Development and Mechanical Characterization of Bioadhesive Semi-Solid, Polymeric Systems Containing Tetracycline for the Treatment of Periodontal Diseases

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Purpose. This study examined the mechanical characteristics and release of tetracycline from bioadhesive, semi-solid systems which were designed for the treatment of periodontal diseases.

Methods. Tetracycline release into phosphate buffered saline (pH 6.8, 0.03 M) was examined using a Caleva 7ST dissolution apparatus at 37°C. The mechanical properties of each formulation (hardness, compressibility, adhesiveness, elasticity and cohesiveness) were determined using texture profile analysis. Syringeability was measured using the texture analyser in compression mode as the work of syringeability i.e. the force required to express the product from a periodontal syringe over a defined distance.

Results. Tetracycline release from all formulations was zero-order for 24–54 h and ranged from 1.59 ± 0.20 to 15.80 ± 0.50 mg h^{-1}. Increased concentrations of hydroxyethylcellulose (HEC) decreased the rate of release of tetracycline, due to the concomitant increase in product viscosity and the subsequent decreased rate of penetration of dissolution fluid into the formulation. Conversely, an increased polyvinylpyrrolidone (PVP) concentration increased tetracycline release rates, due to an increased formulation porosity following dissolution of this polymer. Increased concentrations of HEC and PVP increased the hardness, compressibility and work of syringeability of the semi-solid formulations, due to increased product viscosity. An increase in formulation adhesiveness, a parameter related to bioadhesion, was observed as the concentrations of HEC and PVP were increased, illustrating the adhesive nature of these polymers. Increased concentrations of HEC and PVP enhanced the semi-solid nature of the product, resulting in decreased product elasticity and cohesiveness. Several statistically significant interactions between polymeric formulation components were observed within the factorial design, with respect to rate of release and all mechanical properties. These interactions arose because of variations in the physical states (dissolved or dispersed) of polymeric formulation components.

Conclusions. The optimal choice of bioadhesive formulation for use in periodontal disease will involve a compromise between achieving the necessary release rate of tetracycline and the mechanical characteristics of the formulation, as these factors will affect clinical efficacy and the ease of product application into the periodontal pocket.

KEY WORDS: periodontal diseases; bioadhesive semi-solids; tetracycline; zero-order release; texture profile analysis; syringeability.

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INTRODUCTION

Periodontitis is an inflammatory disease caused by anaerobic bacteria, e.g. *Bacteroides* spp., *Actinobacillus actinomycetemcomitans*, that leads to the destruction of the supporting structures of teeth and the subsequent resorption of the alveolar bone. Tissue destruction is thought to result directly from the effects of sub-gingival bacteria, and indirectly as a consequence of the host response to the bacteria (1). If untreated, increased tooth mobility, and possibly tooth loss, can occur. Treatment of the disease is directed at arresting the progression of the destructive process and preventing recurrence after treatment. This usually achieved through mechanical cleaning of the tooth surface to remove bacterial plaque and calculus (2). However, as specific bacteria are known to play a major role in the disease process, antimicrobial agents, e.g. chlorhexidine, tetracycline or metronidazole, have also been used as adjuncts to mechanical treatment, particularly in treating early-onset and refractory cases (3).

Mouthwashes may be employed to control supragingival plaque. However, due to their inability to penetrate subgingival areas, they exhibit low efficacy against subgingival bacteria and are therefore relatively ineffective in the treatment of periodontal diseases (5). Irrigation devices which deliver solutions of antimicrobial agents directly into the periodontal pocket are frequently used for the treatment of periodontal diseases. Due to their short duration of action, frequent applications are required rendering this approach untenable (5). These obvious disadvantages have evoked an interest in the development of localised drug delivery systems that offer prolonged administration of antimicrobial agents into the periodontal pocket. Earlier studies reported the use of non-biodegradable, drug loaded polymeric systems, often solid strips, that exhibited good clinical activity. However, device removal was necessary at the termination of therapy (6, 7). More recently, therefore, the use of insertable biodegradable drug delivery systems has been suggested and several types have been clinically evaluated. Examples of this approach include, chlorhexidine in a cross-liked protein film (8), tetracycline immobilised onto atelocollagen strips (9), chlorhexidine-polycaprolactone films (10) and tetracycline-poly(lactide-glycolide) films (6). These systems suffer from specific, device related problems including potential immunological reactions and tissue sensitisation due to leaching of chemical cross-linking agents from the above. In addition, implantable films are relatively poorly retained within the pocket as a result of the normal flushing mechanism of crevicular fluid. Also, in many instances the method of preparation of such films is not straightforward, requiring the extraction of casting solvents and/or the use of cross-linking agents.

