Development of an *in situ* gel containing tinidazole-loaded polymeric nanoparticles for oral cavity administration

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Abstract

Background: Tinidazole (TNZ) demonstrates greater efficacy against anaerobic bacteria, particularly Gram-negative strains, compared to metronidazole. Nanosizing TNZ and incorporating it into *in situ* gel formulations for topical periodontitis treatment offers several advantages. **Objectives:** This study aimed to formulate an in situ gel containing preformed Eudragit RSPO-based nanoparticles (NPs) of TNZ and to evaluate its physicochemical properties. **Materials and methods:** Poloxamer 407 was used as a thermosensitive gelling agent, either alone or in combination with other gelling agents. The *in situ* gels containing TNZ NPs were prepared and evaluated for physicochemical properties. **Results:** The *in situ* gel containing TNZ NPs, formulated with Poloxamer 407 and sodium alginate, exhibited a smooth texture, a gelation temperature of 31.33 ± 0.24 °C, a gelation time of less than one minute, a pH of 6.72 ± 0.03, and a stable gel state over an extended period. Compared to the in situ gel with TNZ material, the TNZ NP-loaded gel prolonged drug release. The drug release mechanism was best described by the Higuchi model (with F0). **Conclusion:** This TNZ NP-loaded in situ gel formulation shows promise for further research in periodontitis treatment.

Keywords: *tinidazole, in situ gel, nanoparticle, poloxamer 407.*

1. INTRODUCTION

Periodontitis is a chronic inflammation of the soft tissues that support teeth, causing damage to periodontal structures, alveolar bone loss and even tooth loss [1]. The principal agent primarily involved in the formation and progression of periodontitis is *Porphyromonas gingivalis* (*P. gingivalis*), a gram-negative anaerobic bacterium. Therefore, eradication of *P. gingivalis* is essential in the treatment of periodontitis [2].

Topical antibiotics are the preferred choice in the treatment of periodontitis because they are a simple method and limit unwanted side effects commonly encountered when using systemic antibiotics. However, their effectiveness is limited because most clinically used antibiotics can only remain effective for a short period of time. At the same time, drugs in periodontal pockets are easily washed away by saliva in the gingival pocket, making it difficult to maintain therapeutic concentrations at the site of impact [3].

Besides, resistance can easily occur when using antibiotics continuously because bacteria have the ability to produce biofilm around them to protect them from the host's defense mechanism. These biofilms also act as a biological barrier to prevent the penetration of antibiotics, protecting bacteria from being destroyed by the treatment process, thereby reducing the effectiveness of the drug and leading to drug resistance [2]. Therefore, developing a drug that can penetrate the biofilm and provide long-lasting local effects is a big challenge.

With the development of nanotechnology in medicine and pharmacy, nanomaterials have been developed with many advantages such as small size, increased ability to penetrate cells, reduced toxicity, and biocompatibility,… [2].

Tinidazole (TNZ) exhibits higher susceptibility to anaerobic bacteria, especially Gram-negative bacteria. Moreover, systemic TNZ offers several advantages compared to metronidazole for the oral treatment of periodontitis [4]. Quantum dots containing nanoscale TNZ have been reported to effectively penetrate biofilm layers, thereby inhibiting the growth of *P. gingivalis* [2]. *In vitro* studies have demonstrated sustained drug release for up to 20 days, along with significant antibacterial activity achieved through TNZ-loaded nanofibers [5].

In situ gels are liquid preparations that can be easily injected into periodontal pockets and then form a gel with a specific shape, capable of releasing drug at a controlled rate, maintaining drug concentration in the gingival crevicular fluid for a long time to achieve the desired clinical benefit [6]. Poloxamer 407 (PLX407) was widely used to form *in situ* gels or in combination with other gelling agents [7]. Carbopol 934P (CBP934), when dispersed in water, forms a colloidal dispersion with acidic properties. Upon neutralization, it transforms into a

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high-viscosity gel and is a pH-sensitive polymer [8]. Alginate with a high guluronic acid content enhances gel properties and, upon contact with cations, forms cross-links leading to a sol-gel transition [8, 9].

