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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 mixture was frozen under liquid nitrogen. The temperature of the samples was equilibrated by allowing them to stand in the chamber of a cryostat (−20 °C, 30 min; OTF, Bright Instrument Company Ltd) and segments (5 μm thick) were cut using a steel knife. Particle sections, or complete microspheres, were mounted onto a SEM stub and coated with gold/palladium (sputter coater). The internal and external morphologies of the samples were visualised under a scanning electron microscope (JSM 6100, Jeol, Japan) operating at 10–15 keV.

2.6. Determination of drug loading

Triclosan-containing polymer microspheres (5–10 mg) were weighed accurately into a 10-ml volumetric flask. To these microspheres, 0.5 ml of water (HPLC-grade) were added and the particles were allowed to stand (2 h) in order to facilitate particle swelling. After this time, methanol (HPLC-grade) was added to give a total volume of 10 ml.

To investigate the efficiency of recovery of triclosan in the presence of polymer microspheres, triclosan (5 mg) and polymer microspheres containing no drug (50 mg) were weighed separately into a 100-ml volumetric flask and incubated with 5 ml of water. After 2 h, the flask was filled with methanol to the 100-ml mark. As a control, a solution containing only triclosan (5 mg) was prepared in the same manner.

The solutions were shaken for 1 h and subsequently centrifuged (Jouan centrifuge B4*I*) at 200 g for 5 min. The precipitated polymer was removed by decanting. The UV-absorbance of the supernatant was determined at 282 nm against the blank (methanol/water 95:5) employing a double-beam UV-spectrophotometer (Spectronic Unicam 300). Each batch of microspheres was analysed five times and the absorbances considered in the light of the calibration curve.

2.7. Determination of in vitro drug release

2.7.1. Release of triclosan from microspheres in free aqueous suspension

Triclosan is practically insoluble in water, and was almost undetectable in normal buffer solution, so a medium containing SLS was chosen as not only will it facilitate dissolution but this surfactant is present in many toothpaste formulations. The concentrations chosen, 0.5% w/v SLS in pH 7 phosphate buffered saline was based on that likely to be found when a toothpaste is mixed with saliva on brushing.

About 10 mg of triclosan-containing polymer microspheres were weighed accurately into a 10-ml conical flask. To ensure sink conditions, the weight of the microspheres was selected to give a final triclosan concentration of less than 10% of the saturation concentration of the medium. To the microspheres, 10 ml of dissolution medium (PBS 7 containing 0.375% (w/v) SLS) was added, and the flask was placed immediately into an orbital shaker within a thermostatted waterbath (Grant OLS 200; 37 °C, 135 rpm). Aliquots of 100 μl were removed at time intervals of 2.5 or 5 min, as appropriate, and these volumes were replaced with fresh medium. Samples were analysed by HPLC (Jasco AS-950, PU-980, UV-975; C18-Spherisorb S5-ODS-1 250×4.6, acetonitrile/water 70/30 v/v at 1.5 ml/min, 20 μl sample injection, 282 nm) and the triclosan concentration was determined by means of calibration standards. The release profiles were obtained by plotting the percentage triclosan release versus time; the experiment was performed five times for each polymer.

2.7.2. Release of triclosan from microspheres in a non-aqueous base

The base chosen for this study, glycerol, is a constituent of many toothpaste formulations. Microspheres (ca. 10 mg) were weighed accurately and placed into a 10-ml conical flask. To these, 3.25 g of glycerol (corresponding to 2.5 ml) were added and the mixture was stirred by means of a micro-spatula. The flask was filled to a total volume of 10 ml using dissolution medium (PBS 7 containing 0.5% w/v SLS) and was subsequently placed into an orbital shaker within a thermostatted waterbath (37 °C, 135 rpm). Release profiles were determined as described above.

