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RESEARCH ARTICLE

Preparation and characterization of bioadhesive systems containing propolis or sildenafil for dental pulp protection

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Abstract

Purpose: Binary polymeric systems containing poloxamer 407 (P407) and Carbopol 934P (C934P) were designed to deliver propolis extract (PE) or sildenafil citrate for the endodontic treatment (pulp protection).

Methods: Gelation temperature, rheology (flow), bioadhesion, and *in vitro* drug release of formulations were determined.

Results: Formulations showed thermoresponsive behavior, existing as a liquid at room temperature and gel at 34–37°C. In addition, they exhibited pseudoplastic flow and low degrees of thixotropy or rheopexy. The greatest bioadhesion was noted in the formulation containing 20% P407 (w/w) and 0.10% C934P (w/w). PE release from formulation containing 15% P407 (w/w) and 0.25% C934P (w/w) was controlled by the phenomenon of relaxation of polymer chains. Moreover, sildenafil release from formulation containing 20% P407 (w/w) and 0.10% C934P (w/w) was controlled by Fickian diffusion.

Conclusion: The data obtained on these formulations indicate a potentially useful role in the endodontic treatment (pulp protection) and suggest they are worthy of clinical evaluation.

Keywords: Biodegradable polymers, buccal, formulation, hydrogels, *in vitro* models, mechanical properties, natural products, polymeric drug delivery systems, viscosity

Introduction

Advances in dentistry and endodontics are set to take place. The ability to stimulate endodontic regeneration has been studied and the regenerative endodontic procedures can be defined as biologically-based procedures designed to replace damaged structures, including dentin and root structures, as well as cells of the pulp-dentin complex[1]. Often, dentists face patients whose primary complaint is translated by painful symptoms located in a tooth, frequently with carious lesions, with or without the dental pulp exposed. Thus, the completion of conservative treatment of dental pulp is one of the main activities in dentistry[2]. Actually, direct or indirect pulp protection and pulpotomy are the conservative treatments aimed at decreasing the aggression produced by chemical, biological, mechanical, or thermal agents and preserve the vitality and function of dental pulp[3].

Two main strategies have been used in the preservative treatment of dental pulp: (1) cavity preparation to remove the aggression and isolation of pulp-dentin complex; (2) pulp capping, using materials which can stimulate biological process promoting dentinogenesis[4]. Moreover, pulp-inflammatory reaction after aggression or cavity preparation is characterized by modifications of the blood flow, immune cells, and neural reactivity[5]. Experimental studies indicate that the nitric oxide (NO) participate in all the alterations as a mediator of vascular homeostasis[6], modulator of pro-inflammatory activity[7], and indicator to cell differentiation, following formation of the reparative dentin[8].

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In addition, the presence of NO has been detected in normal or inflamed dental pulps of many species of animals, including human beings[9,10].

In this context, propolis and sildenafil citrate can be used in the conservative treatment of the dental pulp[11–13]. A special case is propolis (bee glue), a strong resinous adhesive product which are collected by honeybees and are derived by extracted it from the beehive, which has been used in endodontics for its pharmaceutical properties, including antimicrobial[14–17], anti-inflammatory[18,19], and antioxidant[20] activity. Alone or incorporated in another dosage form, ethanolic extract of propolis is commonly used in dental treatments, due to its safety and efficacy[18,21,22]. Moreover, sildenafil citrate is a phosphodiesterase type-5 inhibitor used in the management of erectile dysfunction and pulmonary arterial hypertension[23]. However, studies have showed that sildenafil citrate increases the concentration of NO, being important in the pulp protection, reducing the inflammatory process and improving the pulp's condition[11].

In addition, the difficulty of administration and the short residence time of these drugs into the endodontic space have fuelled the interest to develop controlled drug delivery systems. Clinical efficacy of dental-pulp treatments depends intrinsically on the drug release and mechanical properties of the formulation. Thus, ideal formulations should enable easy insertions into the endodontic space, show controlled release of drug, exhibit local retention for the desired period of time, be biodegradable, nontoxic, and nonirritant[1,24].

Currently, there are not commercially available systems to deliver propolis or sildenafil. Thus, semisolid formulations consisting of bioadhesive polymers could improve the intimacy of contact of dosage form and also increase its residence time in the tooth[21,25]. Within the endodontic environment, these polymers can interact with surfaces by means of specific interfacial forces in a process commonly referred as bioadhesion[26]. Furthermore, thermosensitive systems containing poloxamer have been investigated as a convenient dosage form of endodontic application[25]; liquid dosage forms containing poloxamer injected into the endodontic space can undergo a transition to the gel state as a result of physical changes induced by rising temperature, improving their retention time in the endodontic space[21].

