



## Formulation of buccal microemulsions containing fluocinolone acetonide

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### Introduction

Oral lichen planus (OLP) is a common chronic mucocutaneous inflammatory disease. OLP is a T-cell mediated autoimmune disease. OLP can present as small, raised, white, papules, or plaques. Atrophic lesions and erosions are the forms most likely to cause pain. [1] Topical corticosteroids have been widely used for reducing inflammation and pain.[2] Fluocinolone acetonide (FA) was used in 0.1% concentration for oral lichen planus therapy without serious complication in form of oral gel. FA 0.1% can reduce severity of atrophic and erosive lichen planus.[3] Microemulsions (MEs) are clear, stable, and isotropic mixtures of oil, water, surfactant, and co-surfactants at appropriate ratio. MEs are considered as good liquid vehicles for drug delivery systems that their advantages include the thermodynamic stability, ease of preparation, enhancing drug solubilization, high drug loading capacity, penetration-enhancing ability, and small droplet size within range 10-140 nm. In addition, MEs provide a very low interfacial tension resulting in excellent contact with skin surface as well as buccal mucosa.[4, 5] To gain the advantages of microemulsions, FA microemulsions will be prepared for the treatment of OLP. Moreover, suitable ingredients in the formulation for buccal used should be concerned. The purpose of the present work is to formulate buccal microemulsions of FA.

### Materials and methods

Solubility studies for screening of microemulsion components Solubilities of FA in different oils (clove oil, peppermint oil, medium chain triglyceride, and capric/caprylic triglyceride) were determined. An excess amount of the drug was added to 3 mL of various oils filled in amber glass vials and the vials were rotated 360° for 24 hours at room temperature. The samples were filtered, properly diluted and analyzed using High Performance Liquid Chromatography (HPLC) method to determine the drug concentration.

Construction of pseudo-ternary phase diagram In order to determine the concentration ranges of components in MEs, pseudo-ternary phase diagrams were constructed using water titration method. Surfactant mixtures, Tween 80 and PEG 400, were prepared at the ratio of 1:1 and 2:1 by weight. Then each ratio of the surfactant mixtures was added in to the oils at the ratio of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1. Water was added drop by drop to the mixtures under moderate stirring until visual changes in the sample from turbid to transparent and from transparent to turbid. Concentrations of the three components were used for preparing pseudo-ternary phase diagrams. Area in the phase diagram was defined into clear region and turbid or phase-separate region. Only the area covered by the transparent region was termed as the microemulsion existence region.

Selection of the suitable microemulsions Based on the pseudo-ternary phase diagrams, suitable ratios of oil, Smix and water for preparation of oil-in-water MEs were chosen for further study. The combinations were selected in the transparent region of the pseudo-ternary phase diagram. Then 0.1% FA was prepared in the selected microemulsions. The suitable ME was considered when clear 0.1% FA preparations were obtained.

### Results and discussions

Solubility studies for screening of microemulsion components The high solubility is very important to develop microemulsion formulation resulting in high drug loading. In order to screen appropriate oil phase for preparation of MEs, the solubility of FA in different oils was determined and the results are shown in Table 1. Even though, medium chain triglyceride and capric/caprylic triglyceride have been widely used in ME preparation but these oil did not dissolve FA well. Due to high solubility of FA in clove oil (25.22 mg/ml) and peppermint oil (9.5 mg/ml), clove oil and peppermint oil were selected as the oil phase for the development of microemulsion systems. Besides clove oil and peppermint oil were widely used in dental preparations. Clove oil was reported as a natural antibacterial agent against cariogenic and periodontopathogenic bacteria. [6] Both of clove oil and peppermint oil have good odor and taste.