Therefore, in this study we describe the development and physical characterisation of novel, bioadhesive, semi-solid systems containing tetracycline that may be easily applied to the periodontal pocket using a periodontal syringe. Tetracycline has been chosen as a model antimicrobial agent due to its wide spectrum of anti-bacterial activity, low toxicity, high efficacy against Gram-negative bacteria and its reported inhibitory activity against collagenase (11, 12).

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MATERIALS AND METHODS

Materials

Tetracycline (as the hydrochloride salt) was purchased from Sigma Chemical Co., St. Louis, USA. Hydroxyethylcellulose (Natrosol™ HHX 250-Pharm), Polyvinylpyrrolidone (Kollidon™ K90) and Polycarbophil (Noveon™ AA-1) were gifts from Aqualon LTD (Warrington, England), BASF (Ludwigshafen, Germany) and B.F. Goodrich Company, Clevland, Ohio, USA, respectively. All other chemicals were purchased from BDH Laboratory Supplies, Poole, England and were of AnalaR, or equivalent, quality.

Preparation of Semi-Solids Systems

Hydroxyethylcellulose (HEC; 5, 10, 20% w/w) was dissolved with stirring in the required amount of phosphate buffered saline (PBS; pH 6.8, 0.03 M). Polyvinylpyrrolidone (PVP; 5, 10, 20% w/w), polycarbophil (1% w/w) and, finally, tetracycline (5.0% w/w, particle size <63 μm), as the hydrochloride salt, were mixed thoroughly into this gel to form a semi-solid preparation. All formulations were stored in amber ointment jars at 4°C until required.

In Vitro Release of Tetracycline HCl

The release of tetracycline from the bioadhesive formulations was determined in triplicate using a Caleva 7ST dissolution apparatus with paddle stirrers. The release medium was PBS at 37°C and was stirred at 100 rev min^{-1}. Formulations were packed into three-sided plastic moulds and anchored to the bottom of the dissolution vessels. At varying time intervals samples of the dissolution fluid were removed and analysed using ultra-violet spectroscopy at 353 nm (6). The calibration curve for tetracycline hydrochloride was linear over the concentration range 1.0–100.0 μg mL^{-1} ($r > 0.99$, with zero intercept) and the presence of formulation excipients did not interfere with the analysis.

Mechanical Characterisation of Tetracycline-Containing Bioadhesive Semi-Solids

The physical properties of the bioadhesive formulations were examined using texture profile analysis (TPA), as previously described by us (13). In brief, formulations were packed into a 10 mL beaker to a fixed height, avoiding the introduction of air into the samples. A Stable Micro Systems TA-XT2 texture analyser in texture profile analysis mode was employed to examine the mechanical properties. The analytical probe (10 mm diameter) was compressed twice into each sample to a depth of 15 mm and at a rate of 5.0 mm s^{-1}, allowing a delay period of 15 s between the end of the first and beginning of the second compression. All analyses were performed on four replicate samples. From TPA, the following parameters may be derived:

1. product hardness (force required to attain a given deformation)
2. adhesiveness (the work necessary to overcome the attractive forces between the surface of the sample and the surface of the probe)
3. compressibility (the work required to deform the product during the first compression of the probe)
4. elasticity (the ratio of the time required to achieve maximum structural deformation on the second compression cycle to that on the first compression cycle, where successive compressions are separated by a defined recovery period)
5. cohesiveness (the ratio of the area under the force-time curve produced on the second compression cycle to that produced on the first compression cycle, where successive compressions are separated by a defined recovery period).

Determination of Work of Syringeability of Bioadhesive Formulations

The work of syringeability of each formulation was performed using the texture analyser in compression mode, as previously described by us (14). Each formulation was packed into periodontal syringes (of identical dimensions) to a preselected height (3 cm) and the resistance of the formulation to expression via an applied force was measured as the area under the resultant force-time plot. An increase in the force required to fully expel the product from the syringe through a fixed distance denoted an increased work of syringeability.

