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Physical characterization of non-aqueous gels incorporating tetracycline hydrochloride for treatment of periodontitis

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Periodontitis is an inflammatory disease of the periodontal tissues supporting the teeth. The management of the condition generally involves the removal of dental plaque in conjunction with use of antimicrobial agents, e.g. tetracycline (Jones *et al* 1996). Drug delivery systems designed for use in the periodontal pocket include non-aqueous antimicrobial gels. In this study, the rheological and drug release properties of novel viscoelastic non-aqueous gels containing tetracycline hydrochloride (TH), designed for the treatment of periodontitis, were evaluated.

A series of non-aqueous gel bases was formulated by addition of Aerosil® (flumed alumina silicate) to sunflower oil followed by blending for a 5 minute period. Gel bases incorporating 7.5, 10, 12.5 and 15% w/v Aerosil® were prepared and additional bases were formulated to include TH (2 and 5% w/v). A Carri-Med CSL^2-100 rheometer with stainless steel parallel plate geometry (2 cm diameter, 1 mm separation) was employed to investigate the oscillatory properties of all formulations. Measurements were made at 20 ± 0.2°C over a frequency range of 0.01 - 1.0 Hz at a constant strain of 2.5×10^{-3}. Drug release from the gels into PBS was investigated using Caleva dissolution apparatus (100 rev min^{-1}). A fixed mass of each formulation containing drug was placed in a small cylindrical receptacle and then located in the dissolution vessel. At pre-determined time intervals, samples (5 ml) were removed and the concentration of TH in these determined using ultra-violet spectrophotometry at 364 nm (Jones *et al* 1996). The influences of Aerosil® and TH content on formulation rheological characteristics were statistically analysed using a two-way Analysis of Variance (ANOVA), $p < 0.05$ denoting significance.

Results obtained from oscillatory rheometry performed on the gels with and without TH are displayed in table 1. Increasing the proportion of Aerosil® in the gel formulations significantly increased both storage and loss modulus.. Similarly, inclusion of 2% w/v TH in the formulation resulted in a significant increase in storage and loss modulus. These parameters were significantly increased further by the addition of 5% w/v TH.

Table 1. Effect of Aerosil® and TH concentration on storage modulus (G') and loss modulus(G'') of non-aqueous gels (co-efficient of variance < 5% in all cases)

Aerosil® (% w/v)	TH (% w/v)	G' (Pa)	G'' (Pa)
7.5	-	290	76
	2	931	169
	5	9487	384
10.0	-	18440	1001
	2	30510	1475
	5	30630	1531
12.5	-	52570	2923
	2	81700	3056
	5	118500	3294

Release of TH from formulations containing 2 and 5% w/v TH and 7.5% w/v Aerosil® was diffusion controlled ($\alpha \sqrt[2]{\text{time}}$), whereas for all other formulations release was non-Fickian. Increasing the concentration of Aerosil® significantly decreased the time required for release of 50% (t_{50}) of the original mass of TH from formulations containing both 2 and 5% TH (two-way ANOVA, $p<0.05$, table 2). These observations may be attributed to enhanced formulation disintegration in the presence of release medium.

Table 2. Time (hours) for 50% TH release (t_{50}) from gels

TH (% w/v)	Aerosil® (% w/v) 7.5	10.0	12.5
2	99.79	1.24	0.37
5	13.06	0.59	0.04

Increasing TH or Aerosil® content significantly increased both G' and G'' and may be attributed to enhanced elasticity and product consistency in the non-aqueous state. Whilst in the presence of excess water the gels containing higher concentrations of Aerosil® disintegrated, thus destroying their semi-solid properties, this would not be expected in the periodontal pocket due to the low flow rate of crevicular fluid. However, in the final selection of candidate formulations for clinical evaluation a compromise is necessary between the elastic and drug release properties.

Jones, D.S., Woolfson, A.D., Djokic, J., Coulter, W.A. *Pharmaceutical Research* 1996; **13**: 1732-1736