Original Article
Food Science and Technology

ISSN 0101-2061 (Print)
ISSN 1678-457X (Online)

DOI: https://doi.org/10.1590/fst.15422

Development of a novel microemulsion towards improved stability of *Zanthoxylum piasezkii* Maxim. oleoresin

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Abstract

Poor storage stability of *Zanthoxylum piasezkii* Maxim. oleoresin (*Z. piasezkii.* oleoresin), a viscous fluid extracted from *Zanthoxylum piasezkii* Maxim. has limited its utilization in downstream products. The formation of microemulsion (ME) was expected as an ideal protocol for enhanced storage stability of *Z. piasezkii.* oleoresin, which was developed using polyethylene glycol 400 dioleate (PEG400DO) as surfactant and 1,2-propylene glycol (1,2-PG) as cosurfactant. An improvement in ME area, viscosity, and surface tension was found in one system compared to other formulations, with 37.54% of microemulsion formation area, a viscosity value of 242.17 mPa.s, and surface tension of 29.75 mN/m. This ME consisted of 40 wt% essential oil, 1.59 wt% surfactant mixture (3:1 (m:m) of 1,2-PG and PEG400DO), and 58.41 wt% *Z. piasezkii*. oleoresin. Additionally, this system exhibits steady performance, demonstrating the potential of a blend of surfactants-based ME as stable system for the utilization of *Z. piasezkii*. oleoresin as savory flavor.

Keywords: *Zanthoxylum piasezkii* Maxim. oleoresin; microemulsion; viscosity; surface tension; physical stability.

Practical Application: Condiment production, widens the application range of *Zanthoxylum piasezkii* Maxim. Oleoresin.

1 Introduction

Zanthoxylum piasezkii Maxim. (*Z. piasezkii.*) belongs to the genus *Zanthoxylum* L. (prickly ash) in the Rutaceae family. It has been widely used for traditional spicy condiments or medicinal ingredients (Sun et al., 2021). Reports indicated that *Z. piasezkii.* is rich in various components, including essential oils, acid amide phenol components (Kumar et al., 2014), alkaloids (Wansi et al., 2016), and ketones (Wang et al., 2014).

Zanthoxylum piasezkii Maxim. oleoresin (*Z. piasezkii.* oleoresin) is a viscous fluid after being extracted from *Z. piasezkii.* by supercritical or solvent extraction method. It retains natural nutrients of the corresponding *Z. piasezkii.,* among them, acid amide compounds are of particular interest since their concentration can serve as an indication for the internal quality of prickly ash (Fanun, 2008). *Z. piasezkii.* oleoresins exhibit sensitivity to low temperature or oxygen and have short storage lives if not stored properly. Poor storage life of *Z. piasezkii.* oleoresins are a result of oxidative changes involving the amine components. Some chemical changes can also occur in respect of the fatty acid components deterioration due to oxidation in a chain of reactions in which free radicals are formed and finally converted into stable oxidized compounds during prolonged storage (Kapoor et al., 2009; Witt & Stokes, 2015). We found that due to the formation of these stable oxygenated compounds, the acid value and peroxide value increase rapidly, which has a great influence on its application as a "peppery" spice. More researchers focused on the enhancement of the stability of *Z. piasezkii.* oleoresin by antioxidants addition (Coupland & Mcclements, 1996). Besides, synthetic antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and propyl gallate (PG) have been used in food industries, but there are some arguments about the safety and adverse effects of these substances when used as food additives (Kapoor et al., 2009).

