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# Effect of cellulose nanocrystal supplementation on the stability of castor oil microemulsion

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ABSTRACT

Microemulsion (ME) is widely used in food, pharmaceuticals, and medical applications. In the formulation of MEs, a substantial amount of surfactant is needed to stabilize the lipo-hydrophilic interface, which may have adverse effects on biological cells. Cellulose and its derivatives have been extensively utilized as solid emulsifying agents, known as pickering agents, which are added to improve the stability of emulsions. In this study, ME made from a mixture of 5 wt% castor oil, 85 wt% surfactant/co-surfactant and 10 wt% water was modified by the addition of cellulose nanocrystal (CNC) in the aqueous fraction. The effect of CNC addition on the ME formation area, hydrodynamic diameter, and stability of resulting modified-MEs were investigated. While the addition of CNC did not contribute to the expansion of the ME formation area, the CNC supplementation has a significant influence on the hydrodynamic diameter and stability of ME. The results of this study demonstrate that the supplementation of CNC can reduce the usage of surfactant for ME formulation, with the use of CNC suspension containing 0.7 wt% CNC resulting in the most favorable hydrodynamic diameter and stability.



## 1. Introduction

Microemulsion (ME) is a dispersion containing oil and water, stabilized by surfactant and co-surfactant to reduce the interfacial layer [1]. ME is isotropic, optically transparent, thermodynamically stable with hydrodynamic ranging between 20 and 200 nm [2]. There are several applications for ME, including enhanced crude oil recovery [3,4], food formulation [5], and as carrier for drug and protein delivery [6–8]. Castor oil (CO) is considerably more hydrophilic in nature owing to the presence of hydroxylated fatty acid chain, ricinoleic acid, which is mainly comprises the fatty acid of esters consisting up to 90%, with the remaining fatty acid components distributed among linoleic, oleic, and stearic acid [9]. Moreover, CO is also reported to have analgesic and anti-inflammatory properties, which may be beneficial when used in applications related to drug formulation or as a drug carrier [10].

Cellulose nanocrystals (CNC) are typically prepared by hydrolyzing cellulose under acidic conditions to breakdown the cellulose into smaller units, which consequently results in higher surface area [11,12]. CNC has an amphiphilic characteristic and could also adsorb both oil and water, acting similar to a surfactant, commonly referred to as pickering agent. In recent years, the use of cellulose-derivatives such as cellulose fibrils, carboxymethyl cellulose (CMC) [13], cellulose nanocrystals (CNC) [14], cellulose nanofibers (CNF) [15], hydroxypropyl methylcellulose (HPMC) [13], and bacterial cellulose (BC) [13,16,17] to produce pickering emulsion (PE) have been reported. Applications of PE containing cellulose include lipid digestion controller [18], and as carrier for the delivery of bioactive compounds and drugs [19,20]. It has been well described that these cellulosic-material may form a mechanical layer of solids that adsorb both water and oil on their interface, thus stabilize the mixture and prevent coalescence [21–23]. Formulation of nano-sized emulsion has been limited. An emulsion made from hexadecane as the hydrophobic phase and the aqueous phase containing bacterial-CNC (b-CNC) can only be successfully produced after b-CNC was surface-modified with chlorine. The addition of surface-modified b-CNC with choline at 6.5 g/L allows the formulation of ME having emulsion with a hydrodynamic diameter ~250 nm, while the use of unmodified b-CNC resulted in an emulsion with a hydrodynamic diameter of 4 μm even with the addition of more than 2 g/L b-CNC [17]. Yan et al. [24] reported that hydrodynamic diameter of the drug-loaded pickering emulsions stabilized by b-CNC with the

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concentrations of 0.3, 0.6 and 0.9 wt% in the aqueous solution have hydrodynamic diameter of 18.5, 14.6 and 8.8 μm, respectively. With increasing CNC concentration, the size of pickering emulsion droplets became smaller and more uniform. With the proper composition and/or formulation, it is expected that CNC can be adopted in the formulation of ME to achieve hydrodynamic diameter lesser than 200 nm.