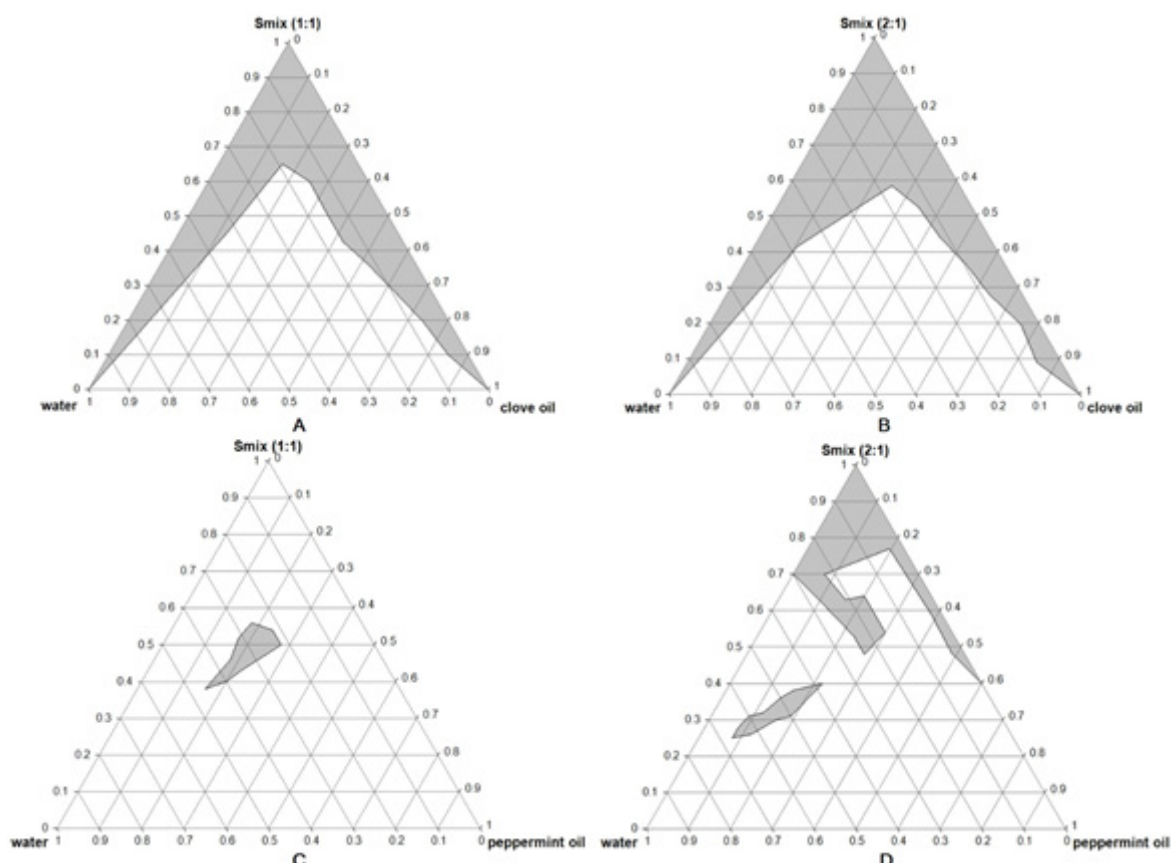
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**Table 1** Solubility of FA in different oils (n=3, mean  $\pm$  SD)