Microemulsion (ME) possesses several characteristics such as high solubility of both lipophilic and hydrophilic compounds (Zainuddin et al., 2021), long-term stability, and low manufacturing costs (Kartsev et al., 2009), which make ME have an important role in protecting the *Z. piasezkii.* oleoresin against destructive changes (Sosa et al., 2021). ME components are usually optimized by using pseudo ternary phase diagrams, and the ME region can be identified in the phase diagram (Kreilgaard, 2002). Generally, ME is stabilized by surfactant and cosurfactant to reduce the interfacial layer (Gunarto et al., 2021) or increase the steric hindrances and/or the electrostatic repulsion between the micelles (He et al., 2017). At present, there are about 65 kinds of food emulsifiers allowed to be used, and the commonly used ones are monoglycerides, sucrose esters, Tween, PEG400DO, 1,2-PG, etc. (Carvalho et al., 2019).

Recently, an increasing interest has been directed towards polymer-modified MEs (Moldes et al., 2016). Polyethylene glycol (PEG) is a polymer with different molecular weights, with various molecular weights that exhibit excellent properties, such as biocompatibility, minimal toxicity, and good solubility

Received 02 Feb., 2022
Accepted 20 Mar., 2022
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(Fan et al., 2020). The system composed of a single surfactant PEG often changed into a viscous state. The main factor determining the range of formation of the microemulsion zone includes the presence of a highly fluid interfacial film of surfactant (Romsted, 2014). Besides, the report demonstrated single surfactant alone is not sufficient to achieve the transient negative interfacial tension and fluid film, thus cosurfactants are often used to allow sufficient film flexibility to attain curvature for microemulsion formation (Maghraby, 2008). The incorporation of short-chained alcohol as cosurfactants was shown to increase the microemulsion zone (Maghraby, 2008). Propylene glycol (PG) contains two hydroxyl groups and is expected to function as short-chained alcohol. The additives di- and tri-propylene glycol possess are known to lower the rigidity of the interface of the ME droplet (van Bommel et al., 2005). So, 1,2-PG was selected in our study. It is therefore expected that the introduction of a blend of PEG and PG can improve the stability of ME and can at the same time protect *Z. piasezkii.* oleoresin against destruction. However, this information had not yet been explored.

The present work was therefore aimed at the improvement on the storage stability of the *Z. piasezkii.* oleoresin. An ME system was constructed using a pseudo ternary phase diagram, and the ideal system to stabilize the *Z. piasezkii.* oleoresin was obtained, together with the mechanism was explored by viscosity and surface tension, as well as its physical stability was further verified by centrifugal experiment, freeze-thaw cycle experiment, and standing experiment. These results provide theoretical data in alleviating the poor storage life of *Z. piasezkii.* oleoresin.

2 Materials and methods

2.1 Materials

Z. piasezkii. oleoresin with the numbness of 325.29 and zanthoxylum essential oil were supplied by Chenguang Biotechnology Group Co., Ltd (Handan, China). Food grade 1,2-PG was purchased from the High-tech Industrial Development Zone (Zhengzhou, China). PEG400DO was food grade, which was purchased from Haian Petrochemical Plant (Jiangsu, China).

2.2 Preparation of MEs

The formulation of microemulsion (Hereinafter referred to as ME) was as follows: PEG400DO as a surfactant, 1,2-PG as cosurfactant, zanthoxylum essential oil as oil phase, respectively. All the components were evenly mixed by magnetic stirrer at 35 °C and rotating speed at 200 rpm. The surfactant/cosurfactant mixture (S_{mix}) were prepared by mixing 1,2-PG and PEG400DO at weight ratios of 4:1, 3:1, 2:1, 1:1, 1:2 or 1:3. According to the requirements of the market specifications, the prepared MEs are adjusted to 190, in which the weight ratio of the zanthoxylum essential oil and the S_{mix} is 40% and 1.59% respectively.

2.3 Pseudo-ternary phase diagram construction

Z. piasezkii. oleoresin and S_{mix} are miscible, Zanthoxylum essential oil and S_{mix} are partially soluble, and Zanthoxylum essential oil and *Z. piasezkii.* oleoresin is mutually soluble, so the solubility of *Z. piasezkii.* oleoresin-essential oil-single surfactant/S_{mix} ternary system is determined by titration. Finally, pseudo ternary phase diagram data was constructed and the ME formation area was obtained according to Zhang and Lee (Zhang et al., 2017; Lee et al., 2018).

