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Original Article

Dentistry Section

Formulation of In-situ Thermoreversible Gel with *Moringa oleifera Lam* Extract as a Local Drug Delivery System for Adjunct Periodontal Treatment

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ABSTRACT

Introduction: Periodontal disease is an outcome of a plethora of molecular mechanisms associated with oxidative stress, inflammation and oral microorganisms is managed by surgical or non surgical therapies with systemic antibiotics. However, local drug delivery system is known to augment the currently available therapies and improves prognosis. Although, there are several local drug delivery systems available, the search for an ideal agent with antioxidant, antimicrobial and anti-inflammatory properties continues. *Moringa oleifera Lam* extracts is one such wonder plant with all the above mentioned effects.

Aim: To formulate an in-situ thermoreversible gel with *Moringa oleifera Lam* extract that could be used as a local drug delivery system as an adjunct to periodontal treatment.

Materials and Methods: This in-vitro study was conducted in Nanotechnology Laboratory, Department of Pharmacology at Saveetha Dental College, from May 2022 to June 2022. For preparation of thermoreversible gel the 19% of thermogelling polymer poloxamer 407 (15% to 30%w/v) which the least concentration that demonstrates thermoreverisibility at 36°C and 0.2% which is the least concentration of mucoadhesive polymer carbapol 934 (0.2% to 0.5% w/v) which forms sol-gel transition and 5% aqueous extract of *Moringa oleifera* and cold deionised water were used. Surface pH, gelation temperature, syringeability, in-vitro drug release, stability, gelation time and Fourier Transform Infrared Spectroscopy (FTIR) analysis was done.

Results: The surface pH of the gel was 6.94±0.091 with a gelation temperature of 34°C±0.5. The gel was flowable with good stability and fast release of eight hours. The chemical components compatability study of *Moringa oleifera Lam* powder, thermoreversible gel without extract and thermoreversible gel with extract were subjected to FITR analysis. The spectral analysis showed no significant chemical interaction between the *Moringa oleifera* and thermoreversible gel.

Conclusion: The study concluded that the thermoreversible gel with *Moringa oleifera Lam* extracts could be used as an adjunct for the management of periodontal disease with good bioavailability. However, future clinical studies have to be conducted to validate the results of the present study.

Keywords: Antioxidant, Anti-inflammatory, Drug release, In-vitro, Local delivery, Periodontitis

INTRODUCTION

Chronic periodontitis results in tissue destruction caused by gram negative microorganisms in periodontal pocket and resultant inflammation [1-3]. The principal aim of periodontal treatment is to eliminate the microorganisms and thereby, ceasing disease progression. The use of systemic antibiotics along with non surgical therapy is not very effective alternative, as it holds many drawbacks. Those are, the required concentration of the antimicrobial agent is not maintained in the gingival crevicular fluid after first pass metabolism, undesirable gastrointestinal side effects, since, it does not have a targeted effect and poor patient compliance [4]. Local drug delivery system can be more effective in reducing the periodontal pocket microbial load as it can have a direct effect on the locally invaded pathogens. Hence, drugs like chlorhexidine, metronidazole, doxycycline were incorporated for local release in non surgical management of periodontitis. However, the biggest challenge is sustained release of the drug against the constant flushing action of oral fluids like Gingival Crevicular Fluid (GCF) and saliva [5]. This could be overcome by the type of vehicle used for drug delivery. Polymers are promising for sustained release of the drug. Local drug delivery for intra pocket administration is delivered as fibres, strips, gels, chip, micro/nano particle and liposomes. Among them, gels easily flows through the delivery device and can reach all over the pocket. It has a faster drug release at the same time it is bioadhesive. These advantages make gels a viable option for sustained local drug delivery in periodontal therapy [6].

