



Injectability and mechanical properties of borneol-based solvent removal-induced *in situ* matrix for periodontal pocket delivery

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Abstract

Solvent removal-induced *in situ* matrices (ISMs) have garnered attention for periodontitis treatment because of their capability to localize antibiotic drug release within the periodontal pocket over an extended duration, effectively targeting and eliminating infecting microbes. In this study, various concentrations of borneol—10%–70%—were used as a matrix agent in ISMs, with a 40% w/w borneol-based ISM selected to load 1% vancomycin HCl. The injectability and mechanical properties of drug-free and vancomycin HCl-loaded borneol ISMs were evaluated with a texture analyzer. Both maximum injection force and energy increased proportionally with borneol concentrations and slightly further with vancomycin HCl. Nevertheless, the injection energy required for borneol-loaded ISMs at 10%–50% was low, from 12.22–25.00 mJ. Consequently, these formulations were considered appropriate and feasible as injectable drug delivery systems, providing ease of administration while promoting patient comfort and compliance. Additionally, a more compact borneol matrix was formed after complete solvent removal; it exhibited plastic deformation, enabling close adaptation to the periodontal pocket geometry.

Keywords: Borneol, Injection feasibility, Mechanical characteristics, *In situ* forming, Periodontitis treatment

1. Introduction

Periodontitis, a chronic inflammatory disease, contributes to periodontal tissue destruction, forming deep crevicular pockets that facilitate bacterial proliferation [1,2]. Localized, sustained antibiotic delivery is required to eradicate bacterial colonization while minimizing systemic side effects [3]. Solvent removal-induced *in situ* forming matrices (ISMs) represent a promising platform for periodontal therapy, providing a liquid-to-solid phase transition upon solvent exchange, enabling prolonged, site-specific drug release [4,5].

Borneol, a naturally occurring bicyclic monoterpene with favorable lipophilicity, has been widely used in traditional medicine and pharmaceutical formulations owing to its biocompatibility, low toxicity, and penetration-enhancing abilities [6,7]. It exhibits bioactive properties, including penetration enhancement *via* the blood–brain barrier and corneal epithelium, anti-inflammatory effects, and antimicrobial activity [8,9]. Notably, borneol has been investigated for use as a matrix-forming agent in ISMs due to its hydrophobicity and ability to create a stable matrix for drug delivery [10]. Although borneol has been utilized in various pharmaceutical applications, its properties in ISMs for periodontal pocket drug delivery remain underexplored.

Vancomycin HCl, a glycopeptide antibiotic, served as a model drug in this study because of its well-established activity against Gram-positive oral pathogens. While its activity against Gram-negative bacteria such as *Porphyromonas gingivalis* is limited, potential susceptibility under specific *in vitro* conditions has been reported [11]. Its poor oral bioavailability and rapid systemic clearance render localized delivery an optimal approach for maintaining therapeutic levels at the site of infection while minimizing systemic exposure [12].

ISMs provide a promising platform for periodontal drug delivery by enabling localized and sustained release of therapeutic agents. These systems are typically composed of polymers or other matrix-forming agents dissolved in biocompatible solvents, which solidify upon solvent removal or exposure to aqueous environments [4].

The mechanical properties and injectability of ISMs are critical parameters influencing their clinical applicability [13]. Optimal injectability ensures ease of administration, patient comfort, and effective matrix deposition within the periodontal pocket; however, suitable mechanical properties ensure the stability and retention of the matrix formed at the target site [14]. Understanding these properties is essential for optimizing ISM formulations and ensuring their practical applicability.

This study focuses on evaluating the injectability and mechanical properties of borneol-based solvent removal-induced ISMs for periodontal pocket delivery. By assessing the force and energy required for injection, as well as the post-injection mechanical behavior of the matrices obtained, this research aims to determine the feasibility of borneol as a matrix-forming agent in ISMs. The findings may provide essential insights into the formulation characteristics of borneol-based ISMs and contribute to a broader investigation of their potential as localized drug delivery systems for periodontitis treatment. Additionally, the results may complement previous research [10] on borneol-based ISMs by elucidating their mechanical behavior, thereby supporting their further development for clinical applications.