2.7.3. Recovery of triclosan

This control experiment was performed to test whether there are any interactions between the polymers and the drug that may hinder drug release into the medium. For this purpose, triclosan and drug-free microspheres were weighed into a vial (at a similar polymer–drug ratio as found for triclosan-containing microspheres) and filled up with 10 ml of dissolution medium (PBS 7 containing 0.375% w/v SLS). The mixture was stirred for 24 h at 37 °C, and after settling of the polymer, the clear supernatant was analysed for its triclosan content by HPLC. The obtained concentration was compared with that of pure triclosan that was incubated in dissolution medium under the same conditions.

3. Results and discussion

3.1. Scanning electron microscopy

Polymer microspheres, both triclosan-free and triclosan-loaded, were prepared under conditions that yielded spheres of 20–40 μm in diameter. These size ranges fulfilled the self-imposed requirement that, to avoid mouthfeel issues, particles should be smaller than 50 μm. Microspheres were of relatively smooth surface appearance (Figs. 1 and 2). The cross-sections (Figs. 3 and 4) revealed their internal consistency: solid, with the exception of triclosan-free Gantrez microspheres, which contained some spherical defects, presumed to be trapped air bubbles; the viscosity of the Gantrez solution used for

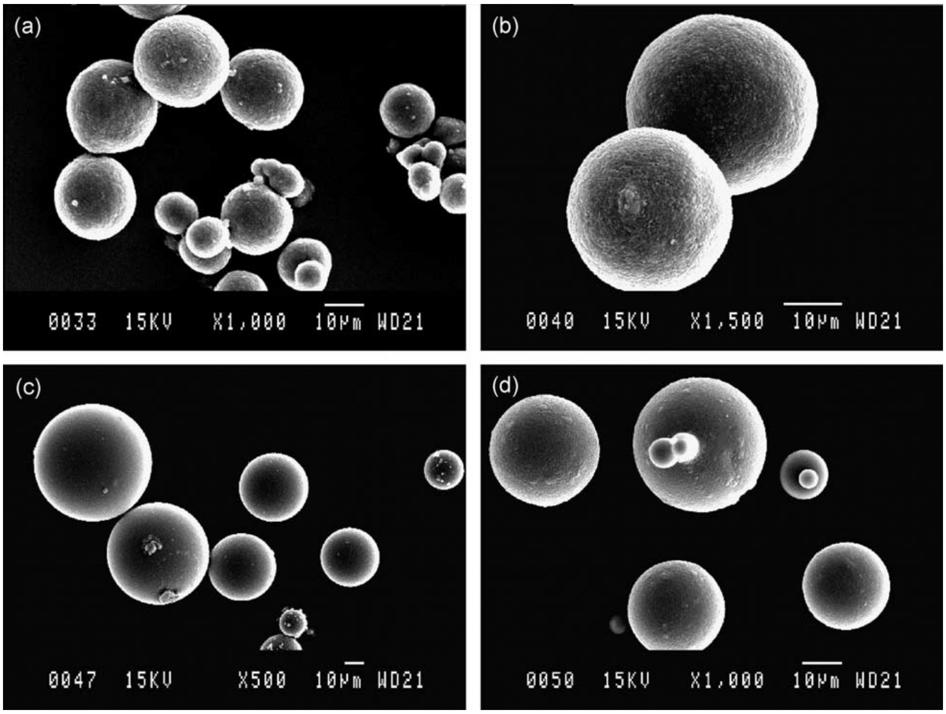

Fig. 1. Scanning electron micrographs of polymer microspheres prepared by O/W emulsification solvent evaporation: (a) Carbopol (1000×); (b) polycarbophil (1500×); (c) chitosan (500×); and (d) Gantrez (1000×).

the preparation of microspheres appeared to be markedly lower than that of the other polymers. In the case of triclosan-loaded Carbopol or polycarbophil microspheres, distinct domains of small size (<0.5 μm) and of spherical geometry—attributed to encapsulation of triclosan within the matrix—were observed. These are distributed throughout the sections but are especially apparent at the surface. Such inclusions are also observed with Gantrez: in this

