Sustained Release of Tetracycline from Polymeric Periodontal Inserts Prepared by Extrusion

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ABSTRACT: The specific aim of this study was to prepare polymeric inserts containing tetracycline that are intended for intraperiodontal pocket application. The inserts were prepared by a simple extrusion method and based on mixtures of polyvinyl alcohol, glyceryl behenate, xanthan gum, carrageenan, hydroxypropyl methylcellulose, and hyaluronic acid in addition to tetracycline HCL. The inserts were characterized regarding average weight, diameter, water content, and average tetracycline content. Zero-order release kinetics of tetracycline were observed in case of three of the four batches of the prepared inserts with release profiles that were essentially similar. The release of the drug was incomplete in all cases. This was due, as shown by the equilibrium dialysis tests, to tetracycline binding by the polymers. However, the inserts performed more than 7 days drug sustained release which indicates promising results for local delivery of tetracycline for treatment of periodontal disease. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 116: 333–336, 2010

Key words: extrusion; drug delivery systems; dental polymers; biocompatibility; biodegradable

INTRODUCTION

Periodontal pockets are spaces between teeth and junctional epithelium and they are formed as a result of a localized pathogenic infection below the gum line. Despite decades of research, periodontal diseases continue to be considered as a major oral health problem.[1,2] The classical approach for treatment of periodontal diseases utilized the oral administration of antibacterial agents either as stand alone chemotherapies or as adjunctive to scaling and root planing.[3,4] However, this approach showed little long term efficacy in the treatment of periodontal diseases in addition to the development of bacterial resistance and side effects.[5,6] Since periodontal pockets are easily accessible from the oral cavity, the local delivery of antimicrobial agents has been investigated as a possible method for controlling this type of infections and treating periodontal disease. The periodontal pockets are convenient sites for localized drug delivery systems that could be inserted into the pockets.[7,8]

Numerous investigations have been conducted to evaluate the potential role of controlled delivery systems in the treatment of periodontitis. Examples of some antimicrobial agents that have been investigated and incorporated in these controlled delivery systems were tetracycline,[9,10] doxycycline,[11,12] amoxicillin,[13] metronidazole,[4,14] chlorhexidine,[15] and others.[16] These antimicrobial agents were fabricated in a variety of specialized systems like fibers, films, microparticles, semisolids, and gels in order to maintain a bactericidal concentration in the gingival crevicular fluid (GCF) for the required period of therapy and higher than that achieved by systemic administration.[7,8]

In this study we will present the preparation of intraperiodontal pocket polymeric inserts for the local delivery of tetracycline HCL (TC) by a simple extrusion method with the study of the *in vitro* release characteristics of TC from these inserts. These inserts are made from common and safe pharmaceutical materials, therefore, the risk of irritative and allergic reactions at the application sites are expected to be almost totally eliminated. The novelty in this periodontal drug delivery system is emphasized in the fact that these inserts, after administration in solid form, are expected to dissociate and biodegrade after releasing the drug in the infected sites, which will eliminate the need for surgical procedure to remove them in case of clinical application. TC has been chosen for this formulation since

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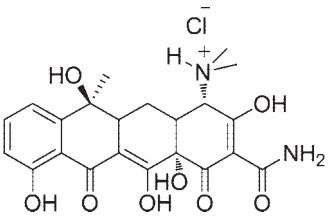

Figure 1 Chemical structure of tetracycline HCL.

it is widely used in the treatment of periodontitis, both systemically and locally. It has been shown that it is active against many of the common periodontitis-causing bacteria, in particular *Prevotella intermedia* and *Porphyromonas gingivalis*.[17] It is obtained from *Streptomyces aureofaciens* or derived from oxytetracycline by semi-synthesis. The molecular weight of TC is 480.9 g/mol and its chemical structure is shown in Figure 1.

The major polymers that were used in this study include xanthan gum (XG), carrageenan (CA), hyaluronic acid (HA), and hydroxypropyl methylcellulose (HPMC). XG is a polysaccharide with high molecular weight (> 2 million). The main chain of this polymer is build up by glucose units and has a chemical structure that is identical to that of cellulose. It has unique properties in controlling the rheological properties of aqueous fluids and several applications in cosmetics, food, and pharmaceutical industry.[18]

CA is a polysaccharide with a number average molecular weight in the region of 100,000. It also has several applications in the cosmetics, food, and pharmaceutical industry as suspending, thickening, and gelling agent. The sodium salt of this polymer is water soluble, whereas the calcium salt yields elastic and thixotropic gels.[19] HA has several applications as a mucoadhesive agent and in hydrogel formation for drug delivery in addition to wound healing properties.[20] HPMC is a well known pharmaceutical excepient with a wide spectrum of applications in drug delivery systems and controlled release.[21]

MATERIALS AND METHODS

Materials

Tetracycline HCL (TC), polyvinyl alcohol (PVA), xanthan gum (XG), and hyaluronic acid sodium salt (HA) were purchased from Sigma Chemical Co., St. Louis, MO. Carrageenan (CA, Viscarin®) was purchased from FMC Corp., Newark, DE. Hydroxypropyl methylcellulose (HPMC, Methocel® E50 Premium LV) was purchased from Colorcon Ltd, Orpington, UK. Glyceryl behenate (GB, Compritol® 888 ATO) was purchased from Gattefossé SA, Saint Priest, France. All other materials were of analytical reagent grade and used as received.