Recently, there has been more interest in exploring the antimicrobial properties of herbs and plant derived products. The advantages of using plants and plant derived products is that they also possess antioxidant and anti-inflammatory properties, that can aid in the management of periodontal disease as the disease is associated with both inflammation and oxidative stress. In this regard, *Moringa oleifera Lam*, a plant of Indian origin termed as drumstick has received attention due to the various phototherapeutic effects. It is currently used as a nutraceutical agent in African countries [7,8].

This wonder herb has various phytochemical constituents such as polyphenols, flavonoids, alkaloids, carotenoids, vitamins, saponins, phenolic acids, isothiocyanates, glucosinolates and tannins [9]. It has been used for the management of infectious diseases such as typhoid and malaria as well as systemic diseases like diabetes and hypertension [10,11]. Among the oral diseases, the effect of *Moringa oleifera Lam* had been studied on oral biofilms, for management of oral thrush and were incorporated in toothpaste to study its anticaries effect [12]. For its effect on periodontitis, there was a reduction in proinflammatory cytokines Tumour Necrosis Factor-α (TNF-α) and Interleukin-1β (IL-1β) in a study conducted on rats periodontitis model [13]. Similarly, *Moringa oleifera Lam* extract showed an antiperiodontitis effect by inhibiting alveolar bone resorption by its

action on p38α MAPK pathway in experimental periondontitis [14]. In addition, the antioxidant and anti-inflammatory properties of the plant have also been previously reported in many studies [15-17].

The thermoreversible gel is made of a biopolymer that changes from sol to a gel form with change in temperature. The sol form of the drug at room temperature gelates at pocket temperature and thus can release the drug for prolonged duration. This makes it an ideal one to locally manage periodontal diseases due to better bioavailability of the drug [18]. Hence, aim of the present study was to formulate an in-situ thermoreversible gel with *Moringa oleifera Lam* extract that can be used as a local drug delivery system as an adjunct to periodontal treatment.

MATERIALS AND METHODS

This in-vitro study was conducted in Nanotechnology Laboratory, Department of Pharmacology at Saveetha Dental College, from May 2022 to June 2022. The approval was obtained from the Ethics Committee of Saveetha Dental College (SDC/Ph.D18/32). The polymers Carbapol 934 and Poloxmer 407 were procured from Sigma Aldrich, Mumbai. The 5% aqueous *Moringa oleifera* extract was prepared based on previous study results on its antioxidant and anti-inflammatory property [19].

Formulation of Thermoreversible Gel

For preparation of thermoreversible gel the 19% of thermogelling polymer poloxamer 407 and 0.2% mucoadhesive polymer Carbapol 934 were selected. This concentration demonstrated thermoreversibility of sol-gel transition at 36°C as observed in thermoreversible gel optimisation studies for local drug delivery in periodontal pockets. And it is the least concentration to produce the effect [20-22]. To this, 5% aqueous extract of *moringa oleifera* and cold deionised water were added. To prepare 50 mL of gel, 2.5 mL of 5% extract was added to 9.25 gm of poloxamer dissolved in 40 mL of water, 0.75 gm carbapol dissolved in 10 mL of water and mixed [20]. Sols were prepared on weight basis using the cold method [21]. Poloxamer 407 was slowly added to cold water (4-5°C) and constant stirring was maintained [Table/Fig-1]. The dispersion was refrigerated until a clear solution was obtained (4-5 hours). To the solution, Carbapol 934 was added in a concentration of 0.2% and mixed thoroughly. Further, *Moringa oleifera* extract was combined and the gel prepared [Table/Fig-2,3].

[Table/Fig-1]: Sol preparation by constant stirring.

[Table/Fig-2]: 5% *moringa oleifera lam* extract.

[Table/Fig-3]: Formulation of *Moringa oleifera* loaded in-situ gel.

Surface pH: The surface pH of the prepared in-situ gel was measured with a digital laboratory pH meter, equilibrated for 1 min.

Gelation temperature: A total of 5 mL sol was taken in test tubes and sealed with aluminum foil. This was placed in thermostat controlled electric water bath at 4°C. Slowly the water bath temperature was increased by 1°C to allow equilibration of the sol for 60 seconds at every degree of temperature rise. Frequent examination for completion of gelation was observed. When the meniscus was static upon tilting the test tube at 90°, showed completion of gelation [21].

