


Asia-Pacific Journal of Science and Technology
<https://www.tci-thaijo.org/index.php/APST/index>

 Published by Research and Innovation Department,
Khon Kaen University, Thailand

Water Tolerance and Matrix Morphology of Aqueous-induced Borneol-based *In Situ* Matrix Formation for Periodontal Pocket Delivery

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Received 11 May 2025

Revised 20 March 2026

Accepted 23 April 2026

Abstract

In situ forming matrix systems (ISMs) have gained increasing attention for localized drug delivery, particularly for periodontal pocket treatment through injection. Crevicular fluid exposure can induce a phase transformation of the ISM from a solution into a matrix. Organic solvents, including ethanol, *N*-methyl pyrrolidone (NMP), dimethyl sulfoxide (DMSO), and 2-pyrrolidone, are typically used in ISM formulations due to their water miscibility and biocompatibility. In this study, 40% borneol solutions in these solvents were used as the matrix former. The water tolerance, defined as the minimum amount of water needed to induce phase inversion from a solution into a matrix, was investigated employing an aqueous titration technique. The water tolerance levels for borneol were 39.65%, 14.77%, 7.40%, and 6.71% v/v in ethanol, NMP, DMSO, and 2-pyrrolidone, respectively. Borneol in DMSO demonstrated low water tolerance and low viscosity (5.61 ± 0.12 cPs), which facilitates rapid matrix formation and ease of administration into the periodontal pocket. Thus, DMSO was considered a suitable solvent for borneol-based ISM. Further, the morphology of the borneol crystal matrix was evaluated under an inverted stereomicroscope at various borneol concentrations (10%–60%). Formulations with lower borneol concentrations required more time to crystallize than those with higher concentrations. The resulting crystal matrix entrapped the drug, thereby retarding its release. The choice of solvent and borneol concentration significantly affected the matrix formation rate and morphology. Therefore, the appropriate selection of solvent and borneol concentration is crucial for developing an aqueous-induced borneol-based ISM for periodontitis treatment.

Keywords: Borneol, *In-situ* forming matrix, Morphology, Periodontal pocket delivery, Water tolerance

1. Introduction

In situ forming matrix systems (ISMs) have attracted attention as an innovative strategy for localized drug delivery, providing a controlled release mechanism particularly suited to treat periodontal pockets [1]. These injectable formulations undergo a transformation from a liquid solution to a semi-solid matrix upon contact with crevicular fluid [2], effectively enabling the drug to be retained and gradually released in the localized target area. This unique property is highly beneficial in periodontal treatment, as it improves drug concentration directly at the infection site while reducing systemic exposure and side effects.

The selection of an appropriate solvent plays a crucial role in the efficiency and biocompatibility of ISM formulations. Solvents, including ethanol, *N*-methyl pyrrolidone (NMP), dimethyl sulfoxide (DMSO), and 2-pyrrolidone, are commonly employed due to their water miscibility and compatibility with biological tissues [3]. Borneol, a bicyclic monoterpene alcohol, has been identified as an effective matrix-forming agent in ISMs due to its ability to precipitate and form a stable matrix upon contact with water [4]. Borneol concentration and

solvent selection significantly influence the matrix formation rate, water tolerance, and morphological characteristics of the resulting system.

This study aims to investigate the water tolerance and crystal growth morphology of borneol-based ISM formulations prepared with various solvents by evaluating the impact of these factors on phase inversion dynamics and matrix stability for periodontal therapy. These findings highlight the significance of solvent selection and borneol concentration in achieving efficient and rapid matrix formation, ultimately improving the therapeutic efficacy of ISMs in localized drug delivery applications.