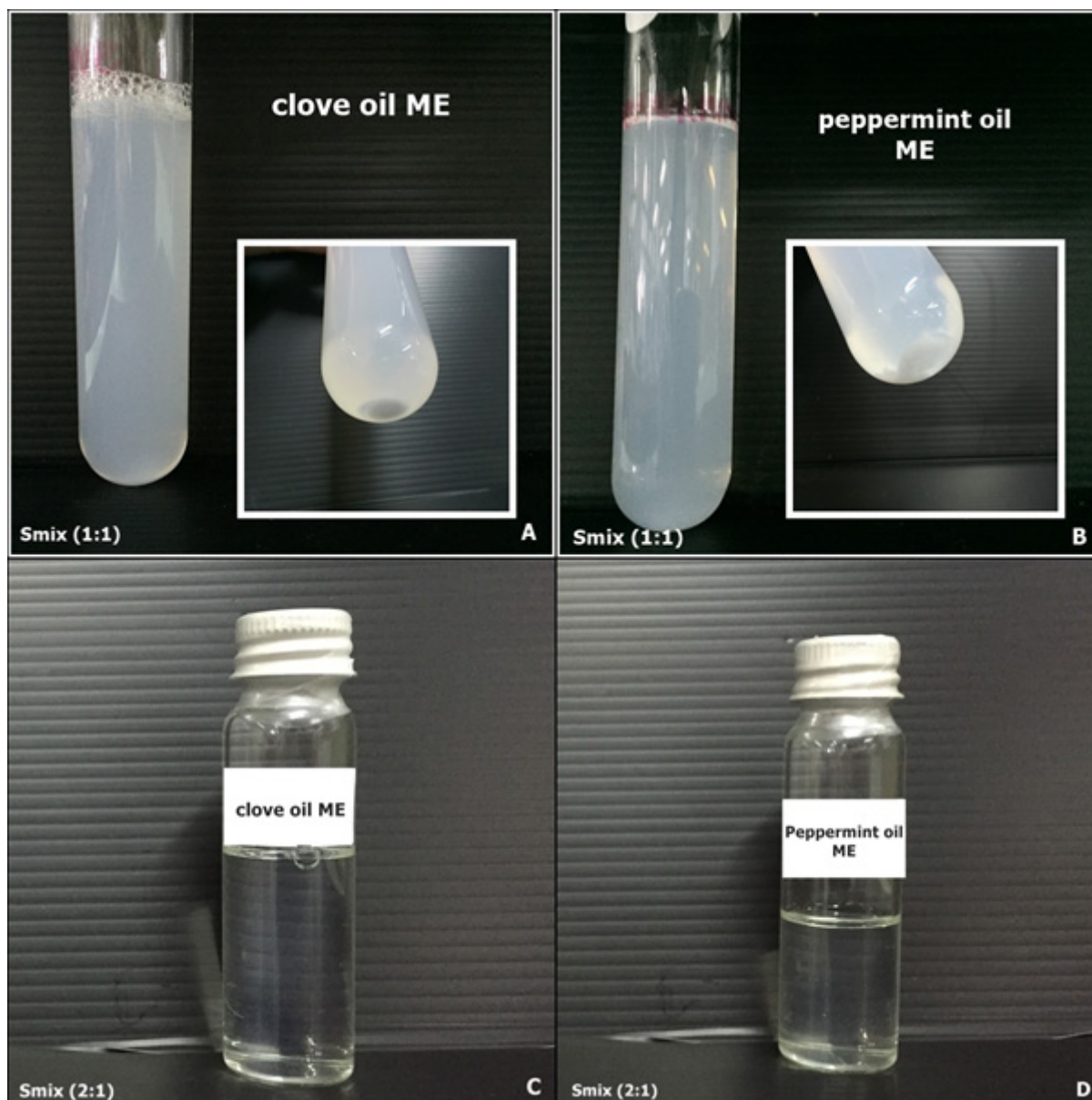
Oil	Solubility (mg/ml)
Clove oil	25.22 $\pm$ 1.32
Peppermint oil	9.50 $\pm$ 0.65
Medium chain triglyceride	1.18 $\pm$ 0.11
Capric/caprylic triglyceride	1.32 $\pm$ 0.11

Construction of pseudo-ternary phase diagrams The pseudo-ternary phase diagrams were constructed to determine the existing region of microemulsion. The pseudo-ternary phase diagram of oil-in-water MEs composed of clove oil or peppermint oil, Tween 80, PEG 400 and water. As shown in Figure 1, the diagram containing Smix (2:1) provided a larger ME region than the one containing Smix (1:1) since increasing ratio of surfactant to co-surfactant can enhance micelle formation which consequently increases the solubilizing capacity of the MEs. [7]

Selection of the suitable microemulsions The criteria for selection of microemulsion formulations were based on their physicochemical properties that should be clear or transparent, no precipitation, low viscosity, and no separation. Turbid 0.1% FA MEs were obtained from the systems containing Smix (1:1) and precipitation of FA was observed in 24 hours as shown in Figure 2. On the other hand, clear 0.1 % FA MEs without precipitation were received when prepared in blank MEs of 3.5% clove oil, 31.5% Smix(2:1), 65 % water and 15% peppermint oil, 35% Smix(2:1), 50% water.



**Figure 1** Pseudo-ternary phase diagrams composed of clove oil (A,B) or peppermint oil (C,D), surfactant mixture (Smix) and water and shade area representing ME region



**Figure 2** 0.1% FA in MEs containing Smix (1:1) ratio (A,B) and Smix (2:1) ratio (C, D)

### Conclusion

Pseudo-ternary phase diagrams containing clove oil or peppermint oil were constructed in order to formulate microemulsions. The use of Smix (2:1) ratio of Tween80 to PEG400 provided a larger ME region in phase diagrams compared with Smix (1:1) ratio. In addition, the blank MEs containing Smix (2:1) dissolved FA better than the one containing Smix (1:1) ratio because 0.1% FA in MEs of Smix (1:1) ratio became turbid.

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