2. Materials and methods

2.1 Materials

The matrix-forming agent, borneol, was purchased from Chareorsuk-Osot (Nakhon Pathom, Thailand) and contained low impurity levels (camphor <0.5%, non-volatile matter <0.035%), acceptable heavy metal contents, and a melting point of 207.1°C–208.0°C. Its identity and physicochemical properties were verified using FTIR, DSC, TGA, and PXRD. Vancomycin HCl (Lot no. WXBB5169V) was supplied by Sigma-Aldrich Co. (USA) and generously provided by Millimed Pharmaceutical Factory located in Samut Prakan Province (Thailand). Dimethyl sulfoxide (DMSO; Lot no. 453242) was purchased from Fluka, Switzerland. Phosphate-buffered saline (PBS, pH 6.8) was freshly prepared by combining sodium hydroxide (NaOH; Lot no. AF310315, Ajax Finechem, Australia) and potassium dihydrogen phosphate (KH_2PO_4 ; Lot no. E24W59, Ajax Finechem, Australia) in appropriate proportions.

2.2 Fabrication of ISM solutions based on borneol

To prepare borneol-based ISM solutions, borneol ranging from 10% to 70% w/w (DB10–DB70) was dissolved in DMSO. The mixtures were stirred with a magnetic stirrer for ≥ 30 min or until complete dissolution was confirmed by the formation of a clear solution, marking completion of preparation. The same process was also used to create a formulation known as VDB, which included 40% by weight borneol in DMSO and 1% w/w vancomycin HCl. Additionally, a control solution (VD) was prepared by dissolving 1% w/w vancomycin HCl in DMSO without borneol.

2.3 Injectability testing

The injectability of the formulations was assessed to ascertain their ease of injection. The force needed to fill a 1 mL plastic syringe fitted with a 27-G needle was measured using a texture analyzer (TA.XTplus, Stable Micro Systems, UK) in compression mode. To depress the syringe plunger until it contacted the base of the syringe barrel, the instrument's top probe advanced at a speed of 1.0 mm.s^{-1} while applying a constant force (0.1 N). The expulsion energy was computed based on the corresponding force–displacement curve after the highest expulsion force was noted.

2.4 Mechanical properties testing

The TA.XTplus was used to evaluate the mechanical properties of the matrix obtained following complete solvent exchange. Agarose powder—0.6% w/w—was dispersed in PBS to create an agarose gel, which was then cast onto Petri plates until the gel reached 1 cm in height. Following gel setting, a cylindrical cutter, 7 mm in diameter, was used to carve a cylinder from the center of each gel. To achieve complete phase inversion and matrix formation, 150 μL of the ISM solution was added to this hollow space within the agarose gel. The Petri plates were then covered to minimize water evaporation and stored under refrigerated conditions (4°C–6°C) for 3 days to allow complete matrix formation. A spherical probe—5 mm in diameter—was used to compress the borneol matrix at a rate of 0.5 mm.s^{-1} and investigate its mechanical properties. The probe was withdrawn at a speed of 10 mm.s^{-1} after insertion to a depth of 1.5 mm and held in position for 60 s. Force–displacement data were recorded. After a minute of holding, the remaining and maximal penetration forces were recorded. The greatest force experienced upon probe withdrawal was the adhesion force [13]. This mechanical property is

expressed as the ratio between these two forces. A higher ratio denotes more elasticity, whereas a lower ratio suggests more plasticity. All measurements were performed at 25°C in triplicate [14].

2.5 Statistical analysis

The data were expressed as the mean $\pm$ standard deviation (SD). SPSS was employed for statistical analysis. One-way analysis of variance and the LSD post-hoc test were used to assess the differences. Statistical significance was considered at $p < 0.05$.