2. Materials and methods

2.1 Materials

Borneol was collected from Chareonsukosop, Nakhon Pathom, Thailand. Solvents used in the formulation included NMP (lot no. A0251390; Fluka, New Jersey, USA), DMSO (lot no. 3058461; Fluka, Switzerland), 2-pyrrolidone (lot no. BCBF5715V; Fluka, Germany), and absolute ethanol. The model drug included vancomycin hydrochloride (V) (lot no. WA456779T), obtained from Sigma-Aldrich Co. (USA) and supplied by Millimed Pharmaceutical Factory in Samut Prakan Province, Thailand. Sodium hydroxide (lot no. AF310204, Ajax Finechem, Australia) and potassium dihydrogen orthophosphate (lot no. E23W60; Ajax Finechem, Australia) were used to prepare a phosphate-buffered saline (PBS) solution (pH 6.8). Agarose (Lot H7014714, Vivantis, Malaysia) was utilized as supplied without further modification.

2.2 Preparation of borneol-ISM formulations

A series of ISM formulations was prepared using a 40% w/w borneol solution as the matrix-forming agent in four solvents: ethanol, NMP, DMSO, and 2-pyrrolidone. These solvents were selected for their water miscibility and biocompatibility, which are critical attributes for effective *in situ* forming systems. Further, DMSO was used to dissolve various borneol concentrations (10%–60% w/w, labeled as DB10–DB60). To ensure precise proportions, the weight of each component was identified as a percentage of the overall formulation weight. The mixtures, contained in glass bottles, were stirred using a magnetic stirrer (Benchmark H3770-HS-E Digital Hotplate Stirrer, Benchmark Scientific Inc., Sayreville, NJ, USA) until clear solutions were achieved. A separate formulation combining 1% w/w vancomycin hydrochloride with 40% w/w borneol in DMSO (VDB40) was prepared employing the same method. A solution of 1% w/w vancomycin hydrochloride in DMSO (VD) was prepared for control purposes. Table 1 lists the detailed compositions of these formulations.

Table 1 Composition of drug-free and vancomycin HCl-loaded ISM formulations in various solvents

Formulation	Amount (%w/w)		
	Vancomycin HCl	Borneol	Solvent
EB40	-	40	60 (Ethanol)
NB40	-	40	60 (NMP)
PB40	-	40	60 (PYR)
DB10	-	10	90 (DMSO)
DB20	-	20	80 (DMSO)
DB30	-	30	70 (DMSO)
DB40	-	40	60 (DMSO)
DB50	-	50	50 (DMSO)
DB60	-	60	40 (DMSO)
VDB40	1	40	59 (DMSO)
VD	1	-	99 (DMSO)

* DMSO = dimethyl sulfoxide, NMP = *N*-methyl pyrrolidone, PYR = 2-pyrrolidone

2.3 Evaluations

2.3.1 Water tolerance

The water tolerance of each antisolvent-based *in situ* forming matrix (ISM) formulation was determined by identifying the maximum water volume required to induce turbidity, which indicates the onset of matrix phase separation. For each measurement, 5 g of the ISM formulation was placed in a 50 mL Erlenmeyer flask and titrated with distilled water at a constant rate of 0.05 mL/s using a burette. The sample was continuously stirred at 150 rpm using a magnetic stirrer to maintain solution homogeneity throughout the titration process. Titration

continued until visible turbidity was achieved, signifying the water tolerance threshold. The volume of water added at this stage was recorded, and water tolerance was calculated as a percentage using Equation (1) with experiments conducted in triplicate. Lower water tolerance values indicate higher sensitivity of the formulation to aqueous environments, thereby facilitating rapid phase transition into a solid matrix.

$$\% \text{ water tolerance} = \frac{\text{volume of water (ml)}}{\text{volume of water+solution (ml)}} \times 100. \quad (1)$$

2.3.2 Morphology of matrix formation

The interfacial interaction between the ISM formulation and agarose gel was analyzed to explore the phase transition dynamics, employing methodologies adapted from previous research [5]. A 0.6% w/w agarose solution was made by dissolving agarose in PBS at a pH of 6.8 and heating it to 60°C. This solution was then spread onto a glass slide to create a 2 mm-thick agarose gel. After solidification, the gel was carefully trimmed to form a smooth edge and positioned 2 cm away from one side of the glass slide. A 200 µL sample of the ISM formulation was placed adjacent to the trimmed edge of the agarose gel. After exposure of the formulations to PBS within the agarose gel, morphological changes caused by phase inversion at the interface were documented at different time intervals using an inverted microscope (Nikon Eclipse TE2000-S model, Nikon Instruments Inc., USA) at a magnification of 100×.