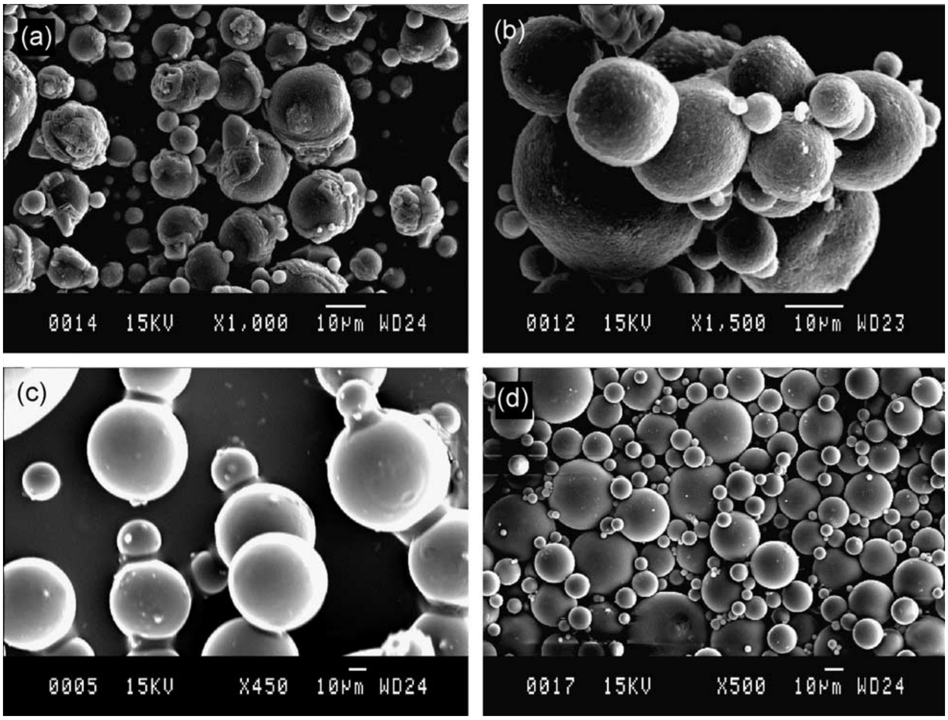

Fig. 2. Scanning electron micrographs of triclosan-containing microspheres prepared by O/W/O emulsification solvent evaporation: (a) Carbopol (1000×); (b) polycarbophil (1500×); (c) chitosan (450×); and (d) Gantrez (500×).

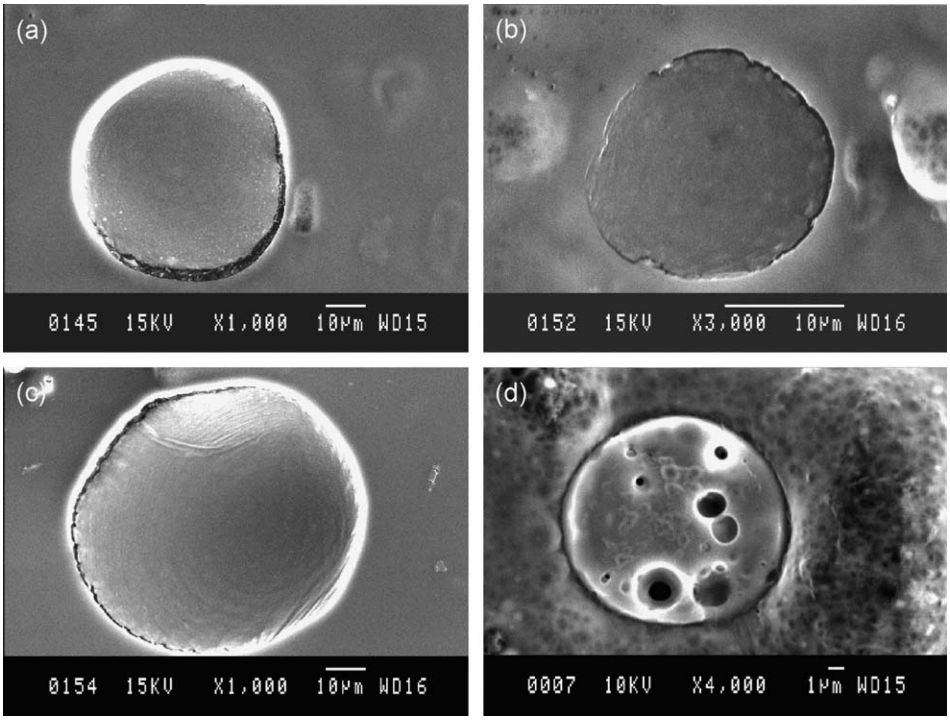

Fig. 3. Scanning electron micrographs of cryotommed sections of polymer microspheres: (a) Carbopol (1000×); (b) polycarbophil (3000×); (c) chitosan (1000×); and (d) Gantrez (4000×).