3. Results and discussion

3.1 Injectability

Injectability refers to the force or energy required to administer an ISM solution through a syringe and needle [15]. As shown in Figure 1, the maximum force and energy required for injection increased with borneol concentrations and rose slightly with vancomycin HCl. The energy required for injecting borneol-loaded ISMs (10%–50%) remained low, ranging from 12.22 to 25.00 mJ. Compared to the energy values of previously reported polymer-based *in situ* forming gels, our values were similar or slightly lower than those of formulations ranging from 5% to 20% by weight ethyl cellulose (21–42 mJ), 15% to 30% by weight bleached shellac (12–28 mJ), and 15% to 35% by weight Eudragit RS (8–24 mJ) [16]. All borneol-based ISM formulations demonstrated a maximum injection force of <10 N—ranging from 2 to 6.5 N—supporting their potential for ease of injection and minimal pain at the site of administration [17]. The lower injection force observed in formulations containing borneol, compared to those utilizing other polymers, can be attributed to its lower viscosity (3–18 cP) [10]. Borneol, owing to its density, compact molecular size, and uncomplicated chemical structure, also contributed to lowering the injection force. These characteristics collectively enhance the injectability of borneol-based ISMs, making them more advantageous for administration *via* syringes than other polymer-based ISMs. Therefore, borneol-based ISMs are promising candidates for injectable drug delivery, offering improved patient comfort and compliance [15,17,18].

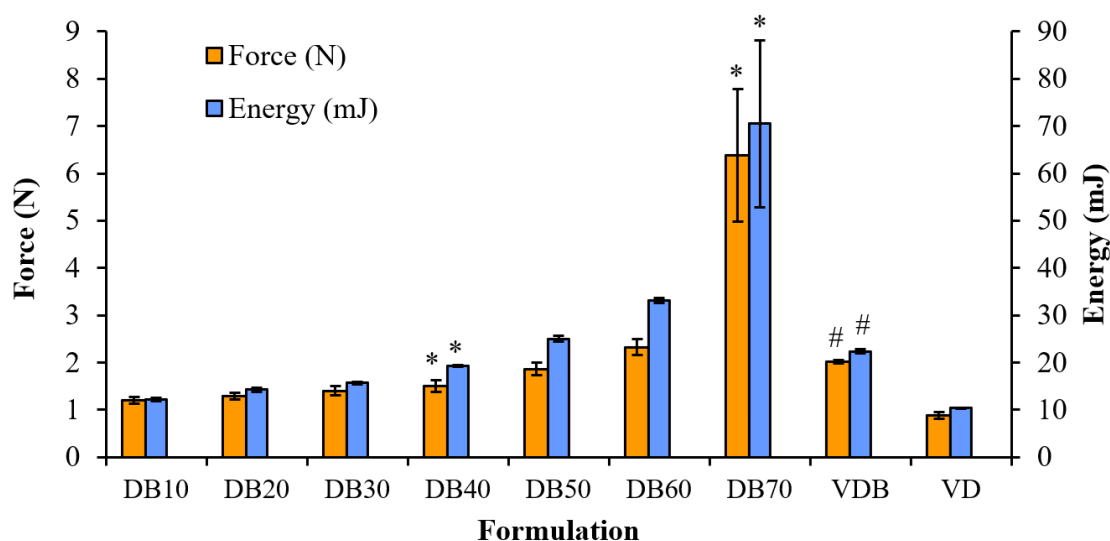


Figure 1 Force and energy required for syringe expulsion ($n = 3$), reported as mean $\pm$ SD. Statistical differences were determined as follows: * $p < 0.05$ compared with DB10; # $p < 0.05$ compared with DB40.

3.2 Mechanical properties

The mechanical properties of the transformed ISMs following phase inversion were evaluated. Each formulation was filled into a hole within the agarose gel, and complete solvent exchange was allowed for 3 days to form the matrices [13]. The maximum penetration and remaining force data are presented in Figure 2. Both these increased with higher borneol concentrations, indicating that matrix hardness positively correlated with borneol content. Ideally, the formulation should not transform rapidly or result in excessive rigidity, allowing the matrix to adapt gradually to the crevicular pocket over time [18]. The surface morphology of borneol-based matrices could not be examined through scanning electron microscopy due to borneol sublimation under vacuum

and high-voltage conditions, which may alter the native structure. Alternatively, morphology observed under an inverted microscope has been reported [10], demonstrating that higher borneol concentrations enhance matrix structure density. Such an observation is consistent with the present results, where increased borneol concentration elevated the maximum force, indicating greater matrix density and mechanical strength.