2.3.3 Surface tension measurement

Surface tension of distilled water and each solvent (ethanol, NMP, DMSO, and 2-pyrrolidone) was identified using the pendant drop method. A droplet of the sample was formed at the tip of a stainless steel needle and suspended in air. A drop shape analyzer (FTA 1000, First Ten Angstroms, USA) was used to capture the droplet profile, and the surface tension was calculated by fitting the droplet shape to the Young–Laplace equation. All measurements were conducted at $20 \pm 1^\circ\text{C}$, and each sample was analyzed in triplicate ($n = 3$).

2.4 Statistical analysis

The data are expressed as the mean $\pm$ standard deviation. Statistical Package for the Social Sciences for Windows (version 11) was used for statistical analysis. A one-way analysis of variance was used to evaluate the significance of the measurements, followed by the least significant difference post hoc test. A p -value of 0.05 indicated statistical significance.

3. Results and Discussion

3.1 Water tolerance

This approach was further applied to evaluate the aqueous sensitivity (water tolerance) of antisolvent-based borneol ISM formulations by quantifying the water volume needed to induce phase separation through titration. Lower water tolerance percentages indicate greater sensitivity of the formulation to aqueous environments, facilitating its ability to rapidly transition into a solid matrix upon contact with water. This characteristic represents a critical parameter in optimizing ISM formulations, particularly in applications where rapid solidification is desired to improve functionality or performance.

Critical end points (EPs) identified during the water titration process are crucial for assessing the water tolerance of borneol-based ISM formulations (Figure 1(a)). These EPs, characterized by distinct physical changes in the solution upon incremental water addition, serve as practical indicators of water sensitivity and phase transition behavior. Before visual assessment, each sample was vortex-mixed utilizing a Genie 2 vortex mixer (G560E, Scientific Industries, NY, USA) at 1500 rpm for 20 s per cycle, repeated three consecutive times to ensure uniform dispersion.

End point 1 (EP1) marks the onset of phase separation and is characterized by the appearance of visible matrix precipitates dispersed within the solution. After vortex mixing under the specified conditions, these precipitated particles remained suspended and did not re-dissolve, whereas the surrounding medium remained predominantly transparent. This stage represents the earliest detectable sign of water-induced destabilization.

End point 2 (EP2) is characterized by system transition into a uniformly turbid and opaque state throughout the entire test tube. No clear liquid phase or discrete dispersed particles are visually distinguishable after vortex mixing. This stage represents the global destabilization of the system and the formation of a homogeneous opaque dispersion. Due to its clear visual distinction and reproducibility, EP2 is considered the primary marker for identifying water tolerance.

End point 3 (EP3) is characterized by the opaque system exhibiting a pronounced increase in viscosity. The formulation demonstrates significantly reduced flowability compared with EP2 upon tilting the test tube. Further water addition does not produce additional changes in turbidity, indicating the completion of phase inversion and matrix consolidation. Visual identification of EP3 may be less precise than EP2 and may require complementary analytical approaches for objective confirmation.

Systematic assessment of EP1, EP2, and EP3 provides insights into the aqueous sensitivity of ISM formulations. In this study, EP2 is highlighted as the preferred measure of water tolerance due to its sensitivity and reproducibility. Water was added at a controlled rate, and the same operator performed observations under identical lighting conditions. Each experiment was conducted in triplicate. Endpoint determination relies on visual assessment; thus, operator experience is important to ensure consistent and reproducible results.