case they appear to be fewer in number but of bigger size (1–2 µm). In the case of triclosan-loaded chitosan, a more even distribution of these features was observed throughout the matrix.

3.2. Drug loadings

Drug loadings and the calculated efficiencies of triclosan entrapment are summarised in Table 2. Overall,

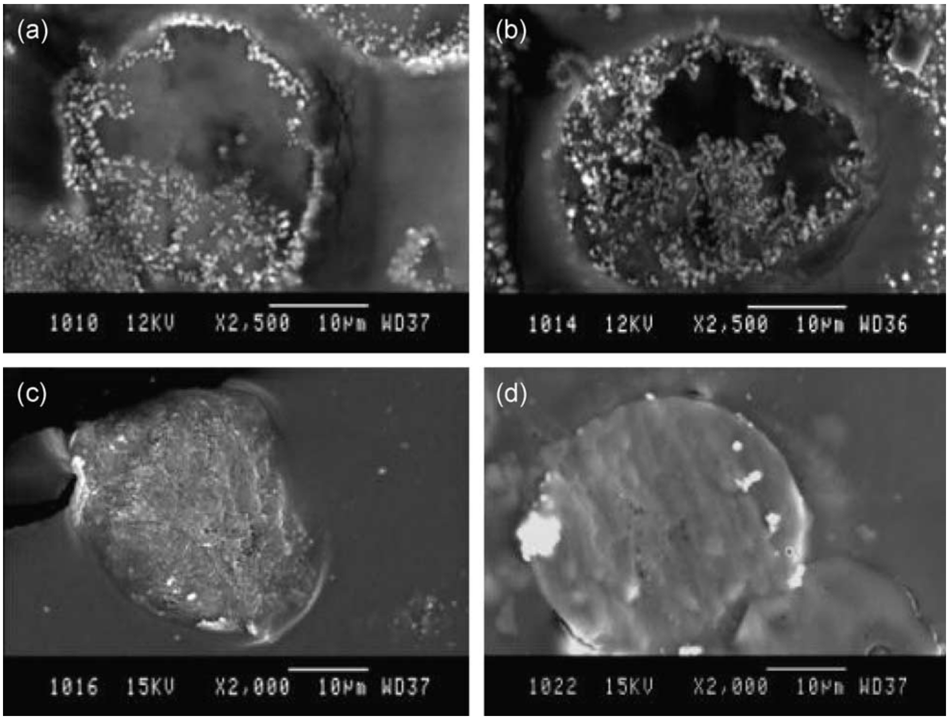

Fig. 4. Scanning electron micrographs of cryotommed sections of triclosan containing microspheres: (a) Carbopol (2500×); (b) polycarbophil (2500×); (c) chitosan (2000×); and (d) Gantrez (2000×).

Table 2
Mean triclosan content and efficiency-of-loading of polymer microspheres (mean ± SD; $n=5$)

Batch	Triclosan content in microspheres (%, w/w)			
	Carbopol	Polycarb	Chitosan	Gantrez
I	2.4 ± 0.2	5.3 ± 0.2	6.2 ± 0.1	5.0 ± 0.1
II	4.0 ± 0.1	4.1 ± 0.2	9.6 ± 0.1	4.9 ± 0.1
III	2.8 ± 0.2	3.4 ± 0.1	9.1 ± 0.1	9.9 ± 0.2
IV	4.2 ± 0.2	4.2 ± 0.3	6.8 ± 0.1	5.0 ± 0.1
V	2.6 ± 0.2	1.5 ± 0.4	6.3 ± 0.2	4.0 ± 0.1
Mean	3.2 ± 0.8	3.7 ± 1.4	7.6 ± 1.6	5.8 ± 2.3
Loading efficiency	29 ± 7	34 ± 13	69 ± 15	27 ± 11