The adhesion force remained <0.03 N and was largely unaffected by borneol concentration (Figure 3). The adhesion value reflects the interaction between the formulation and the texture analyzer probe; this method was primarily used to compare tackiness among formulations. Although the adhesion force was relatively low, all borneol-based ISMs were denser than water, which may contribute to their retention within periodontal pockets. In addition, *in vitro* drug release studies using a periodontal pocket-simulating model demonstrated that the formulation could remain intact for up to 14 days [10]. These findings suggest that the formulations possess adequate physical integrity under the test conditions; however, further studies on biological substrates can fully evaluate their mucoadhesive performance.

The ratio of remaining force to maximum penetration force was employed to assess the material's deformation behavior, as well as elastic and plastic properties. A ratio close to 1.00 represents a material that deforms elastically and returns to its initial shape, whereas a lower value indicates plastic deformation, resulting in permanent structural changes. This elasticity–plasticity interplay is a determining factor for adhesion properties that govern the formulation's retention within crevicular pockets [13]. For all formulations, this ratio ranged from 0.27 to 0.39 (Figure 3), indicating minimal variations, suggesting that the borneol matrix exhibited plastic deformation. Such a characteristic enables the matrix to progressively adjust to the dimensions and form of the periodontal pocket. The DB10 formulation, having a lower proportion of the matrix-forming component, was structurally weak and therefore excluded from testing. In comparison, polymer-based *in situ* forming implants exhibit marked plastic deformability. For instance, systems composed of poly(D,L-lactic-co-glycolic acid) combined with plasticizers such as acetyl tributyl citrate or dibutyl sebacate have ratios <0.15 . Moreover, the commercial dental gel Parocline[®]—formulated with 2% minocycline, hydroxyethyl cellulose, and Eudragit[®] RS—demonstrates a ratio approaching 0.4 [13]. Interestingly, the ratio obtained for VDB was similar to that of Parocline[®], indicating comparable deformability and suggesting applicability in clinical settings. The mechanical evaluation of borneol-based ISMs demonstrated favorable plastic deformation properties, allowing the matrices to conform to periodontal pockets over time. The formulations exhibited sufficient retention without excessive rigidity, suggesting their adaptability for periodontal drug delivery. Notably, the deformability of VDB was comparable to that of Parocline[®], indicating a similar capacity for maintaining its structure at the application site.