Briefly, a certain amount of *Z. piasezkii.* oleoresin and a small amount of essential oil were blended at 35 °C, the system was kept stirring at the speed of 200 rpm with a magnetic stirrer. Adding the essential oil dropwise until the transparent system appears, record the volume of the essential oil added, followed by adding the single surfactant/S_{mix} dropwise when the system becomes turbid. The total amount of surfactant or S_{mix} added was recorded. Repeat the above operation to obtain a series of critical values.

2.4 Determination of viscosity

According to the literature (Zheng et al., 2020; Poomanee et al., 2017; Kreilgaard, 2002), the viscosity of the various microemulsions was measured as follows. 15 mL of ME samples were put into a centrifuge tube, and it is first dissolved at 50 °C, and then measured using Anton Paar Rheometer CC27-cylindrical rheometer probe (Physica MCR 301, Austria). All measurements were performed in triplicate.

2.5 Surface tension

The ME in this article has a higher viscosity, so the platinum plate method is used to measure its surface tension (Rajinder, 2001). First, prepare the ME according to the 2.2 methods and then take a part of the sample and measure its surface tension on a surface tensioner (HX-205, Beijing, China). All measurements were performed in triplicate.

2.6 Stability study of ME

Centrifugal test

ME samples investigated here are dispersed mixtures, and they may crystallize during storage as the standing time increases. However, it is not ideal to leave the prepared samples for too long. Therefore, the relationship between centrifugation and gravity is used to calculate the relationship between centrifugation time and standing time (Rajinder, 2001). The MEs prepared from *Z. piasezkii.* oleoresin, essential oil, and different proportions of S_{mix} were centrifuged in a centrifuge for 70 min under the conditions of 7000 r/min, 8000 r/min, 9000 r/min, 10000 r/min, 11000 r/min, and 12000 r/min, and the centrifugation temperature was set to 35 °C. After centrifugation, observed phase separation, transparency, and the sediments of ME. The relationship between centrifugal force and gravity is as follows (Equations 1-2):

$$G = R \times 1.18 \times 10^{-5} \times rpm^2 \quad (1)$$

$$t_g = t_c \times \frac{\omega^2 \times R}{g} \quad (2)$$

Among them: G — centrifugal force (g)

R — centrifugal radius (cm)

rpm — Rotation speed (rad/min)

t_g — Stability time in a gravitational field (s)

t_c — Stability time in the centrifugal field (s)

ω — Centrifugal angular velocity (rad/s)

g — Gravitational acceleration (m/s^2)

Standing experiment

The ME samples prepared by the above method were subjected to a static experiment under the conditions of the same numbness of 190 and temperature of 25 °C. Observe the static ME samples with the naked eye or with the aid of a flashlight every day to see if phase separation, turbidity, and sedimentation occurred.

Freeze-thaw cycle

The ME was put into air-tight containers under 6 freezing-thawing cycles with -20 °C for 48 h followed by 35 °C for 48 h as 1 cycle. Phase separation, transparency, and the sediments of ME were observed.

2.7 Data-analysis

Results were determined and presented as means with standard deviation (Mean ± SD) for three independent replicates. A pseudo-ternary phase diagram was constructed on a weight basis using origin software 9.0. ME formation area was obtained by image pro plus 6.0 software. Data were subjected to a one-way analysis of variance using the SPSS version 10.0 software package (SPSS Inc., Chicago, USA). Comparisons between means were carried out using Duncan's multiple range test at a significance level of $p < 0.05$.

3 Results and discussion

3.1 Ternary phase diagram of Zanthoxylum ME

According to the literature, the larger the area of the microemulsion area, the better its stability (Singh et al., 2010). Therefore, the pseudo-ternary phase diagram can be used to determine the microemulsion area to explore the stability of ME. The results of the pseudo-ternary phase diagram of the MEs are shown in Figure 1 and Table 1.