Statistical Analysis

The experimental design was factorial (3 × 3). The effects of HEC and PVP on the rates of release of tetracycline, product hardness, adhesiveness, compressibility, elasticity, cohesiveness and work of syringeability were evaluated statistically using a two way Analysis of Variance (ANOVA, $P < 0.05$ denoting significance). Post-hoc statistical analyses of the means of individual groups were peformed using Fischer's Least Significant Difference test ($P < 0.05$ denoting significance).

RESULTS

The effects of an increasing concentration of HEC (5, 10 and 20% w/w) on the release of tetracycline from formulations containing polycarbophil (1% w/w) and PVP (5%, 10% and 20% w/w) are illustrated in Figures 1, 2 and 3 and Table I. All formulations examined released tetracycline in a zero-order fashion for time periods ranging from 24–54 h. Increasing the concentration of HEC from 5 to 10% w/w, from 10 to 20% w/w and from 5 to 20% w/w significantly reduced the rate of release of tetracycline at all concentrations of PVP (all $P < 0.0001$). Conversely, increasing the concentration of PVP from 5 to 10% w/w ($P = 0.045$), from 10 to 20% w/w ($P < 0.0001$) and from 5 to 20% w/w ($P < 0.0001$) significantly increased the rate of tetracycline release, regardless of concentration of HEC. The range of mean (±s.d.) release rates of tetracycline exhibited by the formulations under examination was 1.59 ± 0.20 (20% w/w HEC, 5% w/w PVP, 1% w/w polycarbophil) to 15.80 ± 0.50 (5% w/w HEC, 20% w/w PVP, 1% w/w polycarbophil).

The mechanical properties, i.e. hardness, adhesiveness, compressibility, elasticity and cohesiveness, of the formulations under examination are presented in Table II. As the concentrations of either HEC or PVP in the semi-solid formulations

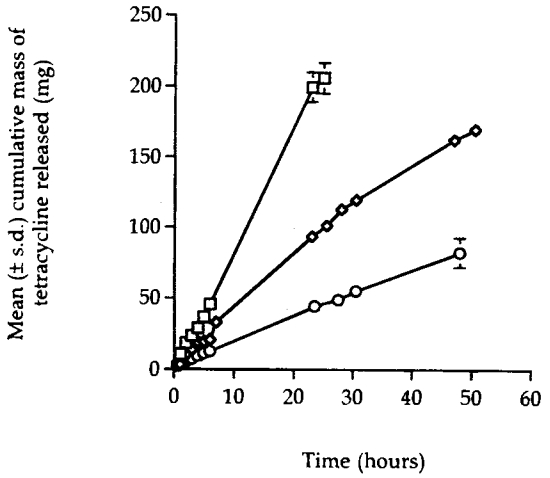

Fig. 1. The effects of hydroxyethylcellulose concentration (□ 5% w/w, ◇ 10%w/w, ○ 20%w/w) on the release of tetracycline (initial concentration 5%w/w, as the hydrochloride) from semi-solid formulations containing polyvinylpyrrolidone (5%w/w) and polycarbophil (1%w/w). Each datum point represents the mean (±s.d.) of three replicates.

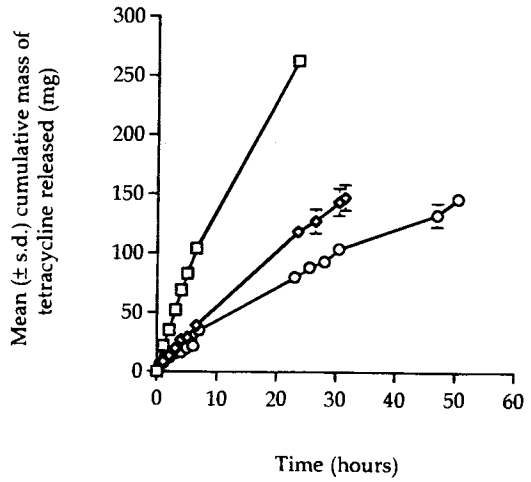

Fig. 3. The effects of hydroxyethylcellulose concentration (□ 5% w/w, ◇ 10% w/w, ○ 20% w/w) on the release of tetracycline (initial concentration 5% w/w, as the hydrochloride) from semi-solid formulations containing polyvinylpyrrolidone (20%w/w) and polycarbophil (1% w/w). Each datum point represents the mean (±s.d.) of three replicates.

were increased, there were concomitant increases in formulation hardness, adhesiveness, compressibility, work of syringeability and numerical values of elasticity whereas cohesiveness values were decreased. However, in TPA lower numerical values in the elasticity mode indicate greater product elasticity, and therefore, increasing the concentrations of either HEC or PVP resulted in decreased product elasticity.