The aqueous sensitivity of the EB40, NB40, DB40, and PB40 formulations corresponded to water usage levels of 39.7%, 14.8%, 7.4%, and 6.7% v/v, respectively (Figure 1(b)). Conversely, borneol demonstrated substantial solubility in ethanol, NMP, DMSO, and 2-pyrrolidone, measured at 71.5%, 66.1%, 67.5%, and 53.8% w/v, respectively, with corresponding log *P*-values of -0.31 , -0.46 , -1.35 , and -0.85 , reflecting the relative polarity of these solvents [6-8]. Water tolerance determination was primarily performed to assess the effect of the solvent type and identify the most suitable solvent for matrix formation. The study focused on concentration-dependent matrix morphology after solvent selection. The influence of borneol concentration on water tolerance has previously been established [5], where increasing borneol content decreased water tolerance values due to enhanced hydrophobicity. Borneol, a bicyclic monoterpene alcohol with a log *P* of 2.85, is classified as a nonpolar substance [9]. Borneol demonstrates hydrophobic behavior more comparable to ethanol than to other solvents due to their similar polarities, leading to the highest water tolerance for the EB40 formulation. As supported by previously reported solubility data [10], the interaction between the hydroxyl group of borneol and ethanol is characterized by strong intermolecular hydrogen bonding, a common behavior observed in binary mixtures of monohydroxy alcohols [11]. This interaction significantly improves the stability of the EB40 formulation, making it more resistant to water interference. Previous research on electrospun borneol-PVP nanocomposites revealed improved physical stability of borneol against sublimation during long-term storage by immobilizing borneol molecules through hydrogen bonding with PVP [12]. Conversely, dipole-dipole interactions primarily dominated the interaction forces between borneol and polar aprotic solvents (NMP, DMSO, and 2-pyrrolidone) due to the high dipole moments of these solvents [13, 14], which lack the strong hydrogen-bonding donor capability found in the borneol-ethanol system. The superior interaction strength in the EB40 formulation impedes water from effectively disrupting the borneol-ethanol molecular arrangement, requiring a larger amount of water to induce phase inversion and borneol separation. This behavior underscores the importance of hydrogen bonding in improving the stability and water tolerance of borneol-based formulations.

The measured surface tension at 20°C for water, ethanol, NMP, DMSO, and 2-pyrrolidone was 72.7, 22.3, 42.4, 43.5, and 46.3 mN·m⁻¹, respectively, affecting their solubility, intermolecular interactions, and overall behavior in various formulations [15-18]. Borneol readily dissolved and interacted with these solvents, showing compatibility. During water titration, the greater density of distilled water caused it to settle within the bulk liquid rather than interact with the surface solution. Meanwhile, the lower density borneol-solvent mixture remained afloat, thereby facilitating phase separation [19]. The variation in surface tension between water and each solvent plays a crucial role in identifying the water tolerance of borneol formulations. Among the formulations, EB40 demonstrated the highest surface tension difference at 50.4 mN·m⁻¹, compared with NB40 at 30.3 mN·m⁻¹, DB40 at 29.1 mN·m⁻¹, and PB40 at 26.3 mN·m⁻¹, requiring a larger volume of water to induce phase inversion and matrix transformation. This explains the superior water tolerance of EB40 relative to other formulations. PB40 showed slightly lower water tolerance than DB40; however, its solvent, 2-pyrrolidone, has substantially higher viscosity (13.30 cps vs. 2.01 cps for DMSO at 25°C) [20, 21], which may slow down the matrix formation process. Conversely, DMSO, with its lower water tolerance and viscosity, facilitates faster matrix formation, making it a suitable solvent for the ISM formation of borneol. These results highlight the interplay between surface tension, viscosity, and solvent interactions in identifying the efficiency and stability of borneol formulations. Furthermore, the formulation comprising 1% w/w vancomycin hydrochloride combined with 40% w/w borneol in DMSO (VDB40) demonstrated a water tolerance of 7.17% v/v, which is not significantly different from the drug-free formulation (VD), with a tolerance of 7.40% v/v ($p > 0.05$). This indicates that the incorporation of vancomycin hydrochloride did not interfere with the phase separation process or the ability of the formulation to transition into a solid matrix when in contact with water.