Gelation time: Gelation time was determined under motion condition using a magnetic stirrer. The sol with magnetic stirrer (IKA, Germany) at hundred revolutions per minute was done. The time taken for the magnetic bead to become static was calculated as the gelation time and the experiments were done in triplicate [23].

Syringeability: A 1 mL of the formulated gel was loaded into a syringe of 5 mL capacity with 21 gauge needle. The test was considered positive, if the gel was disseminated through the syringe.

Fourier Transform Infrared Spectroscopy (FTIS): The chemical components interaction between *Moringa oleifera* and polaxamer was analysed by attenuated total reflectance-FTIR (Bruker Alpha II FTIR) in the spectral region of 4000-400 cm-1 wavelength with 4 cm-1 resolution at total scans of 32. The test samples *Moringa oleifera* powder, plain thermoreversible gel and thermoreversible gel with extract were made into pellets and investigated. The IR spectroscopy provides with a quantitative output analysis depending upon the proportion of infrared absorption of the chemical components. This helps in identifying the functional groups [24].

In-vitro drug release: The targeted location of the prepared thermoreversible *Moringa* gel is periodontal pocket. It is a confined

space bathed by continuous Gingival Crevicular Fluid (GCF) flow of pH between 6.8 to 7.4 [21]. Since, the flow of GCF could not be represented in-vitro, a static dissolution model was adopted. In this model, the phosphate buffer of pH 7.2 represented the dissolution medium similar to gingival fluid and the amount of drug release into the medium was assessed spectrophotometrically at fixed time intervals [25]. The procedure involves to 5 mL of the buffer taken in a test tube, 1 mL of the prepared formulation was laid and temperature of the buffer was maintained at 37±1°C similar to periodontal pocket temperature [26]. On completion of the scheduled specific time interval (1, 2, 3, 4, 8 and 12 hourly) spectrophotometric analysis of 1 mL of the sample taken from the medium was done at 261.5 nm. Replacement of the buffer with new buffer medium was done after analysis [21].

Stability test: The prepared gel was assessed for its stability during storage at a refrigerator temperature between 2 to 50 c. At a time interval of 7, 15 and 30 days, a sample of the formulation for subjected to spectrometric analysis.

Palatability: It is the test used to assess the acceptance of the preparation by one's mind. The test was conducted between the age group of 24-35 years among six volunteers. The sample size was calculated according to study by Kumari N and Pathak K [27]. A 5 mL of the formulated gel was given and advised to swish and spit after one minute The taste perceived at the end were recorded on a VAS score.