In our previous study [10], Eudragit ESPO-based polymeric nanoparticles (NPs) of TNZ were successfully prepared. Nanosizing TNZ and incorporating it into *in situ* gel formulations for topical periodontitis treatment offers several advantages, including improved bioavailability, controlled drug release directly at the site of action, and optimized dosing and duration. To the best of our knowledge, this is the first time polymeric TNZ NPs have been incorporated into an *in situ* gel. Therefore, the aim of this study was to develop an *in situ* gel containing TNZ NPs and to evaluate its physicochemical properties.

2. MATERIALS AND METHODS

2.1. Materials

TNZ (European Pharmacopoeia 10) was purchased from Zhejiang Supor Pharmaceuticals Co. Ltd. (Zhejiang, China). Standard TNZ (99.7%, batch number C0120363.01) was obtained from the National Institute of Drug Quality Control (Hanoi, Vietnam). Eudragit RSPO was obtained from Evonik (Essen, Germany). PLX407 was purchased from BASF (Ludwigshafen am Rhein, Germany). CBP934 and sodium alginate (SA) were obtained from China. All other chemicals were of analytical grade.

Equipments

The following instruments were used in this study: a Zetasizer Lab instrument (Malvern, England), a NovaSEM microscope (Hitachi S-4800, Japan), a centrifuge (Z326K, Hermlé, Germany), a sonicator (Ultrasonic Processor VCX130, USA), an evaporator (Buchi Rotavapor R-300, Switzerland), a magnetic stirrer (IKA C-MAG HS 7 digital, Germany), a pH meter (Sension PH3, HACH, Spain), a balance (Sartorius Quintix 125D–1S, Germany), a diffusion device (Hanson Research, USA), a high-performance liquid chromatography system (HPLC, Shimadzu LC–20A, Japan), centrifugal filters (10 kDa, Sartorius, England), a dialysis bag (MWCO 12–14 kDa, Visking Tubes, Medicell Membranes Ltd, London, UK), and other equipment used for the preparation and characterization of NPs and *in situ* gels.

2.2. Methods

2.2.1. Formulation of in situ gels containing tinidazole nanoparticles

Eudragit RSPO-based TNZ NPs were prepared using the emulsification-solvent evaporation method, as described in our previous research [10]. *In situ* gels were formulated using gelling excipients such as PLX407, either alone or in combination with CBP934 and SA at various concentrations. Briefly, the gel-forming excipients were soaked in the NP suspension at 4°C in a refrigerator overnight to ensure complete swelling. The resulting gels were then mechanically homogenized. An *in situ* gel containing TNZ material was prepared using the same procedure described above.

2.2.2. Characterization of in situ gel containing polymeric TNZ NPs

Appearance and pH

The resulting *in situ* gels were visually observed for color and physical properties. The pH of *in situ* gels were evaluated using a pH meter (pH Sension PH3, HACH, Loveland, CO) at 25 °C.

Gelation temperature and time of gelation

Two milliliters of the *in situ* gels were added into glass tubes sealed with paraffin, and immersed in a beaker of water at 4 °C. The temperature of the beaker was gradually increased at a rate of 1.0 °C/min for temperatures below 20 °C, or 0.5 °C/min for temperatures above 20 °C, using a combination of magnetic stirring and heating on a magnetic stirrer (IKA C-MAG HS 7 digital, Staufen, Germany). Following each temperature increment, the system will be allowed to equilibrate for 15 minutes at the new setpoint. The gelation temperature was recorded at the point where the gel exhibited no movement when tilted 90°. All measurements were performed in triplicate [11].

The time of gelation was determined by the inversion method. Briefly, two milliliters of the formulation were transferred into glass tubes. These tubes were placed in water beakers at 37 ± 0.5 °C and time of gelation was recorded [11].