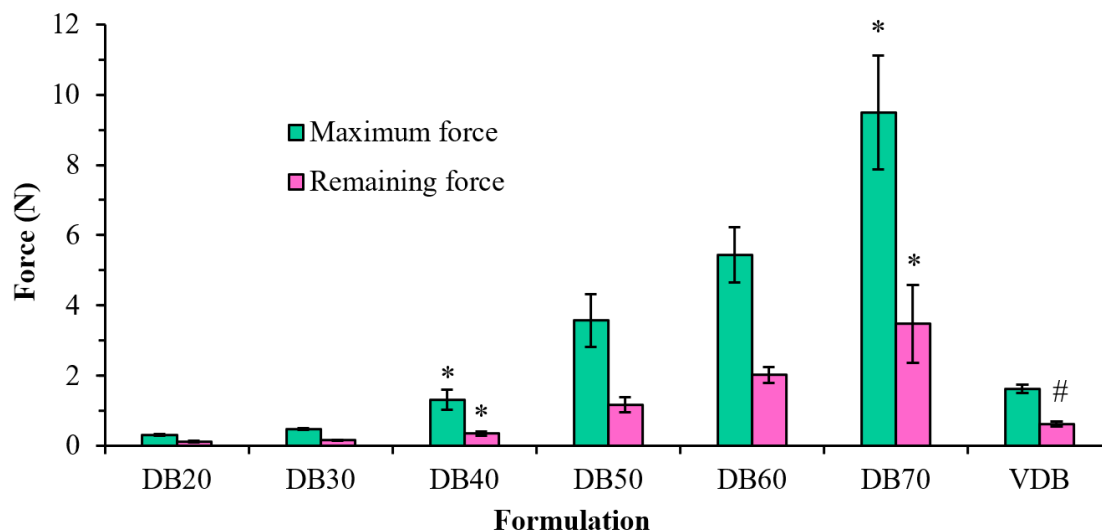


Figure 2 Maximum and remaining compression forces of varied matrix formulations ($n = 3$), reported as the mean $\pm$ SD. Statistical significance of the differences was determined as follows: * $p < 0.05$ compared with DB20; # $p < 0.05$ compared with DB40.

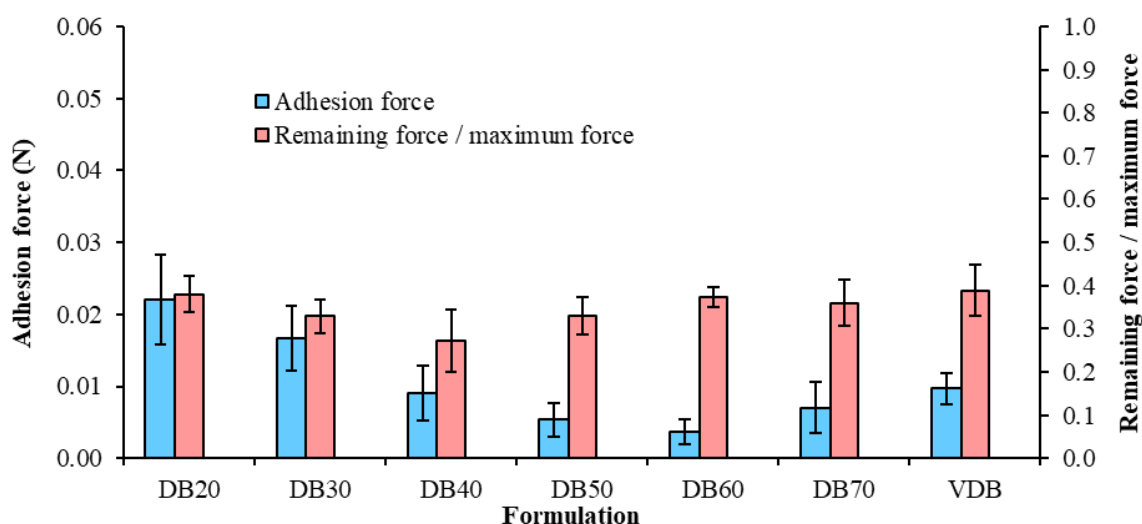


Figure 3 Adhesion force and mechanical properties of various matrix formulations (n = 3), reported as the mean $\pm$ SD.

4. Conclusion

This study demonstrated the feasibility of borneol-based solvent removal-induced ISMs for drug delivery to the periodontal pocket. Injectability evaluation confirmed that all test formulations exhibited a low injection force (1 - 7 N) and energy requirements (12.22 - 25.00 mJ), ensuring ease of injection and minimal discomfort. Mechanical characterization revealed that the solidified matrices displayed plastic deformation, with the ratio of remaining to maximum penetration force ranging from 0.27 to 0.39, allowing them to adapt to the periodontal pocket's shape, essential for effective drug retention and prolonged therapeutic action. The mechanical strength and deformability of 40% (w/w) borneol-based ISM were comparable to commercial products like Parocline®, indicating its potential for clinical application. These findings highlight borneol's ability as a matrix-forming agent in ISMs, leveraging its hydrophobic nature to enhance matrix stability while maintaining favorable injectability. The combination of such properties confirmed that 40% by weight borneol-based ISM is a promising candidate for localized periodontal drug delivery. Additionally, this study builds upon earlier research by specifically addressing the mechanical and injectability of borneol-based ISMs, providing a deeper understanding of their practical applicability. Future studies should explore long-term drug release profiles and *in vivo* performance to further optimize these systems for clinical use in periodontitis treatment.

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6. Author Contributions

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

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