Therefore, this study describes the development and characterization of semisolid systems containing propolis or sildenafil prepared from Carbopol 934P and poloxamer 407, designed for endodontic application.

Materials and methods

Materials

Poloxamer 407 (P407) was a kind gifted from BASF (Sao Paulo, São Paulo, Brazil) and Carbopol 934P (C934P) was purchased from B. F. Goodrich (Brecksville, OH). Triethanolamine (TEA) was purchased from Galena (Campinas, São Paulo, Brazil) was used as a neutralizing agent. Propolis was collected from an experimental apiary in the farm of the State University of Maringa (Parana State, Brazil) and propolis extract (PE) was obtained as described by Bruschi et al.[22,27] Sildenafil citrate was purchased from Pfizer (Dongcheng District, Beijing, China). All other chemicals were purchased from Merck (Darmstadt, Germany) or Synth (Diadema, Brazil) and were of analytical, or equivalent quality.

Preparation of formulations

C934P (0.10, 0.25 or 0.50%, w/w) was initially dissolved in distilled water using a mechanical stirrer. Following complete dissolution, P407 (15 or 20%, w/w) was added to this gel and the mixture was stored at 4°C for 12 h to ensure complete wetting. Formulations were then stirred, to ensure complete mixing of the two components, neutralized with TEA and stored at 4°C for 24 h[21].

PE was prepared with a propolis/ethanol ratio of 30/70 (w/w) by turbo extraction, filtered through filter paper and made up to the initial weight with the ethanol[27,28]. The PE was added to the formulations at 4% (w/w), the amount normally used in therapy, by the dripping technique, at 20°C and with magnetic stirring, for 30 min[18,22,27,28]. On the other hand, sildenafil was added to the formulations at 0.015% (w/w) by manual stirring. All samples were then transferred into amber ointment jars, evacuated to remove incorporated air and then stored at 4°C for at least 24 h prior to further analysis.

Determination of gelation temperature of formulations

A 20-mL transparent vial containing a magnetic bar and 10 g of each polymeric system was placed in a low-temperature thermostat plate. A thermometer was immersed in the system which was heated at a constant rate with constant stirring. When the magnetic bar stopped moving due to gelation, the temperature displayed on the thermometer was taken as the gelation temperature or sol/gel transition temperature ($T_{sol/gel}$)[21,29].

Continuous shear (flow) rheometry of formulations

The rheological analysis of formulations was performed at 20°C in a ViscoStar– Plus R controlled shear rate rotating viscometer (Fungilab, Barcelona, Spain), equipped with spindle R4 or R5, according to the consistency of each formulation[21,30]. Samples were carefully applied to the cup, ensuring that formulation shearing was minimized, and allowed to equilibrate for at least 5 min prior to analysis. In continuous shear analysis (viscosity), upward and downward flow curves for each formulation were recorded over shear rates ranging from 0.3 to 200 rpm. Shearing rate was increased over a period of 150 s, held at the upper limit for 10 s, and then decreased

over a period of 150 s. In each case, the continuous shear properties of at least three replicates were determined.

Assessment of bioadhesive strength of formulations

The bioadhesive strength of the formulations under investigation was evaluated by measuring the force required to detach the formulation from an exposed dentin of bovine tooth, using a TA-XTplus Texture Analyser (Stable Micro Systems, Surrey, England) in tension mode[21]. The specimen was horizontally attached to the lower end of the cylindrical probe (length 5 cm, diameter 1 cm) using double-sided adhesive tape. At temperature of 37°C, samples of each formulation, previously packed into shallow cylindrical vessels, were placed under the analytical probe which was then lowered until the specimen was in contact with the surface of the sample. Without delay, a downward force of 0.1 N was applied for a predefined time (30 s) to ensure intimate contact between the specimen and the sample. The probe was then moved upwards at a constant speed of 1.0 mms^{-1} and the force required to detach the tooth from the surface of each formulation was determined from the resulting force-time plot. All measurements were performed in at least five replicates.