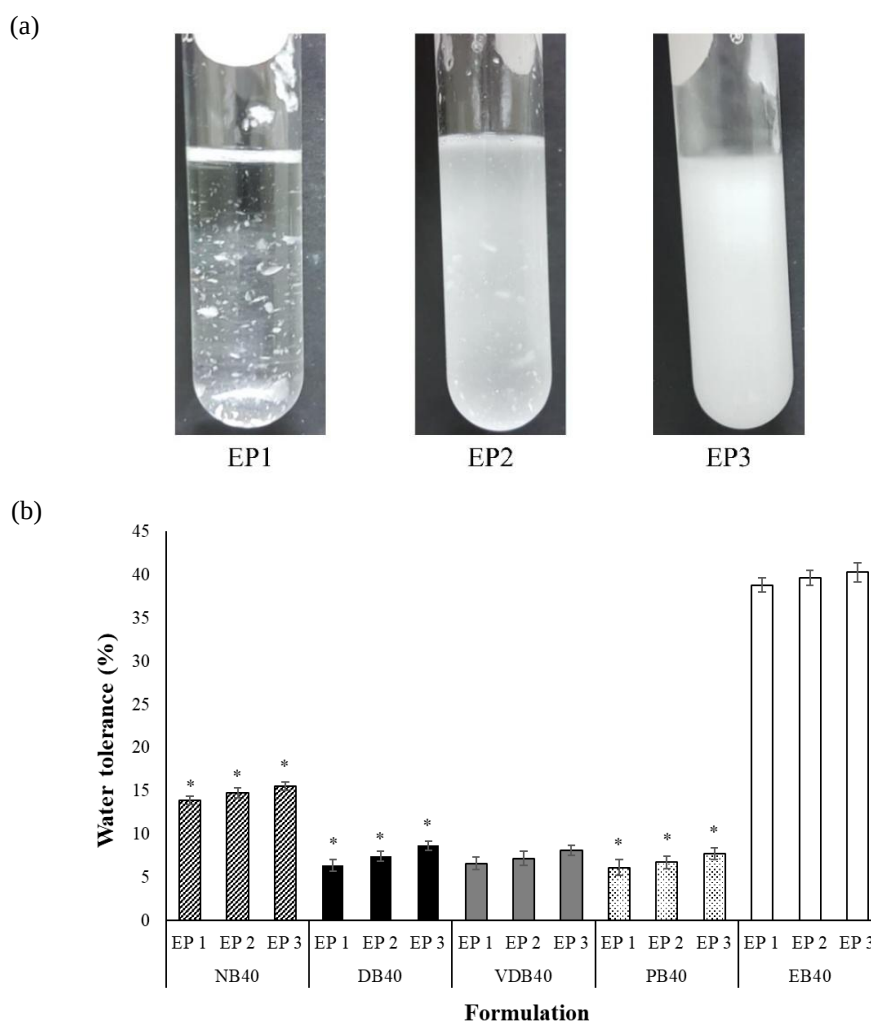


Figure 1 (a) End point (EP) of the water tolerance test, demonstrating the distinct physical changes in the solution as water is titrated. (b) Water tolerance of different formulations expressed as mean $\pm$ standard deviation (SD) ($n = 3$). Statistical significance is denoted by * $p < 0.05$ when compared with the ethanol-based formulation (EB40).