Castor oil and tween 80 as components of ME formulation was also studied by Choi et al. [25], where rutaecarpine-loaded ME was stable for 6 months. From a related work [26], ME made from castor oil, tween 80, ethanol, and DI water were found to be stable during storage at 25 °C, 4 °C, and 50 °C for a period of 160 days, with its hydrodynamic diameter increasing by 4.43% to 13.49% during the storage period. Addition of CNC as pickering agent is proposed to suppress the increase in hydrodynamic diameter of ME formulated. Tween 80 as surfactant and ethanol as co-surfactant are widely used in ME formulation and possessed largest ME area by combination with castor oil.

In this study, the addition of CNC was explored to determine the possibility of improving the microemulsion region and reduce the hydrodynamic diameter of mixtures prepared from CO with Tween 80 and ethanol as co-surfactant. Further the influence of CNC towards the stability of the ME during storage under various extreme conditions of temperature and gravitational pull is also investigated, with hydrodynamic diameter as the main parameter monitored to ensure that the mixture still qualifies as a ME.

## 2. Materials and methods

### 2.1. Materials

Castor oil and surfactant Tween 80 (TW80) were purchased from Sigma-Aldrich (Lanchasire, UK). The acquired CO consists of 5.55% monoglyceride (MG), 10.29% diglyceride (DG), 82.28% triglyceride (TG), and 1.88% unsaponifiable matter. The fatty acid distribution of the CO is as follows, 1.57% palmitic acid (C16:0), 1.47% stearic acid (C18:0), 5.08% oleic acid (C18:1), 4.6% linoleic acid (C18:2), 84.85% ricinoleic acid (C18:1), and 0.86% arachidonic acid (C20:4). Lipid and fatty acid profiles were determined using gas chromatography (GC-2010 Plus, Shimadzu), with chromatographic peaks compared with analytical standards obtained from Sigma Aldrich, following methods previously established [27], while unsaponifiable matter content was determined following standard methods from AOAC [28]. Ethanol (99% purity) was obtained from Echo Chemical (Taipei, Taiwan). Sulfuric acid (95–98% purity) was obtained from Scharlau (Spain, European Union). All chemicals were directly used as purchased without further purification. The detailed preparation of cellulose nanocrystal (CNC) from filter paper can be found elsewhere [29].

### 2.2. Construction of phase diagram

Water titration method was adopted to gather data for constructing the pseudoternary phase diagrams. The surfactant-co-surfactant mixture ($S_{mix}$) were prepared by mixing TW80 and ethanol at weight ratios of 1:2, 1:1 or 2:1, subsequently called as $S_{mix}$ 0.5, $S_{mix}$ 1, and $S_{mix}$ 2. The $S_{mix}$ was then added to oil at different weight ratios of 10:1, 8:1, 6:1, 3:1, 2:1,1:1, 1:2, 1:3, 1:6, 1:8, 1:10 and 1:50. Meanwhile, CNC-suspension was prepared by suspending corresponding amounts of CNC in water to result in a mixture having 0.05, 0.1, 0.3, 0.5 or 0.7 wt% CNC. The CNC suspension was added dropwise to the $S_{mix}$-oil mixture, and then vigorously mixed by a Vortex Mixer (Scientific, Vortex Genie II) at room temperature. Phase clarity was assessed visually, samples with transparent and/or translucent appearance were considered as ME. These MEs were then characterized and its stability was investigated. The ME formation area from pseudoternary phase diagram was obtained by Origin software and calculated following Eq. (1).

$$\%ME\ formation\ area = \frac{area\ obtained\ from\ Origin}{0.5} \times 100 \quad (1)$$

### 2.3. Characterization of MEs

In the assessment of the storage stability of the ME formulated using CO-TW80-Ethanol-Water, the formulation containing 0.75 g of CO, 12.75 g of surfactant mixture ($S_{mix}$), 1.5 g of water or CNC-suspension was adopted in reference to the work of Gunarto et al. [26]. Surfactant mixture will be varied to contain different weight ratio of TW80 to ethanol of either 1:2, 1:1 or 2:1. As for the CNC suspension concentrations of CNC dispersed in water will be varied from 0 to 0.7 wt%. A total of 15 formulations were prepared and tested of their stability as detailed in the following subsections.

#### 2.3.1. Determination of hydrodynamic diameter

The hydrodynamic diameter, polydispersity and zeta potential were measured using a Zeta Potential & Particle Size Analyzer (ZetaPALS, Zeta Potential Analyzer, Brookhaven) at 298 K and a fixed angle of 90°. To avoid multiple scattering effects in the measurements, samples were diluted 100-fold with double-distilled water immediately before measurement. Triplicate analyses were carried out for each condition.