Development of analytical method to quantify sildenafil

A sildenafil reference standard stock solution of 2.5 mg. mL^{-1} was prepared in purified water. Calibration standard solutions at six levels were prepared by serially diluting the stock solution to concentrations of 12.50, 18.75, 25.00, 31.25, 37.50, and 43.75 $\mu g.mL^{-1}$. Samples were analyzed by UV-1650PC spectrophotometer (Shimadzu, Tokyo, Japan) at $\lambda = 292$ nm[31]. Each analysis was repeated five times, and the calibration curves were fitted by linear regression. The linearity was determined for the calibration curve and the specificity, defined as the ability of the method to measure the analyte accurately and specifically in the presence of components in the sample matrix, was determined by analysis of spectrum of the standard solution. The limit of detection (LOD) and limit of quantification (LOQ) were calculated based on the standard deviation (SD) and the slope (S) of the calibration curve[27,28,32]. The precision of the method was determined following ICH (The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guidelines. For evaluation of the repeatability, the SD and relative standard deviation (RSD) of five analyses were considered. The accuracy was determined by recovery analyses, adding measured amount of sildenafil to simulated sample. The recovery experiments were performed in triplicate. The recovery data were determined by dividing the value obtained for the sample prepared with the added standard, by the amount added and then multiplied by 100%[33].

In vitro release studies

In vitro release of propolis and sildenafil from formulations was determined (at least in triplicate) using Franz cell apparatus containing cellulose acetate membrane. The release medium was 50 mL of purified water at 37 ± 0.5°C and constant magnetic stirring was employed. Each formulation was analyzed in triplicate.

Release of propolis from formulations

Exactly 2.0 mL of formulation containing 15% (w/w) of P407, 0.25% (w/w) of C934P and PE were evaluated. Samples were placed on the membrane, sink conditions were maintained, at predetermined time intervals (30 min, 1 h, 2 h, 4 h, 6 h, and 8 h) aliquots (1.0 mL) of the dissolution fluid were collected and the propolis concentration (total flavonoids drift) was analyzed by spectrophotometry ($\lambda = 425$ nm), as previously described by Bruschi et al. (2003)[27,28]. None of the formulation components was found to interfere with the analysis.

Release of sildenafil from formulations

The amount of 2.0 mL of formulation containing 20% (w/w) of P407, 0.10% (w/w) of C934P and 0.015% (w/w) of sildenafil were evaluated. Samples were placed on the membrane, sink conditions were maintained, at predetermined time intervals (30 min, 1 h, 2 h, 4 h, 6 h, and 8 h) aliquots (1.0 mL) of the dissolution fluid were collected and the sildenafil concentration was analyzed by spectrophotometry ($\lambda = 292$ nm). None of the formulation components was found to interfere with the analysis.

Drug-release kinetics

The drug-release kinetics were analyzed by plotting the measured drug concentration in the release solution with time. To investigate the mechanism of drug release, the data generated from these release studies were fitted to the general release Equation 1 using logarithmic transformations and least squares regression analysis[21]:

$$\frac{M_t}{M_\infty} = kt^n, \quad (1)$$

where M_t is the amount of drug released at time t, M_∞ is the total drug content; k is a constant incorporating structural and geometric characteristic of the device, and n is the release exponent which may indicate the mechanism of drug release.

Statistical analysis

The effects of polymer concentration on the gelation temperature were statistically evaluated using one-way analysis of variance (ANOVA). Similarly, the effects of the drug presence on the force required to overcome the dentin adhesive bond were statistically evaluated using one-way ANOVA. Furthermore, the effects of polymer concentration on the time required for the release of defined percentages of the original mass of propolis and sildenafil from each system (10, 30, and 50%) were statistically evaluated using one-way ANOVA. In all cases of ANOVA analysis, post-hoc comparisons of the means of

individual groups were performed using Tukey's Honestly Significant Difference test. In all tests, a value of $P < 0.05$ was taken to denote significance[34] and Statview software (Abacus Concepts, CA) was used throughout.

Results

Determination of gelation temperature of formulations

The preparations described in this study were easy to manufacture and the different contents of P407 and C934P in the structure of these products provided formulations with a wide range of consistency. Formulations containing 15% P407 yielded homogeneously dispersed preparations with $T_{sol/gel}$ between 28.17°C and 31.23°C. Moreover, the formulations containing 20% (w/w) of P407 showed $T_{sol/gel}$ below 25°C (Table 1). The incorporation of C934P (0.10–0.25%, w/w) significantly affected the $T_{sol/gel}$ of binary systems. Moreover, the sequential increase in concentration of P407 significantly decreased the sol/gel temperature of these systems as well, according previous studies[21,25]. Table 2 shows the $T_{sol/gel}$ for formulations containing drug. The addition of PE did not change significantly the $T_{sol/gel}$ of formulations containing 15% (w/w) of P407, but the addition of sildenafil decreased the $T_{sol/gel}$ of these formulations significantly. The addition of the drugs in the formulations containing 20% (w/w) P407 significantly decreased the $T_{sol/gel}$. The decrement was more evident to the formulations where PE was added, according to previous studies[21,25].