Figure 4 is an illustration of the effects of HEC and PVP on the work of formulation syringeability. Increased concentrations of either HEC or PVP resulted in significant increases in the work of formulation syringeability, as denoted by the increased force required to fully expel the formulation from the syringe by moving it through a given distance.

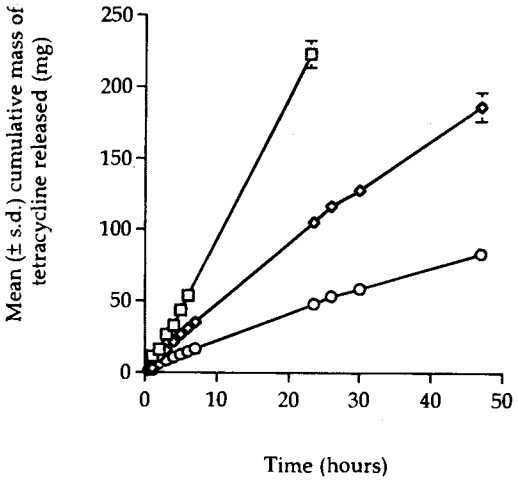

Fig. 2. The effects of hydroxyethylcellulose concentration (□ 5% w/w, ◇ 10% w/w, ○ 20% w/w) on the release of tetracycline (initial concentration 5%w/w, as the hydrochloride) from semi-solid formulations containing polyvinylpyrrolidone (10% w/w) and polycarbophil (1%w/w). Each datum point represents the mean (±s.d.) of three replicates.

Interestingly, for all physical properties (hardness, adhesiveness, compressibility, elasticity and cohesiveness), there were statistical interactions observed within the factorial design. Concerning hardness, adhesiveness and compressibility, the effect of HEC on each physical property was significantly greater in the presence of the highest concentration of PVP (20% w/w) than the two lower concentrations of this polymer (5 and 10% w/w). By contrast, the elasticity and cohesiveness of formulations containing 5% w/w each of HEC and PVP, in addition to 1% w/w polycarbophil, were unexpectedly high in comparison to all other formulations. These apparent disparities accounted for the observed statistical interactions. Finally, a further statistical interaction was observed concerning the effects of HEC and PVP on the subsequent release rate of tetracycline. In this, the effect of increasing the concentration of HEC from 5 to 20% w/w on the subsequent release rate of

Table I. The Effects of Concentration of Hydroxyethylcellulose (HEC; 5. 10 20% w/w) and Polyvinylpyrrolidone (PVP; 5, 10, 20% w/w) on the Rate of Release of Tetracycline[a] (Initial Concentration 5% w/w), as the Hydrochloride, from Semi-solid Preparations Containing Polycarbophil (1% w/w)

Concentration of HEC (% w/w)	Concentration of PVP (% w/w)	Mean (±s.d.) Release Rate (mg h^{-1})
5	5	8.44 ± 0.89
5	10	9.75 ± 0.44
5	20	15.81 ± 0.46
10	5	3.54 ± 0.12
10	10	3.79 ± 0.17
10	20	4.59 ± 0.40
20	5	1.59 ± 0.22
20	10	1.62 ± 0.13
20	20	2.75 ± 0.13

[a] All release rates were observed to be zero-order.

Table II. The Effects of Hydroxyethylcellulose (HEC) and Polyvinylpyrrolidone (PVP) on the Hardness (N), Adhesiveness (N mm), Compressibility (N mm), Numerical Values of Elasticity (no units) and Cohesiveness (no units) of Formulations Containing Tetracycline (5% w/w, as the hydrochloride salt) and Polycarbophil (1% w/w), as Determined Using Texture Profile Analysis