more efficient drug loading was achieved for microspheres that were prepared from chitosan or Gantrez than for those that were prepared from Carbopol or polycarbophil. The loading efficiencies for Carbopol, polycarbophil and Gantrez were calculated at about 30% whereas for chitosan a figure of approximately 70% was obtained. It may, therefore, be reasoned that the entrapment of drug, which is dependent on the successful molecular-level association of the drug with the polymer, is dictated by the moieties and functional groups make up the constitutional repeat unit of the polymer molecule. A localised higher pH within the chitosan microparticle might encourage a partial dissociation of the phenolic triclosan, leading to the possibility of an electrostatic interaction between these molecules. The presence of cyclic molecular structures, as is the case with chitosan and Gantrez, could further promote efficient molecular association through enhanced van der Waals' interactions. By contrast, for the linear macromolecules that display a high distribution of negative charges under basic conditions (Carbopol and polycarbophil), the association with the lipophilic drug molecule appears to be less efficient. In all cases, the intra-batch variations for the incorporation of triclosan are relatively small (1–8%) suggesting that, within each batch, the drug was distributed uniformly. Inter-batch variations ranged from 21% for chitosan to 40% for Gantrez and may be attributed to the manufacturing process, which involved saturation of the mineral oil phase with triclosan; it is possible that, due to daily changes in ambient temperature, saturation levels differ between batches. Control experiments confirmed that the presence of triclosan-free microspheres does not affect the efficiency of the recovery of triclosan from solution.

3.3. In vitro drug release

3.3.1. Release of triclosan in free aqueous suspension

The release of triclosan from a free aqueous suspension of Gantrez microspheres at neutral pH was complete within 2.5 min (Fig. 5). This burst-release effect is presumably due to the rapid swelling and dissolution of the polymer in the aqueous environment. Depletion of the drug from Carbopol or polycarbophil microspheres was accomplished within 15 min (Fig. 5); the release profiles from microspheres of these polymers were indistinguishable (two-sample *t*-test, 95% confidence level). As with Gantrez structures, the relatively fast release may again be related to the ease-of-swelling of the polymers in the dissolution medium. For chitosan-based microspheres, the release profile was found to be markedly different (Fig. 6): triclosan release was not exhausted even after ca. 8 h; chitosan is insoluble at this pH (9). It is likely that the outer layers of the microspheres may have hydrated to form a gel layer but water penetration into the core of the particles is impeded, providing little medium for the transport of the drug. Control experiments revealed that triclosan associates with chitosan: only 86.5 ± 1.3% ($n=5$) of triclosan could be recovered after incubation for 24 h at 37 °C in dissolution medium containing drug-free chitosan particles. This interaction reduces the amount of detectable triclosan in the medium by ca. 14% and accounts for the majority of unrecovered triclosan during the dissolution experiment.

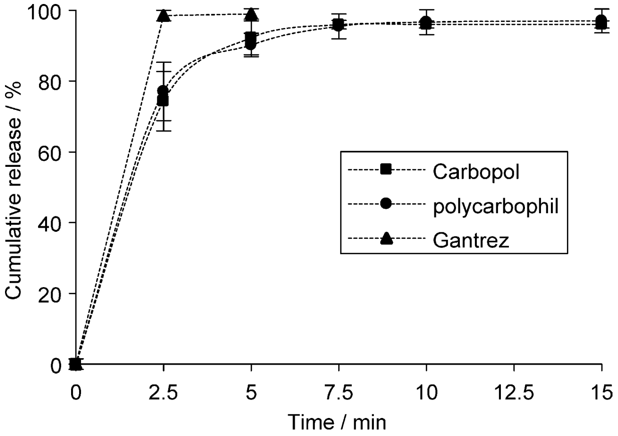

Fig. 5. Release of triclosan into PBS 7/0.375% (w/v) SLS; data are for Carbopol, polycarbophil and Gantrez microspheres in free suspension (error bars = ± 1 SD; $n=5$).