ME stability was investigated based on its consistency during storage and thermal inflation treatment. After each conducted treatment, MEs were analyzed for their hydrodynamic diameter, polydispersity and zeta potential. Three-stage thermal treatment was applied on ME samples to determine their thermal stability.

#### 2.3.2. Heating-cooling

First, the freshly formulated MEs were subjected to 6 heating-cooling cycles at temperature 40 °C and 4 °C, with 48 h duration for each temperature [30]. After each temperature adjustment, the samples were collected and examined. The samples which remained stable after underwent 24 days the heating-cooling treatments, were subjected to centrifugation test.

#### 2.3.3. Centrifugation test

Considering that MEs are a type of dispersed mixture or suspension, it may over time settle and form distinct phases during storage. Unfortunately, it would not be practical to carryout actual storage test for 1 year. Thus, samples were exposed to induced gravitational force via centrifugation, where the test was conducted at 9200 rpm (7920 xg) for 5 h. At an interval of 1 h, the samples were observed to ensure that no phase separation occurred. Induced centrifugal force equivalent to gravitational pull for a period of one-year [44] was used to determine the influence of gravity of the ME stability during storage.

#### 2.3.4. Freeze-thaw cycle

The samples which did not show cracking, creaming, nor any phase separation were progressed to 6 freeze-thaw cycles. The freeze-thaw treatment was done at temperature −21 °C and +25 °C, with 48 h duration per subjected temperature change [9]. Then, the samples were collected and examined.

### 2.4. Statistical analysis

All experiments were repeated at least three times and data were displayed as mean value with standard deviation. Statistical significance was tested by two-way analysis of variance (ANOVA) by GraphPad Prism program.

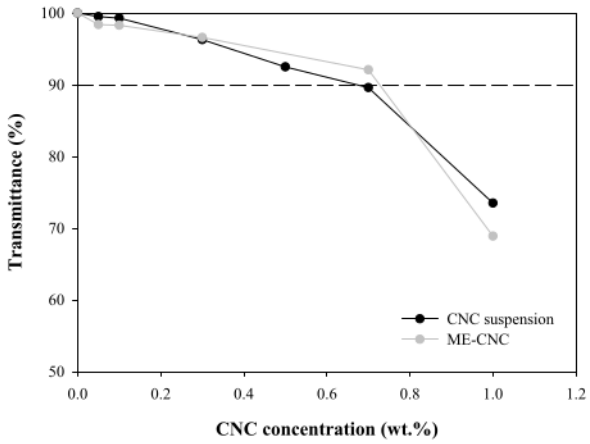


**Fig. 1.** %Transmittance of CNC suspension and ME-CNC (5 wt% CO, 85 wt% $S_{mix}$, and 10 wt% CNC suspension) with various CNC concentration at 650 nm.

## 3. Results and discussion

### 3.1. Effect of CNC addition on ME formation zone

Prior to the actual formulation and testing of different ME, it had to be made sure that the addition of CNC will allow the formulation of an isotropic mixture. The influence of CNC concentration as suspended in water and its addition in the ME matrix was investigated. The percent transmittance (%T) at 650 nm of different CNC suspension and when used in formulating ME was determined and results are presented in Fig. 1. The increase in CNC concentrations up to 0.7 wt% resulted in the gradual decrease in the %T for both CNC suspension and ME-CNC. However, increasing the CNC concentration to 1 wt% resulted in a sharp decrease in the %T to a value below 90%. In most case, a %T higher than 90% is one of the requirement for ME [32], and thus further investigation were limited to a CNC suspension containing up to 0.7 wt% of CNC.

A pseudoternary phase diagram is used to determine the proportion of oil phase, surfactant, and co-surfactant for ME formulation, which is necessary for further applications such as drug loading and release profiling [26,32,33]. The constructed pseudoternary phase diagram for CO and aqueous system with different $S_{mix}$ (0.5, 1, and 2), and with different concentrations of CNC suspension (0.05, 0.1, 0.3, 0.5 and 0.7 wt%) are presented in Fig. S1 –S3, and the formation area summarized in Table 1.