Preparation of the inserts

The major components of the formulation were TC, PVA, and GB. Four formulations were prepared containing constant ratios from these components. To the solutions of these components, other polymers were added (XG, CA, HPMC, and HA) in different ratios. The compositions of these formulations are shown in Table I.

The materials were dispersed in 50% aqueous solution of ethanol. The resulting mixture was homogenized and gently evaporated under a current of warm air, while kneading in a glass mortar until it acquires the consistency of a thick paste. The residual solvent content was determined to be around 20% by weight loss. The paste was subsequently placed in a periodontal tube and squeezed out through a 1.5 mm needle to be extruded from the tube in the form of spaghetti-like rods; 10–15 cm long. The extruded rods were cut into 3 mm long portions and subsequently dried and stored in an evacuated dessicator. The final inserts were tested for the following characteristics: average weight, diameter, water content according to Karl-Fischer method, and average TC content using UV spectrophotometer (Centra 5 UV-visible Spectrophotometer, GBC Scientific Equipment, Australia) at 357 nm after dissolution in water and filtration through 0.45 μm membrane filters (Millipore).

In vitro drug release experiments

For these experiments, two inserts were placed in a small stainless steel woven wire basket (50 mesh, diameter 18 mm, height 20 mm) rotating at 50 rpm. The receiving solution consisted of 100 mL of pH 6.8 phosphate buffer (to simulate the GCF) thermostated at 37°C. Samples from this solution (2 mL) were withdrawn at specified time intervals and replaced with fresh buffer. The content of TC was determined in the samples at 357 nm.

Tetracycline binding by the polymers

The objective of this experiment was to determine if there is any possible binding between TC and the polymers used in the preparation of the inserts. The binding was determined by using the equilibrium dialysis technique. Solutions of TC in pH 6.8

TABLE I
Composition of the Inserts (% w/w)

Batch No.	PVA	XG	CA	HPMC	HA	GB	TC
1	30	25	5	5	5	15	15
2	30	5	25	5	5	15	15
3	30	5	5	25	5	15	15
4	30	5	5	5	25	15	15

phosphate buffer (10 mL) were introduced in prehydrated dialysis bags of molecular weight cutoff 6000–8000. The bags were placed in bottles containing 10 mL of dispersions of the polymers under investigation (PVA, XA, CA, HPMC, or HA) in the same buffer. The bottles were stoppered and agitated in a thermostated shaking water bath at 37°C for 24 hr. Separate experiments carried out in the absence of polymers proved that binding of TC by the dialysis bags was negligible. The content of TC in the solutions inside the bags was determined spectrophotometrically as previously indicated.

RESULTS AND DISCUSSION

Different formulations were studied with different ratios of the polymers to determine the optimum ratios to control and sustain the release of TC over an extended period of time. The inserts were composed of some polymers that have been investigated as ingredients in several drug delivery systems. Therefore, they have proven pharmaceutical history as safe and tolerable drug carriers.

The composition of the prepared inserts is shown in Table I. All of them contained fixed proportions of PVA and GB. PVA was used as a binder and GB as a lubricant to assist extrusion. The other polymers (XG, CA, HPMC, and HA) were used in different proportions. This composition was chosen after several preliminary tests in which the proportions of these components were tentatively adjusted regarding the consistency of the prepared paste and the ease of extrusion. The final inserts were evaluated for various physicochemical properties. The water content was 2.6% (as determined by the Karl Fischer method), the average weight was 2.2 mg ± 4%, the diameter was 1.5 mm, and the average TC content was found to be 0.32 mg ± 0.01 (≈ 96% of the theoretical drug loading).