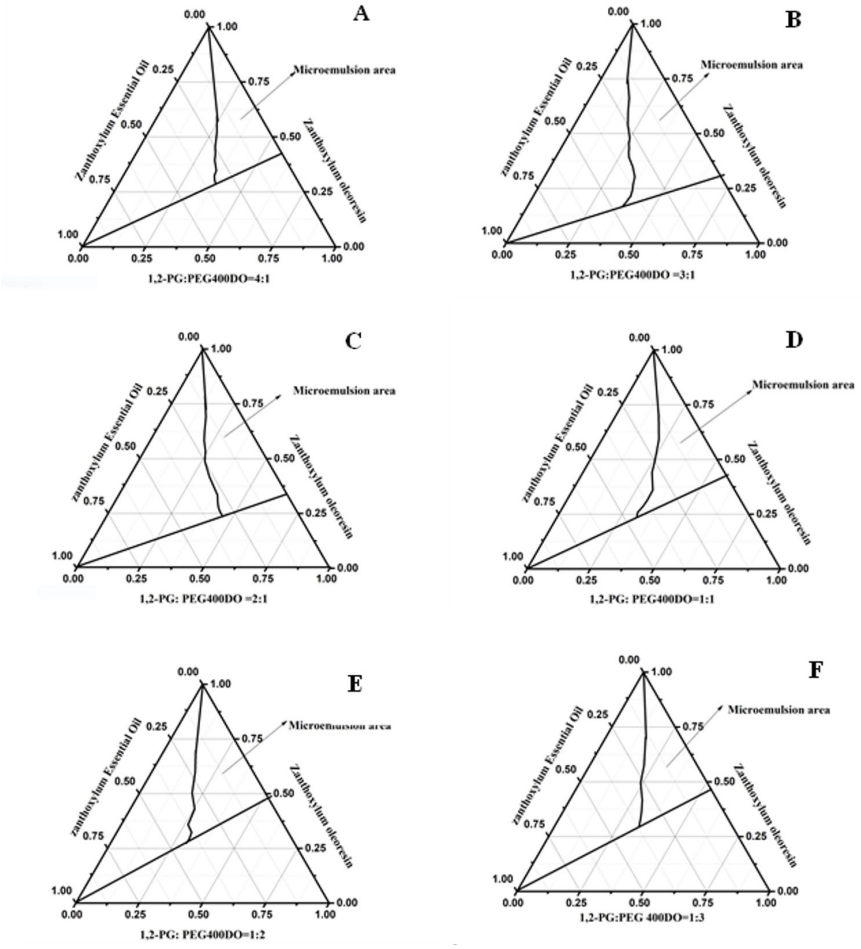

Figure 1. Pseudo ternary phase diagram of MEs with different weight ratio of S_{mix}. A-F represents weight ratio of S_{mix} of 4:1, 3:1, 2:1, 1:1, 1:2 and 1:3, respectively.

The system composed of S_{mix} at the ratio of 3:1 showed the highest microemulsion area (Figure 1B). As the S_{mix} (1,2-PG: PEG400DO) ratio changed from 4:1 to 1:3, the ME area gradually increases (Figure 1A-F and Table 1). Whereas, more 1,2-PG addition is prone to form *Z. piasezkii*. oleoresin oil droplets, which is unfavorable to the formation of the microemulsion, so S_{mix} at the ratio of 4:1 showed a decreased microemulsion area (Figure 1A). In conclusion, the ratio of S_{mix} 3:1 is the optimum ratio due to its highest microemulsion area, and its best stability is expected.