Table 1. Gelation temperature (T_{sol}/gel) of the formulations under study.

Formulation	Concentration (%, w/w) P407	C934P	$T_{sol/gel}$ (°C)[a]
F15/0.10	15	0.10	31.23 ± 0.25
F15/0.15	15	0.15	30.33 ± 1.04
F15/0.20	15	0.20	29.00 ± 1.53
F15/0.25	15	0.25	28.17 ± 0.00
F20/0.10	20	0.10	23.33 ± 1.15
F20/0.15	20	0.15	21.83 ± 0.29
F20/0.20	20	0.20	19.67 ± 0.58
F20/0.25	20	0.25	16.00 ± 0.00

[a]Each value represents the mean (±standard deviation) of at least three replicates.

Continuous shear (flow) rheometry

The flow properties of formulations were determined at 20°C and rheograms were plotted of viscosity (Pa.s) versus velocity rate (rpm), showing a nonlinear response. All the formulations exhibited shear-thinning behavior (pseudoplastic flow) with hysteresis area (Figure 1 and 2). Beside pseudoplastic flow, the formulations F15/0.25 (with and without PE) exhibited low degrees of thixotropy. Moreover, formulations F20/0.10 (with and without sildenafil) exhibited rheopexy.

Evaluation of the bioadhesive strength of formulations

The bioadhesive properties of the systems were examined using a tensile method in which an exposed dentin of a bovine tooth was employed as the model substrate. The forces required to detach each formulation from specimen are presented in Table 3.

As the strength of cohesive bonds associated with formulation F15/0.25 (with and without drug) was lower than semisolid-dentin adhesive bonds, direct measurement of their bioadhesion could not be performed. Fragments of formulation were found to remain adhered to some places of the dentin and, therefore, these tests were deemed to be unsuccessful due to cohesive failure of the sample and of the sample/dentin interface. Only

Table 2. Gelation temperature (T_{sol}/gel) of the containing-drug formulations under study.

Formulation	Concentration (%, w/w) P407	C934P	PE	Sildenafil	$T_{sol/gel}$ (°C)[a]
F15/0.10	15	0.10	0.40	—	32.17 ± 0.00
F15/0.10	15	0.10	—	0.015	28.67 ± 0.58
F15/0.15	15	0.15	0.40	—	31.57 ± 0.50
F15/0.15	15	0.15	—	0.015	25.67 ± 1.15
F15/0.20	15	0.20	0.40	—	28.17 ± 0.00
F15/0.20	15	0.20	—	0.015	22.67 ± 1.15
F15/0.25	15	0.25	0.40	—	29.00 ± 0.46
F15/0.25	15	0.25	—	0.015	22.33 ± 0.58
F20/0.10	20	0.10	0.40	—	16.66 ± 0.58
F20/0.10	20	0.10	—	0.015	19.33 ± 1.53
F20/0.15	20	0.15	0.40	—	17.00 ± 0.00
F20/0.15	20	0.15	—	0.015	19.33 ± 0.29
F20/0.20	20	0.20	0.40	—	14.00 ± 0.50
F20/0.20	20	0.20	—	0.015	15.83 ± 0.29
F20/0.25	20	0.25	0.40	—	12.66 ± 0.58
F20/0.25	20	0.25	—	0.015	14.00 ± 0.87

[a]Each value represents the mean (±standard deviation) of at least three replicates.
PE, propolis extract.

the formulations containing 20% (w/w) of P407 and 0.10% (w/w) of C934P were suitable to perform this test. The vertical detachment force needed to break the bioadhesive bond of the formulations F20/0.10 was increased significantly by the sildenafil addition.

