean droplets size of emulsion with the HLB value of the surfactants and the changes in the oil/surfactant ratio. Bachynsky *et al*. [32], stated that the presence of small amount of oil in the emulsion could reflect the self-emulsification properties of the emulsion. In addition, visual assessment of the self-emulsification properties also reported by Craig *et al*. [33], who found that the good self-emulsification properties was significantly affected by the oil concentration. Also he mentioned that the formulation which has a good self-emulsification property is that has a good spreading characteristics and the ability to form cloud within 60 seconds.

On the other hand, self-emulsification process becomes difficult when the concentrations 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 25 to 115 seconds then system B and C have an emulsification time around 25 to 110 seconds and lastly system D and E showed an emulsification time around 20 to 100 seconds. Tables 2 showed the results of visual examination for the selected self-nanoemulsifying formulations for *Swietenia macrophylla* oil from system A. It showed that all formulations have good spreading properties with different emulsification time. For both oil formulations A, B, E, G and J showed the longest emulsification time between 42 to 58 seconds. While, self-nanoemulsifying formulations with moderate emulsification time around 29 to 37 seconds were C, F and H. On the other hand, formulations D and I showed the best emulsification time 27 to 28 seconds respectively. 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 27 to 58 seconds, which showed that the emulsification time was increased with the decrease in surfactant and co-surfactant concentrations. Overall, the emulsification time for all formulations was good because all of the formulations form cloud within less than 60 seconds.

Table 2: Visual characteristics of Swietenia oil self-nanoemulsifying formulations

Formulation	Spreadability	Time (s) ± 0.5	Appearance
A	Spreadable	45	transparent emulsion
B	Spreadable	42	transparent emulsion
C	Spreadable	35	transparent emulsion
D	Spreadable	27	transparent (yellowish) emulsion
E	Spreadable	48	transparent emulsion
F	Spreadable	29	transparent emulsion
G	Spreadable	57	transparent emulsion
H	Spreadable	37	transparent emulsion
I	Spreadable	28	transparent (yellowish) emulsion
J	Spreadable	58	transparent emulsion

(n= 3).

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 102 to 143 cP. The most viscous formulation was shown in formulation A which has 143.1 cP, followed by formulation B which has 139.7 cP. While formulation D has the lowest viscosity compared to other formulations which was 102.1 cP.

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

Formulation	Tween 20/Labrafil (%)	Labrasol/ Capmul (%)	Swietenia oil (%)	Viscosity (cP)
A	32.0	48.0	20.0	143.1 ± 2.7
B	40.0	40.0	20.0	139.7 ± 3.2
C	32.0	32.0	36.0	120.7 ± 4.5
D	25.0	25.0	50.0	102.1 ± 3.9
E	48.0	32.0	20.0	135.7 ± 3.1
F	38.4	25.6	36.0	112.3 ± 3.5
G	56.0	24.0	20.0	132.9 ± 2.6
H	44.8	19.2	36.0	111.3 ± 3.8
I	35.0	15.0	50.0	109.1 ± 4.1
J	64.0	16.0	20.0	130.4 ± 3.2

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

From table 3, it appears that different formulations showed different viscosity values. The viscosity properties flow was affected due to the concentrations of oil, surfactant and co-surfactant. This can be seen with an increase in the concentrations of surfactant and co-surfactant and decrease in oil concentration. Therefore, 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 the current investigation, 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 helped to reduce the oil droplets 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 20 in the surfactants mixture. In general, the size of the oil droplets was reduced when the concentration of Tween 20 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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