3.2 Viscosity of ME

During the storage period only gravity exists, the shearing effect of the dispersed particles is small. Once the viscosity does not change significantly, the almost unchanged viscosity will help delay any destruction phenomenon, such as stratification or sedimentation (Tadros, 2004). Generally, the higher the viscosity of the ME, the smaller the particle size of the dispersed phase, which is beneficial to the stability of the ME (Allouche et al., 2004).

The results of the viscosity of the MEs are shown in Figure 2, and they are significantly different from each other ($p < 0.05$). It can be seen from Figure 2 that as the proportion of the 1,2-PG in the system decreases, the viscosity of the ME first increases and then decreases. When the S_{mix} ratio reaches 3:1, its viscosity reaches a maximum with a viscosity value of 242.17 mPa.s. The experimental results show that when the S_{mix} ratio is 3:1, the stability is the best and this result is the same as that of the pseudo ternary phase diagram. This is because the higher viscosity can prevent the contact between the emulsions and avoid the flocculation and aggregation of the emulsions (Zheng et al., 2020), so the stability of ME can be improved.

Besides, viscosity changes with storage time also have been investigated. The result of viscosity change with storage time is shown in Figure 3. The viscosity of ME tend to increase in the first week and decreased, while there was no significant change occurred in viscosity under test conditions. These results indicate that the ME prepared contains particles that can disperse well. The almost unchanged viscosity will help delay phase separation, turbidity, and sedimentation. The sediment in ME exists in the form of a crystal, and it can be observed by a polarizing microscope (PLM). It is worth noting that viscosity is the kinetic key parameter that determines the nucleation and growth of crystals in the liquid system. Because the increase of viscosity reflects the increasingly longer time scale for structural rearrangements in the liquid state, which results in a smaller driving force for crystallization. So, S_{mix} ratio of 3:1 with maximum viscosity value has minimum drive force for crystallization.

Table 1. ME formation area on different S_{mix} (1,2-PG: PEG400DO) weight ratio.

S_{mix} ratio (m:m)	Microemulsion formation area (%)
4:1	27.18
3:1	37.54
2:1	33.53
1:1	30.93
1:2	31.19
1:3	27.97

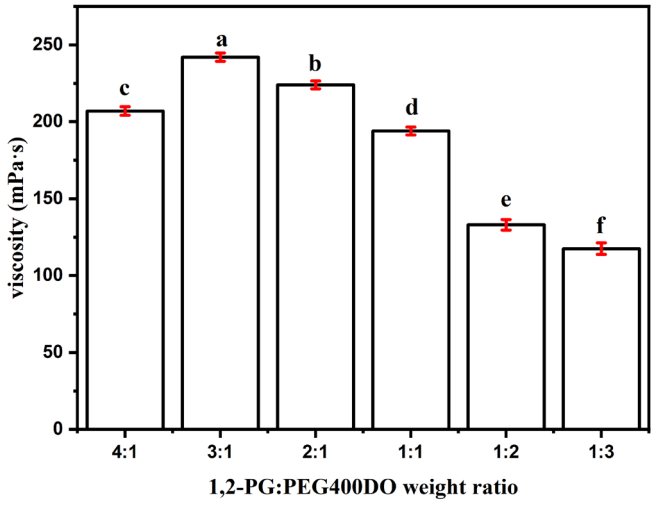

Figure 2. Viscosity of MEs in different weight ratio of S_{mix} (mean ± SE, n = 3). Values followed by the same letter are not significantly different according to Duncan's multiple range test at the 5% level.