Development of analytical method to quantify sildenafil

Based on linear regression analysis, the response for sildenafil standard in related concentration ranges was linear. The calibration equation was $y = 0.0195 \times -0.1047$

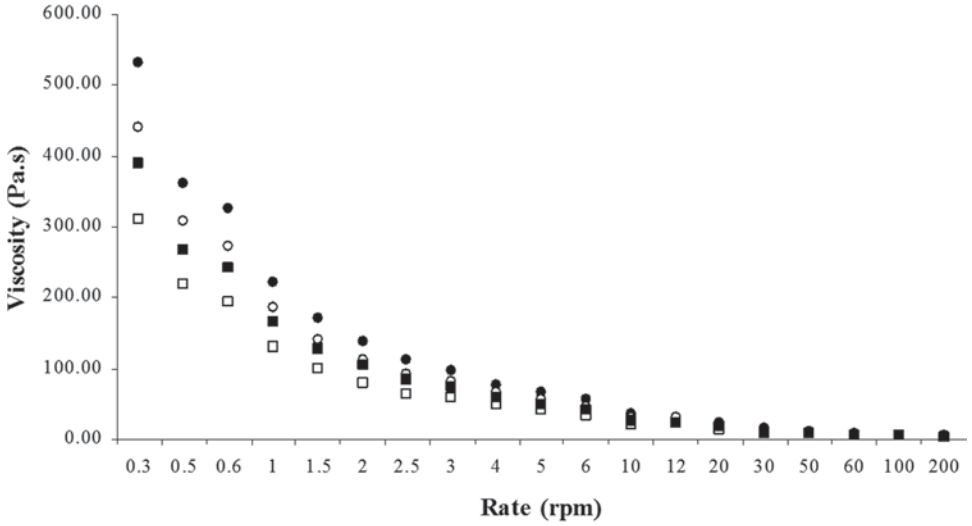

Figure 1. Flow rheograms of binary polymeric formulations P407/C934P (15/0.25%, w/w) at 20°C, without (open squares) and with (open circles) propolis extract. Filled symbols show the upcurve and open symbol the downcurve. Standard deviations have been omitted for clarity; however, in all cases the coefficient of variation of at least three replicate tests was less than 5%.

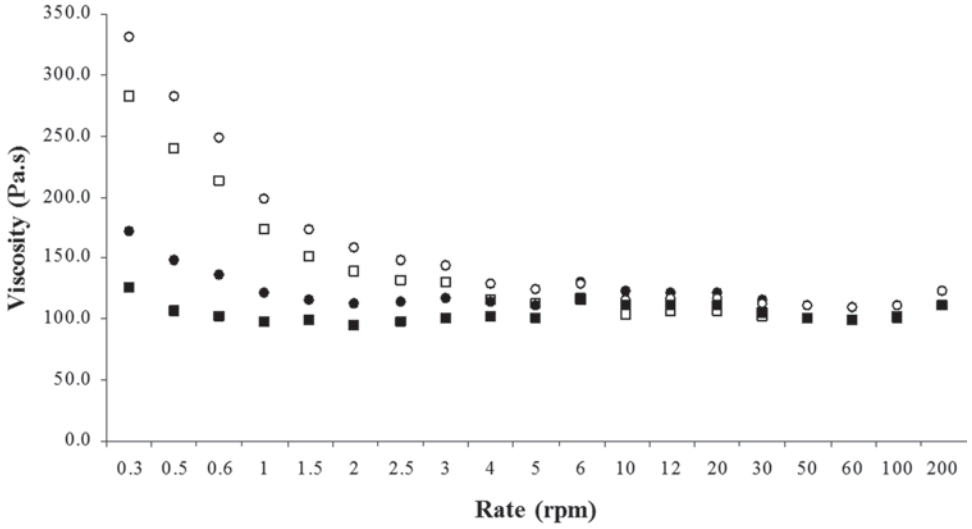

Figure 2. Flow rheograms of binary polymeric formulations P407/C934P (20/0.10%, w/w) at 20°C, without (open squares) and with (open circles) sildenafil. Filled symbols show the upcurve and open symbol the downcurve. Standard deviations have been omitted for clarity; however, in all cases the coefficient of variation of at least three replicate tests was less than 5%.

Table 3. Bioadhesive strength of formulations under study.

	Concentration (%, w/w)				
Formulation	P407	C934P	PE	Sildenafil	Force (*N*)[a]
F15/0.25	15	0.25	—	—	—[b]
	15	0.25	4.0	—	—[b]
F20/0.10	20	0.10	—	—	0.1855 ± 0.0124
	20	0.10	—	0.015	0.1991 ± 0.0028

[a]Each value represents the mean (± standard deviation) of at least five replicates.
[b]Not measured due to cohesive bond failure.
PE, propolis extract.