3.2 Morphology of matrix formation

The crystal morphology of 40% w/w borneol-based ISM formulations prepared using different organic solvents (NMP, DMSO, PYR, and ethanol) has previously been reported [14]. NB40, DB40, and PB40 systems produced smaller precipitates ($\approx 18\text{--}25\ \mu\text{m}$) than intact borneol ($\approx 50\ \mu\text{m}$), whereas EB40 generated larger aggregates and demonstrated less efficient matrix formation. Consistent with the solvent–borneol interaction analysis discussed in Section 3.1, DMSO showed favorable physicochemical compatibility and matrix-forming behavior. Therefore, in the present study, DMSO was selected for further investigation. Figure 2 illustrates the morphological characteristics of the crystalline matrix after complete solvent exchange. Crystalline matrix formation of borneol occurred through solvent exchange upon exposure to PBS (pH: 6.8) from the agarose gel. Formulations with lower borneol concentrations required longer periods for crystalline matrix formation than those with higher concentrations. For instance, DB10 produced regular, large, and transparent crystals due to the slow crystallization process. This observation is consistent with previous research indicating that the matrix formation rate for DB70 was significantly faster than that of DB10 at equivalent time points [4].

The crystalline matrix formation was concentration-dependent, with the rate of matrix formation increasing alongside the borneol concentration. Among the different formulations, DB40 was considered the optimal concentration, striking a balance between rapid matrix formation and desirable morphological characteristics. The rate of matrix formation for DB40 during the initial stages was significantly faster than that of DB10, thereby ensuring effective and timely matrix development. Higher concentrations further accelerated recrystallization, which could lead to excessively dense matrices, potentially compromising drug release dynamics. Conversely, DB40 achieved a crystalline matrix structure that supported controlled drug release, making it suitable for *in situ* applications. Over time, the morphology of borneol crystal growth became more pronounced, and higher borneol

concentrations accelerated the process. However, the incorporation of vancomycin hydrochloride in the DB40-based formulation (VDB40) slightly delayed matrix formation, due to the increased viscosity hindering phase separation. Vancomycin hydrochloride particles were not observed, as the compound is water-soluble, unlike borneol, which precipitates upon contact with water [22, 23]. Interestingly, the borneol crystals in VDB40 were larger and demonstrated looser formations than those in DB40, as the vancomycin hydrochloride in VDB40 interfered with borneol crystallization (Figures 2(d) and 2(g)). Conversely, no crystalline matrix formation was observed in V-loaded DMSO (VD) (Figure 2(h)) or in DMSO alone (Figure 2(i)), emphasizing the necessity of a matrix-forming agent like borneol. These results indicate the crucial role of borneol concentration, with DB40 demonstrating optimal performance in achieving effective and robust matrix formation.