3.3 Surface tension of ME

Studies have shown that the stability of the ME can also be determined by measuring the surface tension. The surface tension results of MEs are shown in Figure 4, which can be seen that as the proportion of S_{mix} decreases, the surface tension of MEs tends to decrease first and then increase. Although there are statistical differences, there is little difference in surface tension values between 29.04 and 29.75 mN/m. When the S_{mix} ratio reaches 3:1, the surface tension reaches the maximum, which is 29.75 mN/m. The constant value of surface tension indicates that the molecules present in the system are not freely available to diffuse to the newly created interface, suggesting the stability of the microemulsion system (Maulvi et al., 2020). This in turn

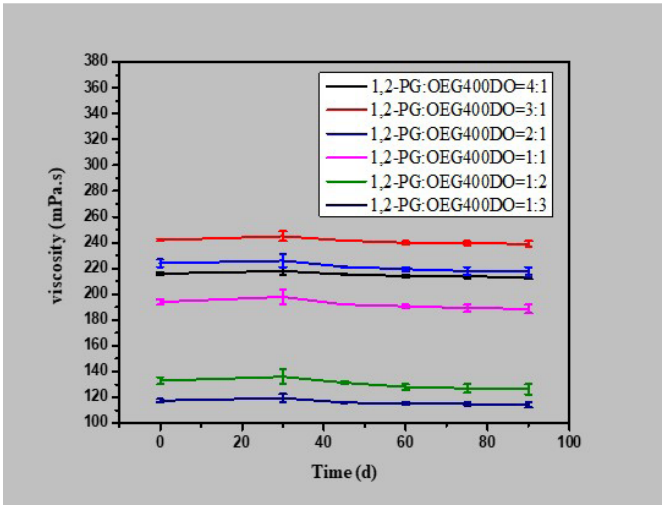

Figure 3. Viscosity of MEs change with storage time for weight ratio of S_{mix}.

demonstrated the physical stability of *Z. piasezkii.* oleoresin was successfully improved via the ME system. Surface tension may not be the main influencing factor for the storage stability of ME.

3.4 Centrifugal experiment on ME

The stability of ME was evaluated by an accelerated stability test (Chen et al., 2000). The MEs were centrifuged for 70 min at 7000 r/min, 8000 r/min, 9000 r/min, 10000 r/min, 11000 r/min, and 12000 r/min, equivalent to 30 d, 40 d, 50 d, 63 d, 77 d, and 90 d, respectively (Gunarto et al., 2021). It can be seen from Table 2 that MEs showed clarity and transparency and were not layered all after a high-speed centrifuge lower than 10000 rpm for 70 min. After centrifugation at 11000 rpm for 70 min, stratification of ME with 1:3 and 1:2 of S_{mix} took place.

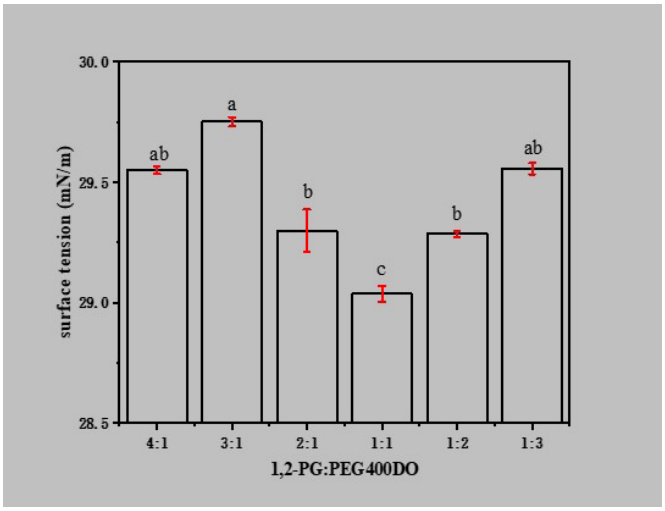

Figure 4. Surface tension of MEs in different weight ratio of S_{mix} (mean ± SE, n = 3). Values followed by the same letter are not significantly different according to Duncan's multiple range test at the 5% level.

Continue to increase the speed to 12000 rpm for 70 min, only 3:1 of S_{mix} witnessed a transparent phenomenon. These results are consistent with the results of the microemulsion area and viscosity mentioned above. A previous study indicated that the centrifugal stability is probably related to viscosity and so on, meaning the microemulsion system has corresponding viscosity which can stabilize microemulsion particles (Grit & Crommelin, 1993).