In vitro gelling capacity

Briefly, 1 mL of the *in situ* gel formulation was added into a glass tube containing 2 mL of simulated saliva (pH 6.8) maintained at 37 ± 0.5 °C using a water bath with the help of a 1 mL pipette. The pipette was placed at the fluid surface, and the formulation was slowly released. Changes in the visual appearance of the gel solution were observed. The *in vitro* gelling capacity was evaluated and categorized into three groups based on gelation time and the duration of the gel state: (+) Gelling after a few minutes, dispersing rapidly; (++) Gelling immediately, maintaining the gel state for a few hours; (+++) Gelling immediately, maintaining the gel state for an extended period [12].

Particle size, size distribution, morphology of TNZ NPs

TNZ NPs before being introduced into gels were diluted with distilled water for size measurement using a Zetasizer Lab (Malvern, England).

In addition, the particle size of TNZ NPs after being introduced into gels was measured. Briefly, about 1.5g of gel was weighed and diluted with 15 ml of distilled water. The dispersion was then stirred to completely dissolve the gel-forming excipients. The mixture was then centrifuged at 5000 rpm (Z326K, Hermlé, Wehingen, Germany) using a centrifugal filter (Molecular weight cut-off [MWCO] 10 kDa, Sartorius, Switzerland) for 10 min, and washed three times with distilled water (3 ml each time). The TNZ NPs in the upper part of the centrifugal filter was used to determine particle size and polydispersity index (PDI) [13].

To observe the morphology of the particles, TNZ NPs were deposited onto aluminum foil and allowed to dry naturally. Once dried, the foil was coated with a conductive material, such as platinum or silver, before being subjected to scanning electron microscopy (SEM) analysis [13].

TNZ assay by high performance liquid chromatography

The concentration of TNZ in the NP suspension, prior to its incorporation into gels, was quantified using HPLC. The test sample was diluted with the mobile phase to achieve a final concentration in the range of 5 to 25 µg/mL. Chromatographic conditions included a mobile phase comprising Acetonitrile:MeOH:Water (10:20:70), a C8 column (3 mm × 250 mm, particle size 5.0 µm), a flow rate of 0.5 mL/min, an injection volume of 20 µL, and a diode array detector set at a wavelength of 320 nm [14].

TNZ in the *in situ* gel (0.1 g, equivalent to 0.1 mg of TNZ) was dispersed in an appropriate volume of distilled water and diluted with the mobile phase to achieve a final concentration of 5 to 25 µg/mL. The solution was then filtered through a 0.45 µm nylon filter and quantified using the HPLC method.

In vitro drug release

In vitro drug release was performed using membrane diffusion through Franz cells [13]. The drug release conditions included a dialysis bag (MWCO 12-14 kDa, Visking Tubes, Medicell Membranes Ltd, London, UK), a release medium of simulated saliva (pH 6.8), a release volume of 7 mL, a temperature of 37 ± 0.5 °C, a diffusion area of 1.76 cm^2, a stirring speed of 250 rpm, and a sample amount of 250–300 mg of *in situ* gel. At specified time intervals, 1 mL of the release medium was withdrawn and replaced with an equal volume of fresh medium. The *in situ* gel containing TNZ material was used as a control. The released drug was quantified using HPLC.

The f2 similarity factor was calculated to compare the two drug release profiles. The drug release profile of TNZ NP *in situ* gel was analyzed using various mathematical models to elucidate the release mechanism with support from the DDSolver Add-In in Microsoft Excel [15].

2.2.3. Statistical analysis

The data were statistically analyzed using Microsoft Excel (Microsoft 365 MSO, Microsoft Corp., Redmond, WA) , and a *p*-value less than *0.05* was considered statistically significant.

3. RESULTS

3.1. Formulation of *in situ* gel containing TNZ NPs

TNZ NPs were prepared using the emulsification and solvent evaporation method based on our previous study [10]. The particle size and PDI of TNZ NPs were 168.9 ± 1.6 nm, and 0.142 ± 0.017, respectively. TNZ NPs were then introduced into *in situ* gels to enhance their ease of local administration at oral cavity.