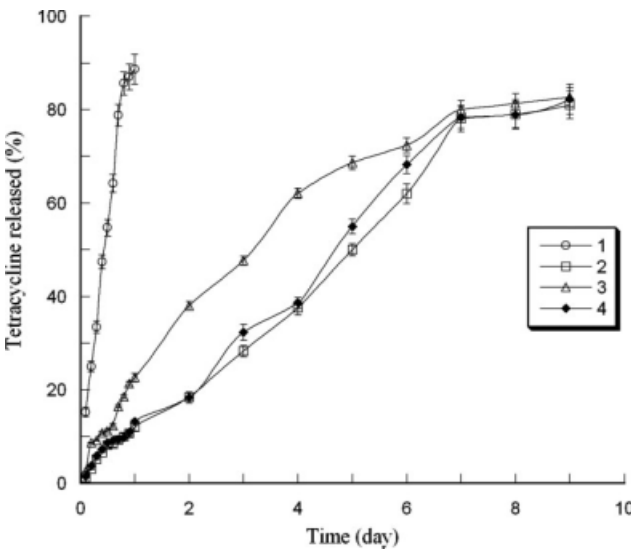

Figure 2 *In vitro* release of tetracycline from inserts 1–4 at pH 6.8 and 37°C (Mean ± SD, $n = 3$).

TABLE II
Binding of Tetracycline to the Polymers According to the Equilibrium Dialysis Tests

Polymer	(Polymer/TC)[a]	Tetracycline bound (%)
PVA	2	0
XG	1.7	16
CA	1.7	26
HPMC	1.7	14
HA	1.7	23

[a] Polymer/TC ratio corresponding to the composition of the inserts.

The *in vitro* release of TC from the prepared inserts is shown in Figure 2. The effect of the composition of each formulation on the release of the drug appears clearly in the graph. In case of inserts containing XG as the highest proportion compared with CA, HPMC, and HA (No. 1, Table I), 50% of TC was released within less than 12 h (≈ 0.5 day), whereas the other inserts released the same percentage of TC within 3–5 days depending on the composition. It can also be noticed from Figure 2 that drug release was incomplete in all cases and ranged from 80–90%. On visual inspection, inserts of batch 1 underwent considerable swelling soon after being placed in the dissolution medium, and then disruption, which explains the approximate total release of the drug within a relatively short period of time compared with the other batches of inserts.

The results of equilibrium dialysis tests are reported in Table II. The results show that there was no binding of TC to PVA, while there was a significant binding to the other polymers to varying extents. These results indicate that binding of the drug to the polymers under investigation may explain the incomplete release of the contained drug during the dissolution experiments. The release data can be correlated to the binding results although the release experiments were carried out under sink conditions, while the binding data were generated at equilibrium. The final release data shown in Figure 2 almost reflect the different binding capacities of the polymers. The lowest extent of release was obtained from inserts of batch 2 which contains CA in the highest proportion. The drug was highly bound to this polymer compared with others.

The drug release kinetics from the prepared inserts were evaluated using the power law equation $Mt/M\infty = Kt^n$ proposed by Korsmeyer et al.[22] In the equation, $Mt/M\infty$ represents the fraction of drug released in time t, K is the structural and geometric constant, and it is characteristic of the system, and n is the release exponent indicative of release kinetics.

TABLE III
***In vitro* Release Parameters**

Batch No.	n	K	$t_{50\%}$ (days)[a]
1	0.82	0.73	0.5
2	1.02	0.084	5
3	1.15	0.072	3.2
4	1.08	0.082	4.8

[a] Time required for release of 50% of TC.

When n value equals 0.5, it indicates Fickian diffusion, while when n equals 1, it is indicative of zero-order kinetics. Values of n between 0.5 and 1 usually indicate anomalous (non-Fickian) transport mechanism.

The results of the *in vitro* release parameters according to the aforementioned equation are presented in Table III. The n value for the inserts of batch 1 was 0.82, which indicates that the liberation of TC from such inserts occurred by anomalous mechanism. The data in Table III indicated that the release of TC from inserts of batches 2, 3, and 4 took place at an approximately constant rate. Inspection of Figure 2 shows that these inserts (2–4) display analogous release profiles with a zero-order mechanism. As mentioned previously, inserts 1 underwent considerable swelling and disruption in the dissolution medium within a relatively short period of time. The other inserts (2–4) behaved similarly after exposure to the dissolution medium where they underwent hydration and swelling and then becoming similar to a lump of jelly approximately after 3–4 days. However, they continued releasing the drug for more than 7 days until they eventually dissociated.

CONCLUSIONS

Periodontal inserts containing tetracycline HCL, a common antibiotic used in the treatment of periodontitis, were prepared relatively by a simple extrusion technique involving materials of common use in the pharmaceutical industry. These inserts are intended for intraperiodontal pockets application for local delivery of the drug. The inserts have shown substantially promising properties regarding constant and prolonged release rate over an extended period of time and they could be suitable for local delivery of antimicrobial and antiinflammatory agents for the treatment of periodontitis. Upon application in the periodontal pockets, the inserts are expected to sustain the release of the drug for more than a weak, and eventually they will dissociate and biodegrade. Therefore, such inserts look very promising for clinical applications.

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