3.5 Standing experiment

Under the conditions of the constant temperature of 26 °C and numbness of 190, the static results of the MEs are shown in Table 3. From Table 3, ME with the S_{mix} ratio of 1:3 can maintain a stable state for 45 d, and the ratio of 1:2 ME can remain stable for 50 d. ME with a ratio of 1:1 can keep transparent for 60 d and ME with a ratio of 2:1 retains stability for 75 d, ME with 4:1 ratio holds for 80 d. Phase separation, transparency, and the sediments did not appear until 90 d for the 3:1 ME. It is in agreement with the conclusions obtained from the results mentioned above. The phenomenon can be also visualized with the aid of a polarizing microscope (Figure 5) after standing for 90 d. No crystallization appears for ME with a ratio of 3:1. Crystal size and quantity decreased in the order as follows: ME with the S_{mix} ratio of 1:3, 1:2, 1:1, 2:1, and 4:1.

3.6 Freeze-thaw test

The freeze-thaw test is one of the physical stability evaluations to determine whether the formula remains stable at low temperatures (Belayneh et al., 2017). Sedimentation took place for the ME with a S_{mix} ratio of 1:3 after the second freeze-thaw cycle, and sediment occurred after the third freeze-thaw cycle for the MEs with a ratio of 1:2 and 1:1 and after the fifth freeze-thaw cycle with the 2:1 ME, respectively. However, no sediment appeared, as to 3:1 and 4:1 MEs after the sixth freeze-thaw cycle, which indicates better stability of

Table 2. Centrifugal phenomenon of MEs in different weight ratio of S_{mix}.

Different speed (r/min)	Phenomenon
7000	No sediment
8000	No sediment
9000	No sediment
10000	No sediment
11000	Stratification of ME with 1:3 and 1:2 of S_{mix} took place
12000	Only 3:1 of S_{mix} witnessed transparent phenomenon

Table 3. The static experiment phenomenon of MEs in different weight ratio of S_{mix} (1,2-PG: PEG400DO).

S_{mix} ratio (m:m)	Numbness	Temperature (°C)	Phenomenon
4:1	190	26	Sediment appeared after standing for 80 d
3:1	190	26	No sediment appeared after standing for 90 d
2:1	190	26	Sediment appeared after standing for 75 d
1:1	190	26	Sediment appeared after standing for 60 d
1:2	190	26	Sediment appeared after standing for 50 d
1:3	190	26	Sediment appeared after standing for 45 d