The effects of gel-forming agents including PLX407, and SA on appearance, pH, gelation temperature and time of gelation of *in situ* gels containing TNZ NPs were investigated (Table 1). Meanwhile, the combination of PLX407 and CBP934 caused the gel to be not homogenous and physically unsatisfactory, so CBP934 was not selected for further investigations. The results demonstrated that the formulation combining PLX407 with CBP934 failed to meet the required physical properties and uniformity standards, resulting in a cloudy *in situ* gel with precipitation.

Table 1. The effect of gelling agents on pH, gelation temperature and time of gelation

PLX407 conc. (%, *w/v*)	SA conc. (%, w/v)	pH	Gelation temperature (°C)	Time of gelation(s)
15		6.32 ± 0.01	> 38	X
16		6.41 ± 0.03	> 38	X
17		6.44 ± 0.01	35.16 ± 0.24	70.33 ± 0.47
18		6.52 ± 0.02	31.33 ± 0.47	36.67 ± 0.47
19		6.55 ± 0.03	27.50 ± 0.41	14.33 ± 0.47
15	1.5	6.65 ±0.02	> 38	X
16	1.5	6.68 ±0.01	38.17 ± 0.23	X
17	1.5	6.72 ±0.03	31.33 ± 0.24	36.3 ± 1.25
18	1.5	6.75 ±0.02	27.50 ± 0.40	19.33 ± 0.47
19	1.5	6.78 ±0.02	24.17 ± 0.23	10.33 ± 0.47

Notes: X: not forming gels at 37 °C

Physically, *in situ* gels prepared with PLX407 had a uniform, smooth texture (Fig. 1). When combining PLX407 with SA, the gel was more viscous.

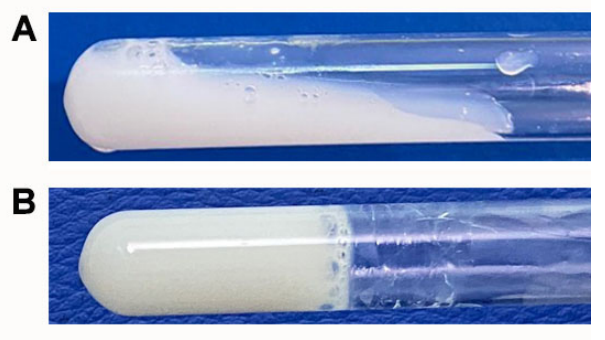

Figure 1. The appearance of *in situ* gels in (A) solution state, (B) gel state when investigating gelation temperature

The pH of *in situ* gels formed using different concentrations of PLX407 alone or in combination with SA was within the required range of 6.2–7.4. Gelation temperature and time gradually decreased as PLX407 concentration increased and in the presence of SA. For the optimal range of gelation temperature of 30–36 °C, the formulations including PLX407 17%, PLX407 18%, the combination of PLX407 17% and SA 1.5% were selected for further investigations.

The gelling capacity of the selected formulations was displayed in Table 2. The formulation using the combination of PLX407 17% and SA 1.5% had good gel-forming capacity and maintained gel state for a long time. Hence, the composition of the best *in situ* gel containing TNZ NPs was TNZ NPs (0.1 %, *w/v*), 17 % (*w/v*) of PLX407, 1.5% (*w/v*) of SA, supplemented with 0.18% (*w/v*) of nipagin, 0.02% (*w/v*) of nipasol as preservatives and deionized water (*q.s*).

Table 2. The *in vitro* gelling capacity of gelling agents

Excipients	Gelling capacity
PLX407 17%	(+)
PLX407 18%	(+)
PLX407 17% + SA 1.5%	(+++)

(+) gelling after a few min, dispersing rapidly; (++) gelling immediately, remaining gel state in a few hours; (+++) gelling immediately, remaining gel state for a long time

3.2. Particle size, PDI and morphology of TNZ NPs in *in situ* gel

The particle size and PDI of TNZ NPs in the *in situ* gel were 181.7 ± 2.4 nm, 0.183 ± 0.020, respectively (Fig. 2A).