The systems made with low concentrations of CNC (0.05, 0.1, and 0.3 wt% CNC) produced the highest ME formation area at $S_{mix}$ 2, followed by $S_{mix}$ 0.5 and 1. Similarly, at high concentration of CNC (0.5 and 0.7 wt%), the highest ME formation area was obtained at $S_{mix}$ 2. It was noted that $S_{mix}$ 2 allows the formation of emulsions having a large ME formation area regardless of CNC content in the system. However, statistical analysis (ANOVA) on the effect of $S_{mix}$ ratio and CNC concentration on the ME formation area were found to be insignificant (Table S1). Nevertheless, further investigation and test revealed that the $S_{mix}$ ratio and CNC influences the characteristic and stability of the formulated ME, which discussed in the following sections.

**Table 1**
ME formation area on different CNC concentration and $S_{mix}$ ratio.

| CNC concentration (wt%) | Microemulsion formation area (%) | | |
|---|---|---|---|
| | $S_{mix}$ 0.5 | $S_{mix}$ 1 | $S_{mix}$ 2 |
| 0 | 16.49 ± 0.02 [26] | 16.54 ± 1.69 [26] | 16.92 ± 1.29 [26] |
| 0.05 | 16.83 ± 0.17 | 16.51 ± 0.72 | 16.93 ± 0.30 |
| 0.1 | 16.92 ± 0.01 | 16.57 ± 0.23 | 16.64 ± 0.34 |
| 0.3 | 16.53 ± 1.08 | 16.31 ± 0.87 | 16.76 ± 0.19 |
| 0.5 | 16.98 ± 1.04 | 16.98 ± 0.19 | 17.54 ± 0.38 |
| 0.7 | 17.02 ± 0.24 | 16.98 ± 0.02 | 17.02 ± 0.24 |

### 3.2. Characterization of ME

Properties of ME is greatly influenced by proportion of the components making up the ME system [34–36]. As can be observed in Fig. 2, the hydrodynamic diameter of the MEs decreased with increasing CNC concentration, from 163.35 to 129.90 nm at $S_{mix}$ 0.5, 156.10 to 115.45 nm at $S_{mix}$ 1, and 128.20 to 98.45 nm at $S_{mix}$ 2. The supplementation of CNC in the ME significantly reduce the hydrodynamic diameter up to 17%. A more detailed comparison from results presented in Fig. 2a, ME formulated at $S_{mix}$ 0.5 (28.3 wt% TW80 and 56.7 wt% ethanol) with 0.1 wt% and 0.3 wt% CNC has a hydrodynamic diameter similar with the one formulated at $S_{mix}$ 1 (42.5 wt% TW80 and 42.5 wt% ethanol) without CNC supplementation. Increasing CNC (0.7 wt%) in the $S_{mix}$ 0.5 system produced ME with a hydrodynamic diameter of 129.90 nm, which is the same as the ME formulated at $S_{mix}$ 1 with lower CNC concentration (0.5 wt%, hydrodynamic diameter 130.00 nm) and $S_{mix}$ 2 (56.7 wt % TW80 and 28.3 wt% ethanol) with no CNC addition (128.20 nm). Since the content of surfactant decreases with decreasing $S_{mix}$, these results imply that the addition of CNC and at increasing concentration effectively reduces the required amount of surfactant in the system to achieve a desired hydrodynamic diameter. Owing to the amphiphilic property of CNC particles, other components of the ME could be effectively adsorbed and serving as the emulsion at the lipophilic/hydrophilic interface [37].

Evaluation of measured zeta potential of the MEs revealed that the zeta potentials of MEs formulated at $S_{mix}$ 0.5, 1, and 2 were between −3.99 to −4.82 mV for the system without CNC addition. At a given CNC concentration, the absolute difference of zeta potential was less than 4 mV, which suggests that the change of $S_{mix}$ have no effect on the zeta potential of ME system. However, at high concentration of CNC, a big increase in the magnitude of zeta potential (−27.06, −23.46, and −25.29 mV for $S_{mix}$ 0.5, 1, and 2, respectively) can be observed. With CNC having negative-charged surface, it may be considered as surface-active particles and may have contributed to their role as an emulsifier or pickering agent [38–40] and could potentially enhance the stability of ME system [38,41,42]. Comparing the data presented in Fig. 3a and b, smaller hydrodynamic diameter obtained at higher CNC concentrations also corresponds to higher absolute values of zeta potential (mV) which is indicative that the smaller