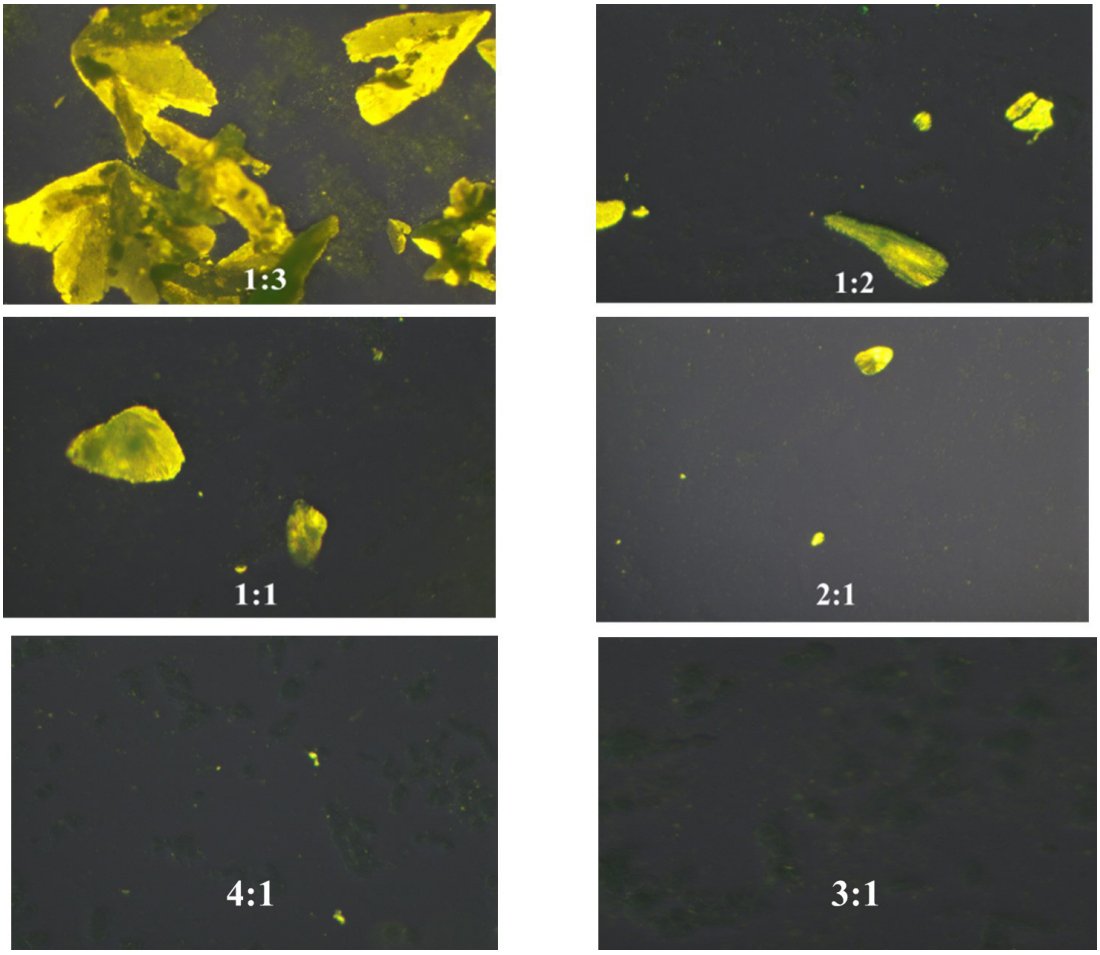

Figure 5. PLM micrographs of the crystallization behavior under different weight ratio of S_{mix}.

ME when the S_{mix} ratio is 3:1 and 4:1. To our knowledge, much 1,2-PG is not permitted to adopt into the system due to the formation of oil droplets in light of the partially soluble system between S_{mix} and essential oil, as well as a complete mutual system of S_{mix} only with appropriate proportion. In addition, a suitable dosage form is needed to formulate *Z. piasezkii.* oleoresin ME, this is to say, much 1,2-PG addition means less PEG400DO, which will reduce the solubility of ME in the oil system and it is not conducive to the latter application of the *Z. piasezkii.* oleoresin. So, combining the previous results we can see that 3:1 (m:m) of S_{mix} was optimal for the preparation of microemulsion.

4 Conclusion

Pseudo ternary phase diagrams of mixtures containing *Z. piasezkii.* oleoresin, essential oil, surfactant PEG400DO, and cosurfactant 1,2-PG were successfully generated. As to the market demand specification of 190 numbness, microemulsions prepared with 40 wt% essential oil, 1.59 wt% surfactant mixture (S_{mix} is 3:1), and 58.41 wt% *Z. piasezkii*. oleoresin was found to have the most favorable characteristics in terms of viscosity, ME area, and physical stability among the different MEs prepared. This study shed new light on the application of *Z. piasezkii.* oleoresin. As an outlook for further applications, cosurfactants should be considered in order to make a system stable enough. The overall effect depended on the type of surfactant and cosurfactant together with an appropriate proportion of S_{mix}.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The present work was supported by the Science and Technology Research and Development Projects of Handan City (grant number 21422012320).

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