The SEM image of polymeric TNZ NPs were consistent with the results obtained by dynamic light scattering method (Fig. 2B). The TNZ content in *in situ* gel was 0.105 ± 0.003 % using HPLC method.

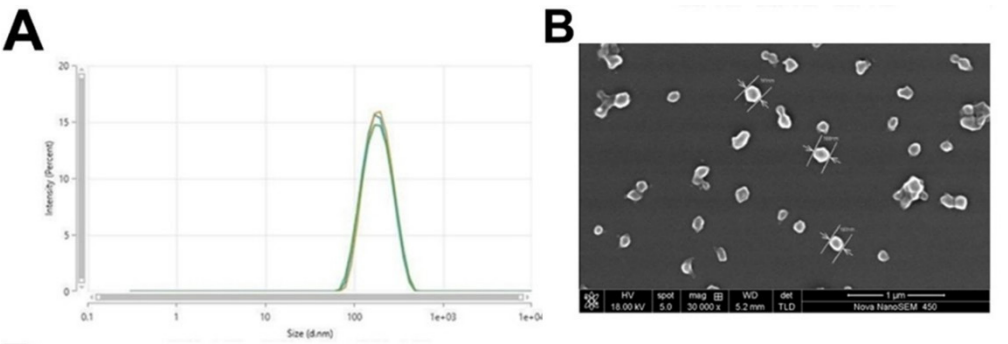

Figure 2. (A) The particle size of TNZ NPs in the *in situ* gel by DLS method; (B) The SEM image of TNZ NPs in the *in situ* gel

3.3. *In vitro* drug release

Fig. 3 showed the *in vitro* drug release of TNZ in *in situ* gels containing TNZ.

The results obtained in Fig. 3 showed that the drug release of TNZ from the *in situ* gel containing TNZ material was faster than that of the *in situ* gel containing TNZ NPs at all time points (f2 = 36.21 < 50). In both samples, rapid drug release through the dialysis membrane was seen within the first 4 h and slow release in the following 4 h. After 8 h, the amount of TNZ released from the *in situ* gel containing TNZ NPs reached 72.96 ± 0.67%, while the amount of TNZ released from the *in situ* gel containing TNZ material was 85.06 ± 0.50% (*p<0.05*).

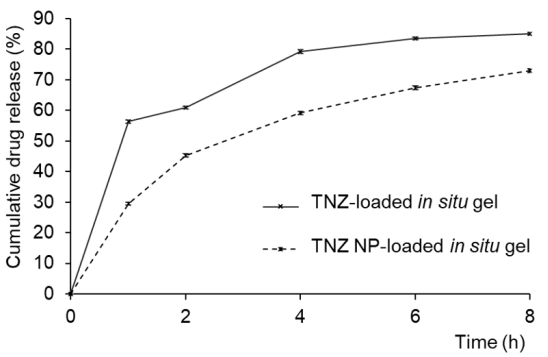

Figure 3. The drug release profiles of *in situ* gels containing TNZ

In order to predict the mechanism of the drug release from the *in situ* gel containing TNZ NPs, drug release data were applied to different mathematical models. The AIC values from different models were presented in Table 3. As shown in Table 3, the Higuchi with F0 model best described the drug release kinetics from the *in situ* gel containing TNZ NPs.