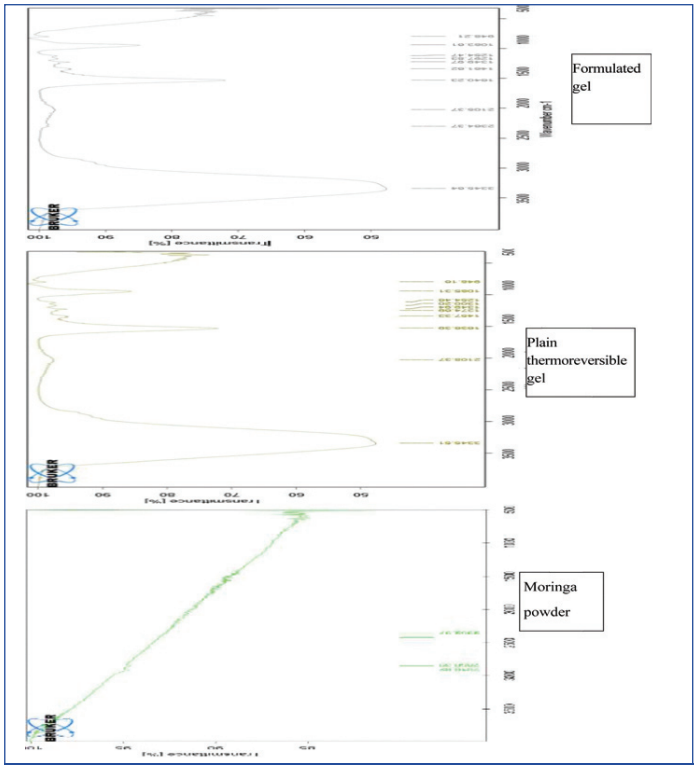
STATISTICAL ANALYSIS

The data was analysed and presented as in tabular and graph form.

RESULTS

The surface pH was found to be 6.94±0.091 and gelation temperature was the gel converted from sol to gel form at 34±0.5°C. The gelation time (time taken for gelation) was 1 min 20 seconds for conversion from sol state to gel. The syringeability-formulation had passed the test, as it had flowed easily. The FTIR analysis graph [Table/Fig-4] was assessed for the peaks and patterns and comparisons were made between the *Moringa oleifera* powder, plain thermoreversible gel and thermoreversible gel with extract. The absorption peaks were noted at 2918.82 cm^{-1} (strong, broad O-H stretching signifying carboxylic acid), 2850.39 cm^{-1} (medium C-H stretching alkane) and 2352.37 cm^{-1} (strong O=C=O, carbondioxide) for *Moringa oleifera*. The IR spectrum of plain thermoreversible gel showed principal peaks at 3345.51 (strong, N-H stretch), 2108.37 (variable C≡C stretch), 1636.39 cm^{-1} (weak C=C alkene), 1300.20 cm^{-1} (strong NO_2 stretch) and strong C-F bond at 1254.46 cm^{-1}. The thermoreversible gel with extract showed functional peaks at 3345.64 (strong, N-H stretch, secondary amine), 2364.37 cm^{-1} (strong O=C=O,carbondioxide), 2105.37 (variable C≡C stretch), 1640.23 cm^{-1} (strong C=C stretching alkene), 1297.83 cm^{-1} (strong strong C-N stretching, aromatic amine) and strong C-O stretching alkyl aryl ether at 1254.47 cm^{-1}. The spectrum results indicated that the physical mixture of *Moringa oleifera* and thermoreversible gel has not shown any interactions among their components [Table/Fig-2].

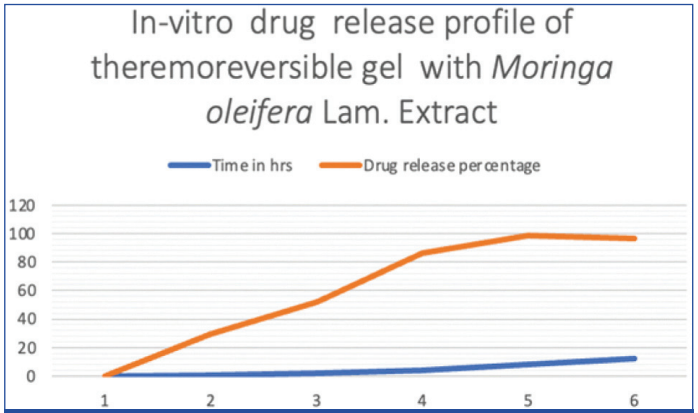
In-vitro drug release revealed a steady increase from 1 hour (29.35%) to 8 hours and reaching a maximum of 98.60% and a slight decrease at 12 hours of 96.21%. the results are depicted in [Table/Fig-5,6]. Palatability- taste perceived by the six volunteers were recorded on the VAS 0 to 10 is presented in [Table/Fig-7]. Mean score observed was 5.16±0.75. 16.66% commented to be poor, 33.3% felt it to be good, and 50% of volunteers recorded it as neither good or bad. In stability tests, the drug was found to be stable up to one month with a drug content of 99.54% when prepared fresh, 99% at one week, 98.57% at 15 days and 98.32% at one month [Table/Fig-8].