($n = 5$, $r^2 = 0.9874$). Table 4 shows the back-fit calculations for curve data for the sildenafil standard used in the validation runs, as well as the precision and accuracy of the back-fit calculations. The value of $F_{reg/res}$ (regression mean square– residual mean square ratio) was 1018.83, showing that the regression was highly significant. Moreover, the linear model did not show a lack-of-fit, displaying the $F_{lfit/perror}$ value (lack-of-fit mean square– pure-error mean square ratio) of 1.38[34]. The LOD and LOQ assess the sensitivity of the method. The LOD, defined as the lowest concentration of sildenafil that can be detected but not necessarily quantified under the stated experimental conditions, was 3.20 μg.mL^{-1}. The LOQ, defined as the lowest concentration of sildenafil that can be determined with acceptable precision and accuracy, was 9.71 μg.mL^{-1}.

Table 4. Curve parameter summary and back-calculated calibration curve concentrations for sildenafil.

Parameter	Result
Linear range (μg/mL)	12.5–43.75
Detection limit (μg/mL)	3.20
Quantitation limit (μg/mL)	9.71
Regression data*	
N	5
Slope (*a*)	0.0195
Standard deviation of the slope	0.0006
Intercept (*b*)	–0.1047
Standard deviation of the intercept	0.0189
Correlation coefficient (r^2)	0.9874
Regression (mean square)	0.7637
Residual (mean square)	0.0007
Lack-of-fit (mean square)	0.00047
Pure-error (mean square)	0.00034

*$y = ax + b$, where x is the concentration of sildenafil and y is the absorbance.

The RSD values of the sildenafil absorbance obtained by spectrophotometry were ≤ 5.0%. These results demonstrated the reproducibility[33]. Preparing a simulated sample containing a known quantity of sildenafil determined the accuracy of the spectrophotometric method for the assay analysis of recovery. The recovery of an added standard sildenafil was 93.98 ± 0.76%. These results referred to the average of three assays and they are in good agreement with the results (80–120%) required[27,28,32,33].

In vitro release of drug from formulations

Thus, to investigate the release of PE and sildenafil from the developed formulations, a Franz cell apparatus was used. The release of PE from formulation is presented in Figure 3. Under sink conditions, the *in vitro* studies showed that formulation F15/0.25 provided prolonged release of PE. The *in vitro* release studies of formulation containing sildenafil showed that F20/0.10 provided a rapid release of the drug (Figure 4). In addition, the times required for drug release (10, 30, and 50% of original drug loading) from each formulation were calculated and statistically compared. These results are presented in Table 5.

Discussion

The endodontic specialty may be able to adopt many of these new scientific advances emerging from regenerative medicine, thereby developing regenerative endodontic procedures and improving patient care[1]. Dental materials research has been driven by an understanding of physicochemical characteristics, toxicity limitations, and biocompatibility of new materials with dental and other oral tissues[35].

Particularly, the physicochemical characteristics of the endodontic drug delivery systems are important for

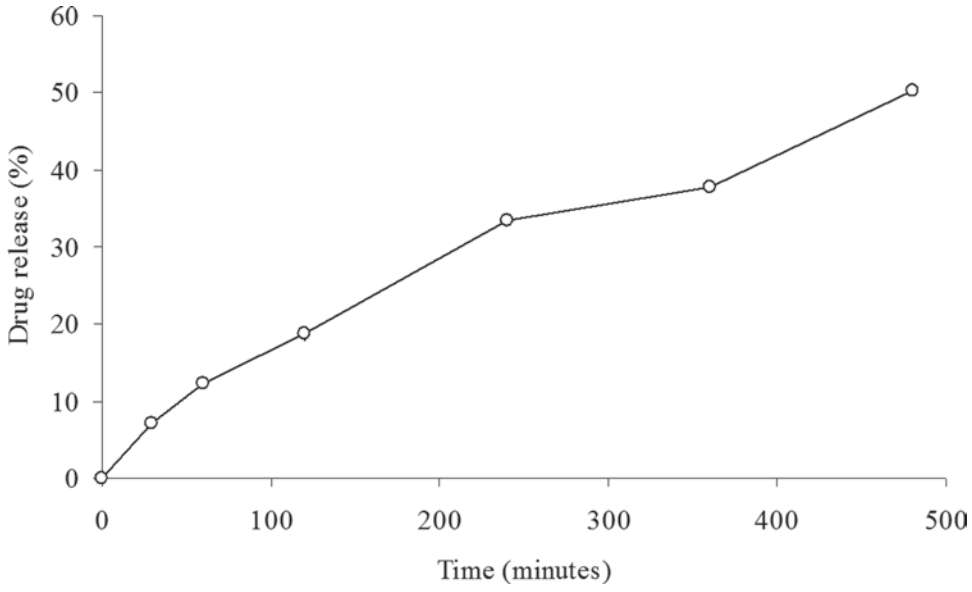

Figure 3. The effects of P407 and C934P on the release of propolis from formulation containing P407 15% (w/w) and C934P 0.25% (w/w). Curve is the mean ± standard deviation of at least three analyses.