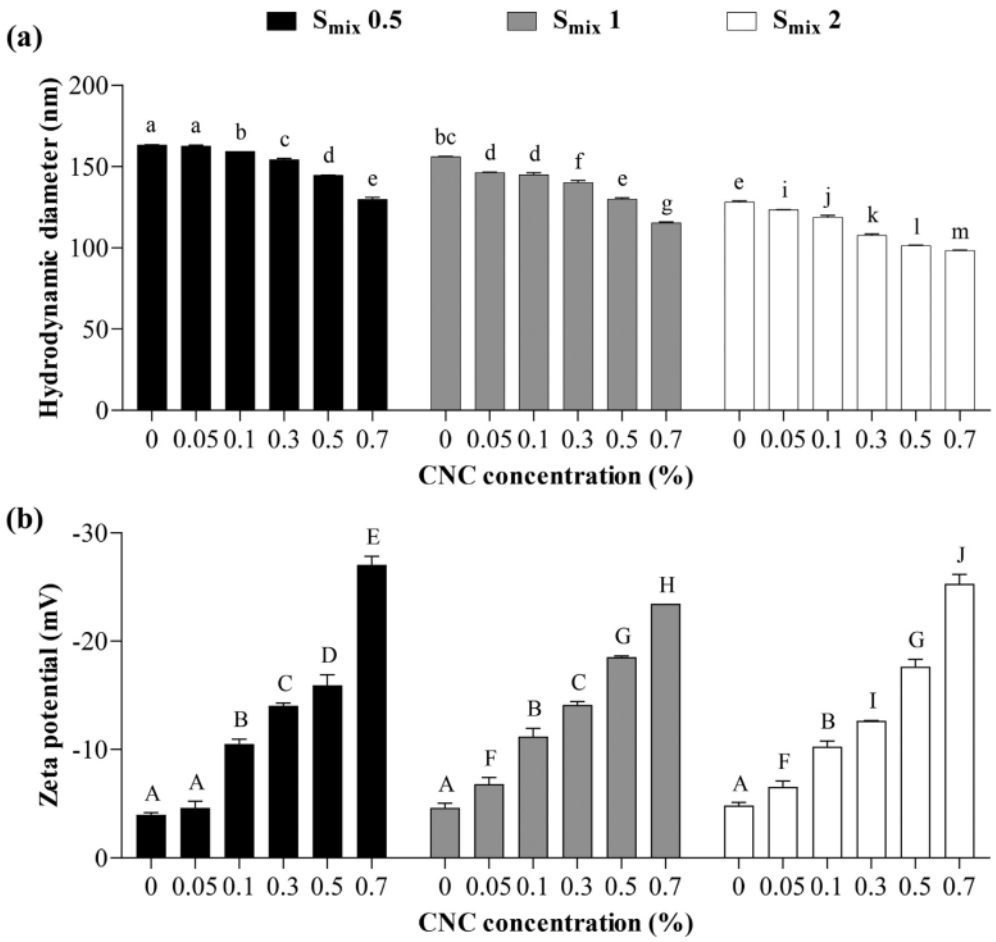


**Fig. 2.** Changes of (a) hydrodynamic diameter and (b) zeta potential of MEs with CNC concentration at three different $S_{mix}$ (0.5, 1 and 2). Multiple comparisons of means were performed using Tukey's test at 0.05 significance level. Different letters indicate a significant difference among ME formulation. The significance in response to hydrodynamic diameter were indicated in lower-case letters, while the one in response to zeta potential value were labeled in capital letter.

hydrodynamic diameter may have resulted owing to the repulsion between particles in the presence of CNC avoiding coalesces.

### 3.3. Effect of CNC addition on ME stability

For later applicati it is necessary that ME remains stable during storage. Considering that the addition of CNC resulted in the increase in the magnitude of the zeta potential, it is indicative that the resulting emulsion is relatively more stable. However, the extent of how much the CNC influences the ME stability during storage would have to be further tested under extreme storage conditions.

The hydrodynamic diameter of samples after subjecting to 6 heating–cooling cycles were presented in Fig. 3. For the system without CNC, at $S_{mix}$ 0.5 and 1, the hydrodynamic diameter 204.10 and 197.85 nm, respectively, tends to exceed the upper limit for ME. The zeta potential measured for systems without CNC is about −4 mV (Table S2). The low zeta potential might contribute to size growth since it cannot provide enough electrostatic repulsion between droplets. In addition, TW80 may have underwent conformation changes under high temperature which resulted in the exposure of the hydrophobic tails, and resulting in the increased the hydrophobic attraction between oil droplets [43]. For ME systems with higher CNC concentrations (0.3 to 0.7 wt%), their hydrodynamic diameters can be maintained below 200 nm.