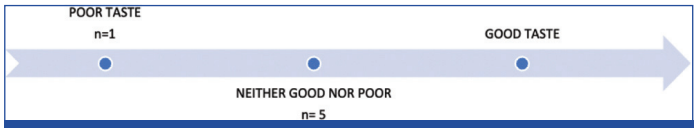
[Table/Fig-4]: FTIR results.

Time (hours)	Drug release percentage
0	0
1	29.35
2	52.26
4	86.28
8	98.60
12	96.21

[Table/Fig-5]: In-vitro drug release profile of thermoreversible gel with *Moringa oleifera Lam* extract.



[Table/Fig-6]: In-vitro drug release profile of thermoreversible gel with *Moringa oleifera Lam*.



[Table/Fig-7]: VAS scale used for palatability.

Stability of drug	Drug content (%)
Freshly prepared	99.54
7th day	99
15th day	98.57
30th day	98.32

[Table/Fig-8]: Stability test of thermoreversible gel with *Moringa oleifera Lam* extract at room temperature.

DISCUSSION

The use of antimicrobial and anti-inflammatory agents as an adjunct to periodontal therapy reduces microbial load and inflammation thereby preventing further destruction of periodontal tissues. However, the use of systemic medications is associated with the major limitation of bioavailability in the gingival crevicular fluid that is in close proximity to the periodontal pocket [3]. Hence, recently Local Drug Delivery (LDD) system is used currently due to the sustained release and bioavailability. For administration of drugs through LDD in periodontal pockets, thermoreversible gel which converts from one form to the other with change in temperature is ideal to maintain the adequate concentration of the drug in periodontal pockets [25].

Although several synthetic molecules such as chlorhexidine, metronidazole, doxycycline are in use, the search for herbal and plant derived products for the management of periodontal disease continues [22,27-29]. The use of plant-derived products have several advantages such as ease of availability, diverse phyto therapeutic properties due to a mixture of active ingredients, less likely to have side effects being diet derived [30]. In this regard, in the present study, aqueous *Moringa oleifera Lam* extracts was chosen due to the fact that it is indigenous to India hence easily available and have several phytochemicals that exert antioxidant, antimicrobial and anti-inflammatory properties to formulate a thermoreversible gel [8].

The main aim of the developing LDD is maintenance of the adequate concentration of the drug at the required site for required duration. In this regard, sustained drug release system maintains the required concentration for a day and controlled release system maintain the concentration of the drug for more than 24 hours [31,32]. Recently the use of biodegradable polymers with thermoreversible property has gained importance as the sol converts into gel form when injected into the periodontal pocket, thereby, providing sustained release [33]. In the present study, the authors used thermos gelling polymer, poloxamer 407 and a mucoadhesive polymer carbopol 934 for formulation of in-situ gel of *Moringa oleifera* by cold method. Similarly, in a study by Balakrishnan P et al., they have used poloxamer 407 (P407)-based thermoreversible gel using Carbopol 934P (C934P) as a mucoadhesive polymer for intranasal drug delivery to improve the solubility and increased absorotion of for Fexofenadine Hydrochloride (FXD HCl) [34]. Similarly, in a narrative review Chen Y et al., have reported the advantages of using Poloxamer 407 for oral formulation that improves the bioavailability of the drug [35].

In the present study, a formulation with the extract was done for direct placement into the periodontal pocket, where the sol form would undergo gelation at periodontal pocket temperarture and pH. Usually the ideal gelation temperature for periodontal gels is 35°C to 37°C. For instance, if the gelation temperature is below 25°C, a gelation could occur at room temperature and hence manufacturing, handling administering and shelf-life could be difficult. If the gelation temperature is greater than 37°C, the gelation would not occur in the oral cavity and hence, bioavailability of the drug would be reduced [33].