Table 5. Time (minutes) required for the release of 10, 30, and 50% of the original mass of PE and sildenafil from the formulations under examination.

Formulation	Concentration (%, w/w)				
	P407	C934P	$t_{10\%}$ [a]	$t_{30\%}$ [a]	$t_{50\%}$ [a]
F15/0.25 + PE	15	0.25	47.30 ± 0.63	230.32 ± 0.76	480.89 ± 5.28
F20/0.10 + Sildenafil	20	0.10	$1.12 \times 10^{-8} \pm 0.67 \times 10^{-9}$	0.0017 ± 0.00006	0.44 ± 0.0076

[a]Values represent the mean (±standard deviation) of at least triplicate determination.
PE, propolis extract.

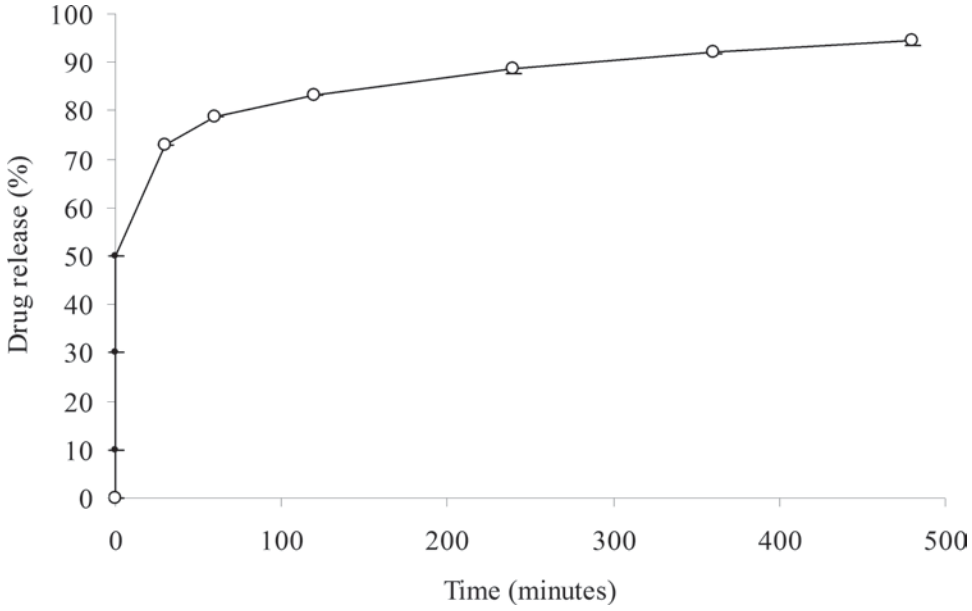

Figure 4. The effects of P407 and C934P on the release of sildenafil from formulation containing P407 20% (w/w) and C934P 0.10% (w/w). Curve is the mean ± standard deviation of at least three analyses.

the clinical success of endodontic treatment (Bruschi et al., 2007)[21]. An ideal candidate formulation for controlled delivery of an agent to the endodontic space should exhibit a variety of characteristics. These include ease of application into and retention within the endodontic space, controlled (prolonged) drug release and ease of manufacture[1,36,37]. There have been several reports of controlled drug delivery systems for improved pulp protection[4,21,38,39]. However, few of these have an ideal product profile for endodontic treatment. Furthermore, sildenafil and PE can be effective in the pulp protection. However, no endodontic drug delivery systems use these agents.

Thermosensitive polymers have been studied to increase the residence time of drug delivery systems at the administration site[21,30,40–42]. Therefore, this study proposed the formulation of semisolid devices based on the use of binary hydrophilic polymer gels that may offer several advantages with respect to clinical performance in the pulp protection. Importantly, the polymers employed in this study, thermoresponsive P407 and highly mucoadhesive C934P, were chosen according to their capacity to form a bioadhesive semisolid polymer network in aqueous solvent, facilitating insertion, to improve the intimacy of contact and the retention time of the formulation into the endodontic space, and for their known biocompatibility, pharmaceutical acceptability, compatibility with other chemicals, high-solubility capacity for different drugs, and good drug-release characteristics[21,25,30].