After heat-cooling cycle test, samples were subjected to centrifugation. No phase separation was observed after centrifugation and there was no significant difference or changes in hydrodynamic diameter after centrifugation (Fig. 3). This indicates that all samples have good stability against gravitational pull when stored for a period of 1 year.

Samples were further subjected to freeze-thaw cycles after they have passed the centrifuge test. The freeze-thaw test is one of the physical stability evaluations to determine whether the formulation will remain stable at low temperature. This test can be associated to the necessity of storing drug/active compound-containing MEs under low temperature while maintaining functionality and preventing degradation. Hydrodynamic diameter of most samples significantly increased after 6 freeze-thaw cycles. Disparate from other systems, the ME formulated with 0.7 wt% CNC at $S_{mix}$ 2 showed non-significant size difference after freeze-thaw treatment (Fig. 3).

Enhanced stability can be noted by comparing the hydrodynamic diameter of ME prepared at $S_{mix}$ 0.5 with CNC 0.1 and 0.3 wt% vs. $S_{mix}$ 1 without CNC, where both systems initially produced ME with similar sizes ranging between 154 and 160 nm. After a set of thermal stability tests, the hydrodynamic diameter of ME without CNC (at $S_{mix}$

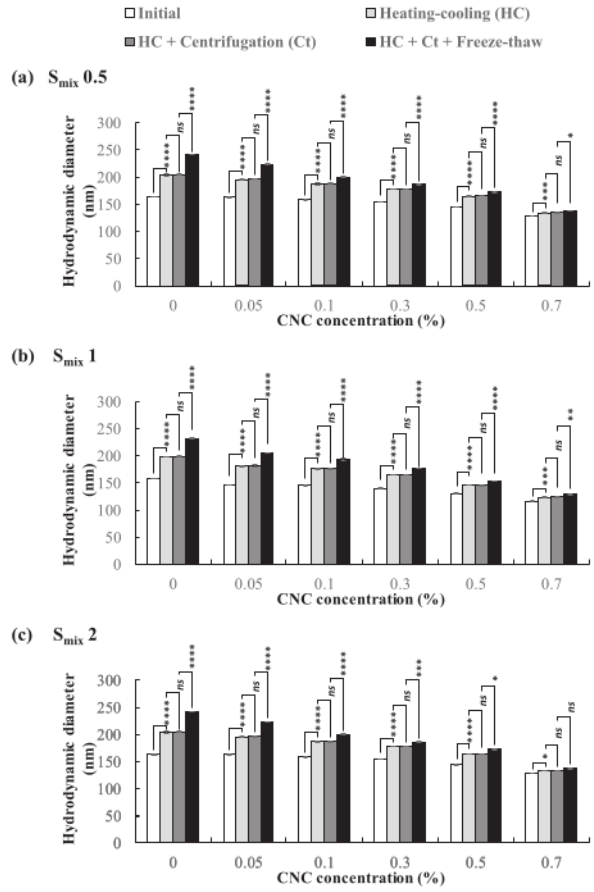


**Fig. 3.** Hydrodynamic diameter of ME formulated at $S_{mix}$ ratio of 0.5 (a), 1 (b), and 10 after consecutive heating-cooling, centrifugation, and freeze-thaw treatments. The asterisks indicate significant differences after treatment tested by ANOVA statistical analysis with Sidak's multiple comparison test. ns, not significant; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$.