The FTIR spectroscopy assessment revealed that the formulated gel with *Moringa oleifera Lam* extract did not undergo changes in chemical composition thereby the functional groups remained unaltered in the prepared gel. The surface pH of the gel was 6.94±0.091 with a gelation temperature of 34±0.5°C. As the temperature of the periodontal pocket ranges between 36°C, and 37°C, authors used the poloxamer 407 and carbopol 934 that may gel below 36°C.

It is a well known fact that there is a reduction in gelation temperature with an increase in concentration of P407 [30]. Hence we chose 19% of thermogelling polymer Poloxamer 407 [16] (15% to 30% w/v) which the least concentration that demonstrates thermoreverisibility at 36°C and 0.2% which is the least concentration of mucoadhesive polymer Carbapol 934 (0.2% to 0.5% w/v) forms sol-gel transition. The pH was also well within the range of the absorption site. The gel was palatable and flowable with good stability with a 99.54% drug in freshly prepared formulation with the slight decrease over a period of time and was found to be 98.32% at one month. However long-term stability studies have to be carried out. The gelation time was 1 minute 20 seconds, which is well within the required range. Considering the release there was a time-dependent increase in drug release from one hour to eight hours and a slight decrease after 12 hours which is adequate for periodontal therapy. The FTIR analysis revealed that *Moringa oleifera Lam* extract was pure and could be used for further study.

Many research works were performed in the formulation of appropriate thermoreversible gel for periodontal pocket delivery. Various antibiotics, host modulating agents and phytochemicals have been tried [20,21,22,27-29]. There were two reported clinical trials [36,27], in one, adjunctive local drug therapy with thermo-reversible green tea gel has been shown to reduce periodontal pocket depth and inflammation when compared to scaling and rootplaning during the four weeks of the clinical trial in patients with chronic periodontitis. The results are attributed to both antimicrobial and anti-inflammatory activity of green tea catechin [36].

In the other clinical study, the effect of combination of levofloxacin, metronidazole with chitosan and poloxamer 407 on clinical signs of periodontal inflammation was determined. Though, there was gain in clinical attachment level and reduction of gingival signs of inflammation, the sample size was too small to conclude on the results [27].

In one of the studies, formulation of thermoreversible gel using simvastatin was researched. In that study, 2.2% simvastatin was used against various concentrations of Poloxamer 407 and methyl cellulose. And the study concluded, 25% Poloxamer and 5% MC was successful combination to show an in-vitro drug release for six days [37]. But, in the present study authors had used Carbapol in place of methylcelluslose since, its proved that for intraoral usage carbapol in combination with poloxamer showed better bioadhesiveness [38].

In yet another study, temperature sensitive intrapocket gel preparation was done with 0.1% w/v chlorhexidene using Poloxamer 407, Poloxamer 188 and carbapol. And among different concentrations Poloxamer 407 in 19% with 0.2% carbapol had the highest desirable outcome for intrapocket delivery. Accordingly in the present study, the observed concentration was adopted to prepare the thermoreversible gel [22].

Many more studies have been conducted with cephalexin [21], metronidazole with serratiopeptidase [27], doxycycline with and without lipoxin [29] and moxifloxacin hydrochloride [20] in the preparation of thermoreversible injecteable gels for local drug delivery of these active agents for the management of periodontitis. Some studies have been listed in [Table/Fig-9] [5,20-22,27,28,36,37].

However, only one study using herb-like green tea was studied and observed to be efficient clinically among patients with periodontitis [21]. The present thermoreversible gel formulated with 5% *Moringa oleifera Lam* extract with adequately investigated. And the present study is the first of its kind to use *Moringa oleifera Lam* extract in thermoreversible gel form for oral usage. It was observed to have adequate retentive characteristics and suitable sol gel transition for intrapocket delivery.