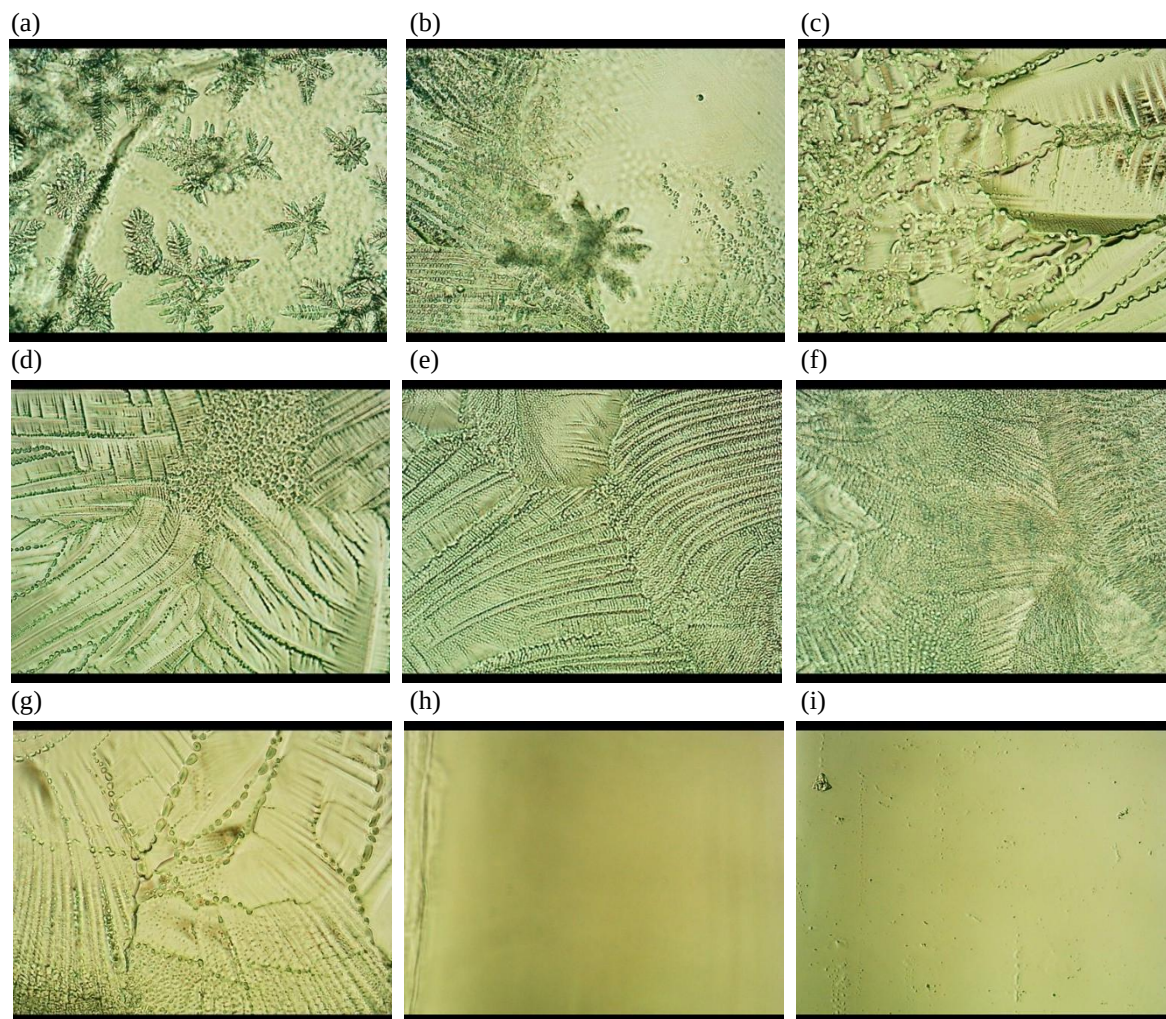


Figure 2 Crystal morphology of borneol-based ISM formulations: (a) DB10, (b) DB20, (c) DB30, (d) DB40, (e) DB50, (f) DB60, (g) VDB40, (h) VD, and (i) DMSO observed under an inverted microscope at 100× magnification.

4. Conclusion

This study highlights the importance of optimizing solvent selection and borneol concentration in designing effective borneol-based ISM systems for periodontal applications. Among the organic solvents evaluated—ethanol, NMP, DMSO, and 2-pyrrolidone—DMSO emerged as the most suitable due to its low water tolerance and viscosity, facilitating rapid phase inversion and efficient matrix formation. The findings indicate that borneol concentration significantly affects crystallization morphology, with higher concentrations leading to faster crystallization and improved drug retention. This supports the development of ISMs tailored to the physiological conditions of periodontal pockets, emphasizing their potential as a localized drug delivery system for periodontitis treatment.

5. Acknowledgements

The researchers would like to express their gratitude to the Faculty of Pharmaceutical Sciences, Burapha University, Thailand, for their support. Special appreciation is also extended to the Faculty of Pharmacy, Silpakorn University, Thailand; the Natural Bioactive and Material for Health Promotion and Drug Delivery System Group (NBM), Faculty of Pharmacy, Silpakorn University, Thailand; and the Faculty of Science and Technology, Rajamangala University of Technology Krungthep, Thailand, for their valuable collaboration on this work.

6. Author Contributions

Chansatidkosol, S.: Conceptualization, Data curation, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing; Phaechamud, T.: Formal analysis, Funding acquisition, Methodology, Resources, Supervision; Warinthip, N.: Data curation, Formal analysis, Investigation, Validation; Lertsuphotvanit, N.: Conceptualization, Formal analysis, Funding acquisition, Project administration, Supervision, Writing – original draft, Writing – review & editing

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