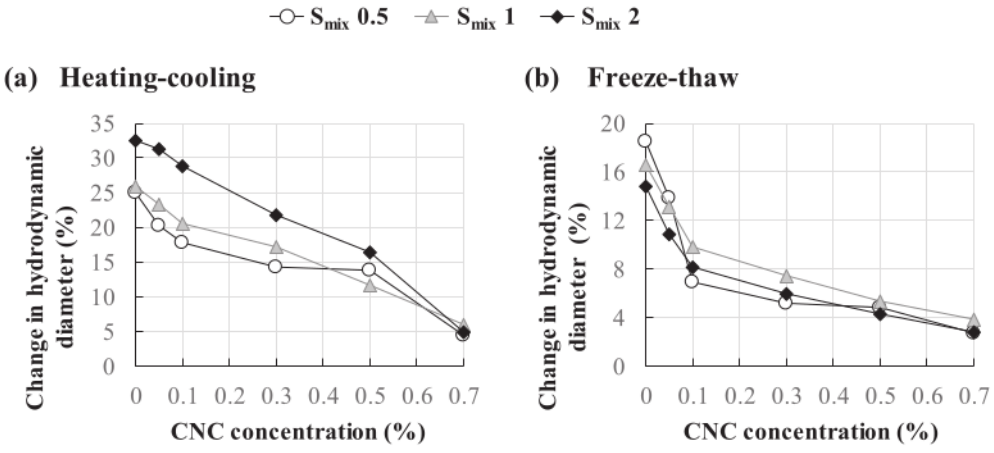


**Fig. 4.** Percent increase in hydrodynamic diameter of ME particle after 6 heating-cooling cycles (a) and 6 freeze-thaw cycles (b).

1) increased to 231.75 nm, while the one with 0.1 and 0.3 wt% CNC supplementation (at $S_{mix}$ 0.5) grew to 200.85 and 187.00 nm. Similar phenomena can be observed by assessing the stability of same-sized ME (~129 nm) which can be obtained at different formulations: $S_{mix}$ 0.5 with 0.7 wt% CNC, $S_{mix}$ 1 with 0.5 wt% CNC, and $S_{mix}$ 2 without CNC. The hydrodynamic diameter of these MEs increased to 137.40 nm, 154.05 nm and 196.20 nm, respectively after thermal stability test. These results imply that the increase in ME hydrodynamic diameter was greater for systems without CNC which demonstrated the contribution of CNC in improving ME stability and maintaining the hydrodynamic diameter of ME (Fig. 4).

Based on the stability test done in this study (Figs. 3 and 4), heating-cooling treatment yielded the most prominent effect on hydrodynamic diameter of MEs without CNC supplementation. Supplementation of CNC substantially enhanced the thermal stability of ME. As presented in Fig. 4a, for $S_{mix}$ 2, after 6 heating-cooling cycles hydrodynamic diameter of the system without CNC increased by 32.45%; while the one supplemented with 0.7 wt% CNC showed significantly smaller hydrodynamic diameter growth (4.98%). Supplementation of 0.7 wt% CNC also hampered the growth of ME droplet from 18.46% to 2.69% in ME with $S_{mix}$ 0.5. The stabilizing effect of CNC can be attributed to its nano-sized droplets, which ensure better contact with oil and water interface, along with its negatively charged surface which provides better hindrance and prevent droplet coalesces.

For comparison, commercial CNC (CelluForce, Canada) was used in the ME formulation with a $S_{mix}$ of 2. Unfortunately, the stability of ME-commercial CNC increased the percentage of hydrodynamic diameter 18.71% after 6 heating-cooling cycles. Further analysis using energy dispersive spectroscopy after electron microscopic scans, the sulfur to carbon weight ratio (S/C) of CNC synthesized in this study and commercial were 0.0233 and 0.0031, respectively. These results also imply that the presence of higher sulfur may have contributed to the more negatively charged surface, which in turn contributed to the more stable ME formulated or produced.

## 4. Conclusion

Pseudoternary phase diagrams of mixtures containing castor oil, surfactants (Tween 80 and ethanol) and suspensions of cellulose nanocrystals containing 0 to 0.7 wt% CNC, were successfully generated with 3 different surfactant mixtures. Presence of CNC in the ME did not result in significant changes in the ME formation area. Microemulsions prepared with 5 wt% CO, 85 wt% surfactant mixture, and 10 wt% CNC-suspension (containing 0.7 wt% CNC) was found to have the most favorable characteristics in terms of hydrodynamic diameter (98.45 nm) and stability among the different ME prepared and tested. The presence of CNC in the ME resulted in the decrease of the hydrodynamic diameter, while at the same time improved the stability of the ME during storage. As a pickering agent, CNC not only improves the stability of the ME may also enable formulation to be made using less amount of Tween 80. The addition of CNC in ME formulation may well serve as means to achieve the desired hydrodynamic diameter to meet requirements in applications like those in drug delivery systems.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molliq.2020.115181.

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