Author's name and year	Place of study	Thermoreversible gel used	Parameters compared	Conclusion
Swain GP et al., 2019 [20]	India	Moxifloxacin hydrochloride with Poloxamer 407, gellan gum, Carbapol 934	Drug content, gelation time, temperature, in-vitro diffusion study.	Optimised formulation contained 19.072% w/v of Poloxamer and 0.245% w/v for periodontal pocket delivery.
Rajendran S et al., 2017 [37]	India	Poloxamer and methylcellulose to 2.2% simvastatin	Drug relese and stability	Poloxamer 25% and methyl cellulose 5% exhibited stability with 98% drug content at 6 months.
Bansal M et al., 2016 [28]	India	20% w/v poloxamer 407, chitosan 1.5%, w/v into the 0.5% v/v acetic acid, Levofloxacin 10%, w/v and Metronidazole 25% w/v	Clinical study- plaque index, gingival index, bleed on probing, probing pocket depth, clinical attachment level.	Clinical attachment gain with all reduction in clinical parameters observed.
Parvathy S et al., 2015 [21]	India	Cephalexin with poloxamer 407 (10%-20% w/v) and carbapol 934 (0.1-0.5%)	Gelation temperature, in-vitro drug release.	18% poloxamer and 0.2% carbapol 934 showed satisfactory results in in-vitro gelling capacity and drug release profile.
Garala K et al., 2013 [22]	India	0.1% w/v chlorhexidene hydrochloride with different Polymers Poloxamer 188, Poloxamer 407, Gellan gum, Carbapol 934	Gelation temperature, in-vitro drug release.	19% poloxamer and 0.2% carbapol 934 had 6 hr drug release with gelation temperature of 33±1°C
Chava VK and Vedula BD [36]	India	Green tea Catechin with 22% poloxamer 407 and 1.5% carbomer w/v	In-vivo study-probing depth, gingival index, relative clinical attachment level.	Statistically significant reduction in pocket depth and clinical signs of inflammation between the test and control groups.
Kumari N and Pathak K, 2011 [27]	India	Poloxamer 407, Aerosil, with metronidazole, and serratiopeptidase.	Mucoadhesive strength, palatability and rheological studies.	Poloxamer 250 mg, aerosol 9 mg with 5 mg serratiopeptidase, metronidazole 40 mg displayed good mucoadhesive strength and palatability.
Jones SD et al., 2002 [5]	Ireland	Metronidazole 5%, w/w) with hydroxyethylcellulose-3 and 5%, w/w or carbopol 3 and 5%, w/w, polycarbophil-1 and 3%, w/w.	Drug release, texture profile, adhesion, syringeability.	The hardness, adhesiveness, syringeability were directly proportional to the concentration of polymers.
Present study, 2022	India	5% aqueous *Moringa oleifera* extract with carbapol 0.2% and 19% Poloxamer 407.	FTIR, surface pH, gelation time and temperature, syringeability, palatability, in-vitro drug release and stability tests.	In the formulated MO thermoreversible gel, sol-gel transition was observed at 34±0.5°C with 96% drug release lasted for 12 hours. FTIR did not show interactions between the components.

[Table/Fig-9]: Previous studies with preparation of thermoreversible injecteable gels of different active agents for local drug delivery in periodontitis [5,20-22,27,28,36,37].

Limitation(s)

The limitation of the study includes that the antioxidant, anti-inflammatory and antimicrobial properties of the gel, have not been assessed. In future, the toxicity studies and evaluation of clinical benefits of thermoreversible in-situ *Moringa oleifera Lam* gel in the treatment of periodontitis should be assessed by well-designed randomised controlled or clinical trial.

CONCLUSION(S)

The prepared in-situ thermoreversible gel with the active agent 5% *Moringa oleifera Lam* extract, hydrogels like Poloxamer 407 (19%) and Carbapol 0.2% established a favourable rheological outcomes much suitable for intaoral pocket delivery. There was a sustained drug release which declined slowly only after 12 hours of activity. In the prepared gel, sol-gel temperature shift was observed to happen at 34±0.5°C which was more comparable with intra oral temperature. This *Moringa oleifera Lam* extract thermosensitive gel has the required properties for local drug delivery in periodontal pocket and could be explored as an adjunct in periodontal treatment, thereby, improving the prognosis of the disease.

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