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Research paper

Mucoadhesive, triclosan-loaded polymer microspheres for application to the oral cavity: preparation and controlled release characteristics

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Abstract

The aim of this study was to develop mucoadhesive microspheres that can be utilised for the controlled release of triclosan in oral-care formulations, specifically dental pastes. Using a double-emulsion solvent evaporation technique, triclosan was incorporated into microspheres that were prepared from Gantrez™ MS-955, Carbopol™ 974P, polycarbophil or chitosan and the profiles for its release were established under simulated 'in use' conditions. Triclosan was rapidly released into a sodium lauryl sulphate containing buffer from all but the chitosan microspheres. The release of triclosan from microspheres suspended in a non-aqueous paste, was found to be sustained over considerable time-periods, which were influenced strongly by the nature of the polymeric carrier. For microspheres that were fabricated from Gantrez, Carbopol or polycarbophil, the release appeared to obey zero-order kinetics whereas in the case of chitosan-derived vehicles, the release profile fitted the *Baker and Lonsdale* model. The work has demonstrated that these polymeric microspheres, particularly those of chitosan, are promising candidates for the sustained release of triclosan in the oral cavity.

Keywords: Polymer microspheres; Triclosan; Double emulsion; Bioadhesion; Oral cavity; Release kinetics

1. Introduction

The efficacy of conventional treatments of oral diseases, e.g. dental caries or fungal infections, is often reduced by the limited retention of the applied formulations within the oral cavity [1]. Saliva flow, the swallowing reflex, mastication and speech can effect the dilution or dislodgement of a dosage form and may lead to a rapid decline in the concentration of the active to sub-therapeutic levels. Thus, there is a need for the development of delivery systems that can bestow improved availability to active constituents whilst allowing reduced dosage frequency.

Various attempts have been made to achieve the prolonged release of active agents; prominent amongst these is the enhanced retention of formulations at their intended site of action by means of bioadhesive formulations [2–4]. Hydrophilic macromolecules containing numerous hydrogen bond forming groups have been identified as being adhesive to mucous membranes [5], particularly those within the oral cavity [6]. Chitosan, carbomers and maleic anhydride copolymers have been investigated in our previous work for their in vitro and in vivo bioadhesive properties within the oral cavity [7,8]. Microspheres, particularly those fabricated from Gantrez and chitosan were also shown to be bioadhesive and 'retentive' in vitro under 'dynamic test conditions [9,10]. The aim of this study is to combine the potential advantages of bioadhesion with those of controlled drug delivery. We describe methods for the preparation of microspheres of Carbopol, polycarbophil, chitosan and Gantrez containing the widely used lipophilic, broad-spectrum antimicrobial triclosan [11–14]. The incorporation of a lipophilic active into a hydrophilic polymer matrix presents significant

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technical difficulties, and a double emulsion method to overcome this is described. In addition, we describe the controlled-release behaviour of these systems in terms of their quality of fit to established mathematical models [15–18].

It is envisaged that these microspheres would be included into a long acting antimicrobial toothpaste formulation; the microspheres being retained on the mucosa surfaces in crevasses and gaps between teeth allowing the slow release of active at sites where plaque removal may be difficult using standard oral hygiene procedures.

2. Materials and methods

2.1. Materials

Carbopol® 974P NF and polycarbophil (Noveon® AA-1) were supplied by BF Goodrich Company, Cleveland, Ohio. Gantrez® MS-955 was received from ISP Europe, Guildford. Chitosan (150,000 MW grade), water (HPLC-grade), methanol (HPLC-grade) and acetonitrile (HPLC-grade) were purchased from Fluka Chemicals, Gillingham, UK. Triclosan was kindly supplied by GlaxoSmithKline Consumer Healthcare, Weybridge, UK. Glacial acetic acid, dichloromethane, sodium chloride, sodium hydroxide, sodium dodecyl sulphate, disodium hydrogen phosphate and sodium dihydrogen phosphate were obtained from BDH Chemicals Ltd, Poole, UK, and were of analytical grade. Light white mineral oil, Span 80 and Tween 80, were purchased from Sigma Chemicals, Poole, UK. Hexane was obtained from Fisher Scientific UK Ltd, Loughborough, UK, and cryostat embedding compound from Bright Company Ltd, Huntingdon, UK.