Conc^n of HEC (% w/w)	Conc^n of PVP % w/w	Mean (±s.d.) Hardness	Mean (±s.d.) Adhesiveness	Mean (±s.d.) Compressibility	Mean (±s.d.) Cohesiveness	Elasticity[a]
5	5	1.55 ± 0.04	29.50 ± 2.40	33.50 ± 1.20	0.89 ± 0.02	0.89 ± 0.02
5	10	2.43 ± 0.15	37.85 ± 3.15	35.45 ± 3.15	0.84 ± 0.02	0.94 ± 0.01
5	20	4.46 ± 0.55	77.25 ± 2.43	65.25 ± 15.05	0.80 ± 0.00	0.96 ± 0.00
10	5	4.49 ± 0.06	47.91 ± 3.55	85.20 ± 6.05	0.81 ± 0.01	0.97 ± 0.01
10	10	8.14 ± 0.32	84.12 ± 3.20	132.30 ± 0.50	0.79 ± 0.01	0.98 ± 0.00
10	20	11.04 ± 2.20	106.15 ± 12.35	216.90 ± 42.75	0.76 ± 0.00	0.99 ± 0.00
20	5	14.40 ± 0.47	117.23 ± 14.51	295.95 ± 10.15	0.71 ± 0.02	0.98 ± 0.00
20	10	20.00 ± 1.07	170.95 ± 23.85	461.71 ± 52.45	0.68 ± 0.00	0.99 ± 0.00
20	20	35.01 ± 3.27	206.25 ± 12.95	728.43 ± 76.25	0.65 ± 0.00	1.00 ± 0.00

[a] Lower numerical values as determined by TPA in the elasticity mode indicate greater product elasticity.

tetracycline was significantly greater in formulations containing 5% w/w HEC than in those containing 10 and 20% w/w HEC.

DISCUSSION

The ideal candidate formulation for the controlled delivery of an antimicrobial agent to the periodontal pocket should exhibit a variety of characteristics. These include ease of application into and retention within the periodontal pocket, controlled (prolonged) drug release, ease of manufacture and eventual clearance from the periodontal pocket by either product biodegradation and/or dissolution. Whilst there have been several reports of controlled drug delivery systems for the treatment of periodontal disease (15), few, if any of these have an ideal product profile. The products described in this study were simple to manufacture and displayed wide ranges of zero-order release rates of tetracycline, textural properties and syringeabilities. In the product manufacturing process, HEC was initially dissolved (5, 10%w/w) and/or dispersed (20%w/w) in PBS.

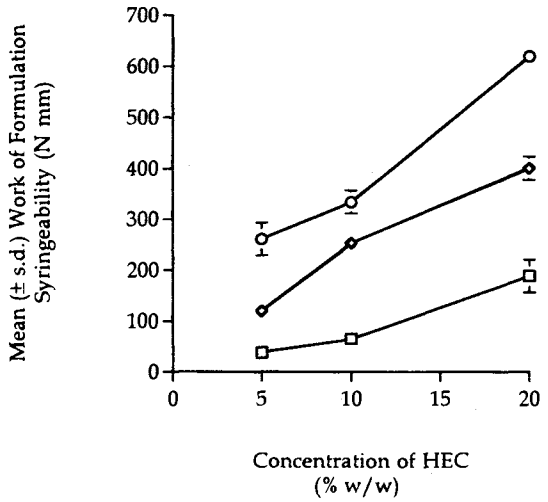

Fig. 4. The effects of polyvinylpyrrolidone (□ 5% w/w, ◇ 10% w/w, ○ 20% w/w) on the work of syringeability of semi-solid formulations containing tetracycline (5% w/w, as the hydrochloride), hydroxyethylcellulose (5, 10, 20% w/w) and polycarbophil (1% w/w). Each datum point represents the mean (±s.d.) of three replicates.

PVP was then dissolved until its saturation solubility was exceeded in the formulation. Further addition of PVP then resulted in suspension of this material within the now semi-solid preparation. Following its addition to each formulation, polycarbophil did not dissolve (due to its cross-linked structure) but exhibited swelling, the extent of which was dependent upon the volume of free water available in the formulation. Following immersion of such formulations into an aqueous environment, product swelling was observed. This was primarily due to the swelling characteristics of polycarbophil and also of suspended HEC and PVP, prior to their dissolution. An increase in polymer concentration will increase the overall product viscosity. Thus, the decreased rates of tetracycline release observed from formulations containing higher concentrations of HEC are most likely due to decreased rates of penetration of dissolution fluid into higher viscosity products. A retarded rate of drug dissolution and, hence, a reduced rate of tetracycline release ensues. In formulations containing 20%w/w HEC, swelling of undissolved (suspended) particles of this polymer will further retard the rate of tetracycline release.