Considering these results and the ambient and endodontic temperature (20°C and 34–37°C, respectively), only F15/0.25 for PE and F20/0.10 for sildenafil were tested further.

The nonlinear responses to shear stresses exhibited by the formulations resulted from structural changes caused by shearing. Probably, the formulations consisted primarily of highly entangled long-chain polymer molecules in a relaxed state. On exposure to a shear stress, the polymer chains disentangled and became aligned along the direction of shear, releasing the solvent that had been previously trapped in the molecular coils. As a result, subsequent shearing occurred more readily and the apparent viscosity was decreased. Shear thinning is a desirable property in formulations intended for endodontic application. For example, during administration, at high rates of shear, the material will flow readily, facilitating successful clinical administration. However, under the conditions of low shear experienced subsequently in the endodontic space, the material will adopt the higher consistency that it possesses before administration. As the preadministration temperature of the binary systems will be up to 20°C and the oral cavity temperature is between 34 and

37°C[39], the recovery of the original rheological properties of formulations will take place together with the gelation of the system. The viscosities observed at 20°C for the binary formulations with and without the drugs indicate that restoration of the relaxed molecular configuration resulted in a greater apparent viscosity and required only a short time after removal of the shearing stress[25,30].

The low degree of thixotropy of formulations F15/0.25 (with and without PE) indicates a short time for restoration of the relaxed molecular configuration. These attributes are desirable in the formulations designed for endodontic delivery, as they enhance retention within this environment[21,30]. In addition, the rheopexy observed to formulations F20/0.10 (with and without sildenafil) could be explained by a fractional increase of temperature that may have occurred, despite the controlled temperature of rheological analysis, increasing the interactions between P407 chains and increasing the viscosity on the downcurve (return)[21,30].

Moreover, it is known that C934P exhibits great bioadhesive properties[25,40,43]. Thus, the provision of a greater contact between the two interfaces allowed for the movement of water from the semisolid to the dentin surface. This process enables the penetration of the polymer chains into the dentin. In response to a rise in temperature, the polypropylene oxide segments of P407 aggregate, forming the core of micelles. In addition, the polyethylene oxide segments are exteriorized forming the corona. As there are hydroxyl groups in polyethylene oxide segments that can form hydrogen bonds with the carboxyl groups of C934P, the later are also exteriorized, contributing to the interpenetration of the polymer chains and those on surface of the dentin[21,25]. Thus, the temperature of the endodontic space is favorable to the good bioadhesive performance of the formulation.

Considering the purpose, the control of drug release is very important in the searching for ideal controlled drug delivery systems for improved endodontic treatment[2,4]. Thus, to investigate the release of PE and sildenafil from the developed formulations, a Franz cell apparatus was used. The release of PE or sildenafil from formulation F15/0.25 or F20/0.10, respectively, was evaluated and the application of the Equation 1 enabled calculation of the release exponent (n) and hence the mechanism of drug release from the systems may be elucidated. In this context, $n = 0.5$ indicates release controlled by Fickian diffusion[44] and $n = 1.0$ indicates release controlled only by relaxation of polymer chains (Case II transport). Intermediate values indicate anomalous behavior (nonFickian kinetics corresponding to the combined phenomenon of diffusion and relaxation of polymer chains)[21,45]. The formulation containing PE (F15/0.25) displayed $n = 0.6940 \pm 0.0073$, indicating nonFickian kinetics corresponding to the combined phenomenon of diffusion and relaxation of polymer chains (anomalous behavior). Moreover, the release of sildenafil from formulation F20/0.10 showed the value of n was 0.0911 ± 0.0034, indicating the sildenafil release was controlled by Fickian diffusion[21,45].

Conclusion

This study has described the design and development of bioadhesive semisolid systems containing propolis or sildenafil for endodontic application. The rheological, mechanical, and bioadhesive properties of these systems were characterized and shown to be beneficial both for insertion of the formulations into the endodontic space and its subsequent retention. Furthermore, the release profile studies showed that the propolis can be released from the system over a prolonged period of time. On the other hand, sildenafil release from bioadhesive system was faster. These properties of the candidate formulations indicate a potentially advantageous role in the treatment of pulp protection and suggest they are worthy of clinical evaluation.

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Declaration of interest

The authors report no declarations of interest.

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