Table 3. Drug release models of the *in situ* gel containing TNZ NPs

Model	Equation[a]	AIC
Zero-order with F0	$F = 30.21 + 5.87 \times t$	27.29
Zero-order	$F = 11.12 \times t$	38.01
First-order	$F = 100 \times (1 - e^{-0.218t})$	30.86
Higuchi with F0	$F = 9.69 + 23.31 \times t^{1/2}$	21.70
Higuchi	$F = 27.78 \times t^{1/2}$	24.15

[a]*F denote the cumulative drug release*

4. DISCUSSION

In situ gels have recently gained attention for drug delivery, transitioning from liquid to gel under physiological conditions (temperature, pH, ions). This enables efficient delivery to periodontal pockets, prolongs drug residence time, and maintains therapeutic concentrations in gingival crevicular fluid [16]. It is found that temperature-sensitive gel-forming excipients are often used as the main *in situ* gel-forming polymers. In this study, we investigated PLX407 as the main gelling excipient for thermosensitive gels containing TNZ NPs.

When evaluating PLX407 at concentrations ranging from 15% to 19%, the results demonstrated that an increase in PLX407 concentration led to a gradual decrease in both gelation temperature and gelation time. These findings are consistent with the study by Dumortier et al., who investigated *in situ* PLX407 gels for ophthalmic administration [17]. Only two PLX407 concentrations, 17% and 18%, met the gelation temperature range of 30 - 36°C, with gelation temperatures of 35.16 °C and 31.33°C, respectively. This temperature range aligns with findings from the study conducted by Yong and colleagues [18].

The formulations with 17% and 18% PLX407 showed limited stability in maintaining the gel state in simulated saliva. The combination of PLX407 with SA yielded uniform, opaque, milky-white solutions. The results showed that SA reduced the gelation temperature and time of gelation of the resulting *in situ* gels. The formulation containing 17% PLX407 and 1.5% SA gave a gelation temperature of 31°C within the allowable range of 30 - 36°C. A decrease in gel temperature when using the combination of PLX407 and SA, was also observed in the study of Liu et al [19]. The formulation with 17% PLX407 and 1.5% SA demonstrated superior gelation, faster formation, and longer retention in simulated saliva compared to the formulation with 17% PLX407 alone. This may be due to SA binding to the PEO chains in PLX407, causing water loss from PLX407 and enhancing molecular interactions, which results in faster gel formation and increased gel stability [20]. Additionally, SA can interact with divalent cations like Ca^{2+} in saliva, stabilizing the gel and enhancing drug retention at the administration site [16].

The particle size of TNZ NPs after loading into the *in situ* gel was about 187 nm, consistent with that of NPs used on the mucosa. Susan Hua's research has shown that the optimal particle size of NPs used for buccal or sublingual administration was usually between 100 - 300 nm [21].

The *in vitro* drug release showed that the *in situ* gel containing TNZ NPs released the drug more slowly than that containing TNZ material at all time points. Besides, it was also observed that the *in situ* formulation had a rapid release in the first 4 h and a slowdown release in the next 4 h. This phenomenon was also reported by Ahmed K. et al in a study on the *in situ* antifungal gel containing voriconazole-loaded NPs for nasal administration [22]. Loading the drug into the *in situ* gel also contributed to the extended release of TNZ for both TNZ-loaded *in situ* gels, especially the first 4 h [10]. The Higuchi model (with F0) was identified as the most suitable for describing drug release kinetics. This suggests that the drug release mechanism from the *in situ* gel containing TNZ NPs follows a diffusion process, in accordance with Fick's law. The mucoadhesive properties, stability, and biological activities of the *in situ* gel containing the formulated TNZ polymeric NPs could be investigated in our future study to evaluate its potential for improved drug delivery in oral cavity.

5. CONCLUSION

The *in situ* gel containing TNZ NPs was successfully fabricated using the combination of PLX407 and SA as gelling agents. The *in situ* gel had a smooth texture, a gelation temperature of 31.33 ± 0.24°C, a gelling capacity less than one minute, pH of 6.72 ± 0.03 and the gel state was maintained for an extended period. The *in situ* gel containing TNZ NPs could extend the drug release as compared to that containing TNZ material. The Higuchi 's model (with F0) best described the drug release mechanism from the *in situ* gel containing TNZ NPs. The *in situ* gel containing TNZ NPs is a candidate for the further investigation on periodontitis treatment.

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