The increased rates of tetracycline release associated with increased concentrations of PVP are not explained by an associated increase in product viscosity, but may be attributed to the effects of dissolution of suspended PVP from the formulation into the dissolution medium. This dissolution process will alter the structural properties of the semi-solid preparations by increasing their porosity, thus allowing more rapid penetration of dissolution fluid into the product and also initiating product surface dissolution/erosion. These factors have been shown to be important in the release of drugs from hydrophilic polymers (16, 17). Therefore, the zero-order release of tetracycline observed in this study may be explained by the distinctive swelling and erosion/dissolution characteristics of these formulations. The former phenomenon ensures that there is a resistance to the ingress of dissolution fluid and, hence, dissolution of drug, whereas controlled product erosion/dissolution allows replenishment of the drug layer adjacent to the dissolution fluid-swollen layer. Interestingly, the effects of PVP on the release rate of tetracycline were more pronounced in the presence of 5%w/w HEC than in higher concentrations of HEC, as indicated by the statistical interaction term. In these formulations, a greater alteration of gel structure occurs following dissolution

of PVP as a result of the proportionately lower initial viscosity of the gel platform (containing 5%w/w HEC) into which this polymer is dispersed. Therefore, dissolution of PVP results in a greater rate of bulk and surface erosion that facilitates more rapid drug release, in comparison to formulations containing 10 and 20%w/w HEC.

The physical properties and work of syringeability of candidate formulations for insertion into the periodontal pocket will be important in the final performance of the product. Product characteristics of interest include ease of product application and adhesion to, and retention within, the periodontal pocket. The increased hardness, compressibility and work of syringeability associated with increased concentrations of either HEC or PVP within the formulation are probably due to the concomitant increase in product viscosities. In addition, the ranked order of contributions of HEC and PVP to these parameters were identical. The statistical interactions between HEC and PVP with respect to hardness, compressibility and work of syringeability were probably due to the unpredicted effects of the proportionally greater mass of suspended solids in formulations containing 20%w/w HEC and 10 and 20%w/w PVP on these parameters, as in these formulations both polymers exist as suspended solids in a (saturated) HEC gel.

A wide range of product adhesiveness values, dependent on the concentrations of both HEC and PVP, was exhibited by the formulations in this study. Previously, we have reported the use of TPA to evaluate the bioadhesive strengths of semi-solid systems (13) and, indeed, the increase in formulation adhesiveness observed with increased concentrations of either HEC or PVP correlates with the known bioadhesive properties of these polymers (18). It is suggested that formulations containing increased concentrations of either HEC or PVP, by virtue of their greater bioadhesive properties, will demonstrate better retention within the milieu of the periodontal pocket. The observed statistical interaction between HEC and PVP concerning adhesiveness is due to the unexpectedly large values observed in formulations containing higher concentrations of HEC and PVP, and is a function of the physical state of each polymer (HEC, PVP, PC) within each formulation. As the concentrations of HEC (primarily) and PVP increase, the mass of PC which exists in the unswollen (i.e. un-neutralised) state increases. The adhesiveness of formulations containing PC are known to increase as both the number of free carboxylic acid groups increases (i.e. whenever un-neutralised) and also whenever the molecule exists in the unswollen state, thus allowing polymer chain mobilisation by moisture and, subsequently, a more effective interpenetration of the polymer with the substrate (13, 19).

Product elasticity and cohesiveness were observed to decrease as the concentrations of HEC and PVP increased. Increased numerical values of elasticity as measured by the texture analyser denote decreased product elasticity. These physical parameters describe temporal (elasticity) and spatial (cohesiveness) aspects of structural reformation following product compression and have been previously reported to be dependent on the pharmaceutical form of the product (13). Therefore, decreased elasticity and cohesiveness observed for products containing increasing concentrations of PVP and 20%w/w HEC are a consequence of the greater masses of suspended solids present. In addition, decreased product elasticity and cohesiveness associated with an increase in concentration of HEC from 5 to 10%w/w is a function of increased viscosity, as this may affect the overall viscoelastic properties of these products. Further examination of these effects revealed that unexpectedly large product elasticity (lowest measured numerical value) and cohesiveness were associated with formulations containing 5%w/w HEC and PVP (in addition to 1%w/w PC), as, in these systems HEC and PVP were primarily in solution. Hence, these formulations displayed a lesser semi-solid structure in comparison to others examined in this study.

In conclusion, bioadhesive semi-solid formulations containing tetracycline have been prepared and examined *in-vitro*. The formulations examined demonstrated a wide range of drug release rates and physical properties. Due to unacceptably high product viscosity and syringeability, a number of formulations were inappropriate for clinical examination. However, the characteristics of several formulations suggest they are worthy of clinical evaluation as potential systems for the treatment of periodontal diseases.

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