2.2. Preparation of polymer and drug solutions

Aqueous polymer solutions were prepared as follows and subsequently stored in hermetically sealed containers at 4 °C for 24 h prior to use: Carbopol or polycarbophil (0.50 g) was dispersed in 50.0 g of de-ionised water under rapid vortexing. The pH of this dispersion was adjusted to 7 using aqueous sodium hydroxide. Finally, 20 mg of sodium chloride were added under stirring. An appropriate mass of chitosan was added gradually to a solution of aqueous acetic acid (1.0% w/w) to yield a concentration of 2.0% (w/w). The mixture was stirred until a viscous gel was obtained. Gantrez was dissolved under vortexing in de-ionised water to give a 5.0% (w/w) solution (pH 6.5).

Triclosan was dissolved in dichloromethane to a concentration of 1.25 or 6.5% (w/v), as appropriate.

2.3. Preparation of triclosan-loaded microspheres

Drug-loaded microspheres were prepared by an oil-in-water-in-oil (O/W/O) double-emulsion method. For the first emulsion, triclosan dissolved in dichloromethane was emulsified into 50.0 g of aqueous polymer solution. The concentrations and amounts applied are summarised in Table 1. The addition of three drops (ca 0.15 ml) of Tween 80 aided the emulsification process. A Silverson homogeniser was used for rapid mixing of the emulsions for 3 min.

Table 1
Amounts and concentrations of aqueous polymer dispersions and triclosan solutions in dichloromethane, as employed for the preparation of triclosan-containing microspheres by double emulsion

Polymer	Concentration (%, w/w)	Triclosan amount (ml)	Concentration (%, w/v)
Carbopol	1.0	5	1.25
Polycarbophil	1.0	5	1.25
Chitosan	2.0	10	1.25
Gantrez	5.0	10	6.5

In initial studies it was noted that in the second emulsificaton step the lipophilic triclosan would tend to migrate into the outer oil phase. This was overcome by presaturating the oil phase with triclosan. To 1 l of mineral oil containing 1.0% v/v Span 80, triclosan was added gradually until super-saturation of the oil with the active was achieved. After overnight stirring, the oil was centrifuged to separate any precipitated material.

The first emulsion (25 ml) was added dropwise to 250 ml of the triclosan-saturated mineral oil. The resulting double emulsions were stirred at 400 rpm in the case of Carbopol, polycarbophil or chitosan, or at 200 rpm in the case of Gantrez. The samples were heated to 40–45 °C (the melting point of triclosan is at 53 °C) to promote evaporation of water. Solid polymer microspheres were subsequently separated from the oil by centrifugation (200 g, 5 min), washed in hexane and dried in a vacuum desiccator. For each polymer, five batches of microspheres were prepared for the purpose of assessing the reproducibility of drug loading by this method.

2.4. Preparation of drug-free microspheres

Drug-free polymer microspheres were prepared by a water-in-oil emulsification solvent evaporation technique. Aqueous polymer solution (25 ml) was added dropwise to 250 ml of mineral oil containing 1.0% v/v Span 80. Continuous stirring of the resulting emulsion facilitated the formation of microspheres (500 rpm for chitosan and Gantrez, 600 rpm for Carbopol and polycarbophil). A temperature of 60 °C was maintained to promote the complete evaporation of the dispersed aqueous phase. The separation and purification of particles was performed as described above.

2.5. External and internal particle morphologies

Drug-free and drug-loaded microspheres were suspended in a few drops of cryostat embedding compound and this