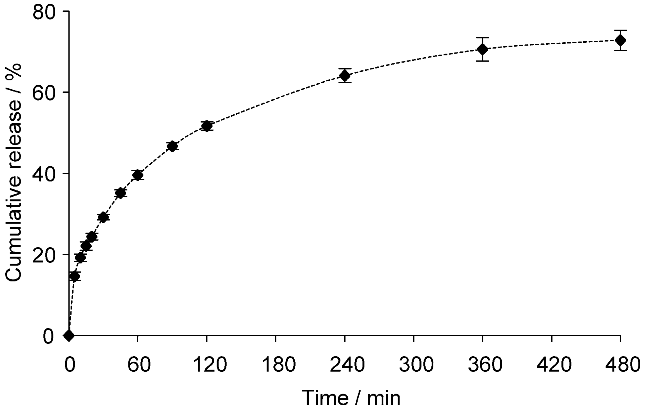

Fig. 6. Release of triclosan into PBS 7/0.375% (w/v) SLS; data are for chitosan microspheres in free suspension (error bars = ± 1 SD; $n=5$).

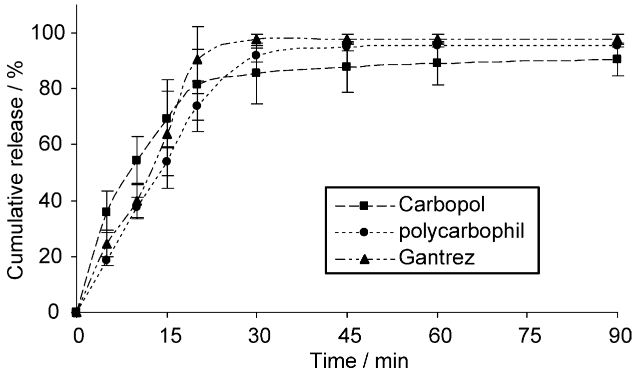

Fig. 7. Release of triclosan into PBS 7/0.5% (w/v) SLS; data are for Carbopol, polycarbophil or Gantrez microspheres suspended in a glycerol base (error bars = ±1 SD; $n = 5$).

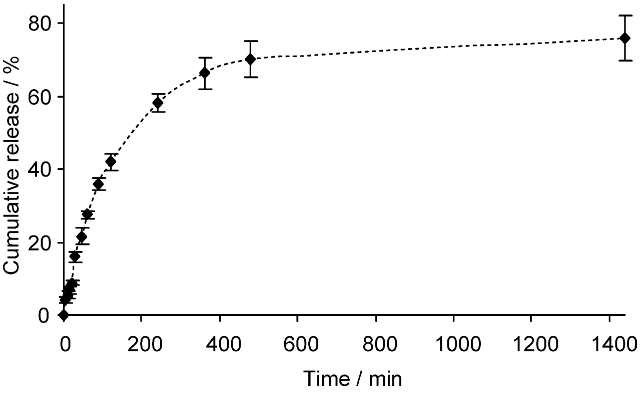

Fig. 8. Release of triclosan into PBS 7/0.5% (w/v) SLS; data are for chitosan microspheres suspended in a glycerol base (error bars = ±1 SD; $n = 5$).

3.3.2. Release of triclosan in a non-aqueous paste

Data for the release of triclosan from microspheres that are suspended in a glycerol-based formulation are presented in Figs. 7 and 8: for Gantrez, Carbopol and polycarbophil microspheres, release of triclosan was maintained over a period of about 60 min. This slowing of the rate of release is probably due to the glycerol initially reducing access of the solvent to the microspheres or the dissolved glycerol reducing the rate of polymer swelling. In contrast, the release profile obtained for chitosan microspheres was broadly similar to that determined for aqueous suspensions.

3.3.3. Investigation of the release kinetics

The mechanism responsible for the release of triclosan from the polymeric microspheres under consideration may be due to diffusion phenomena, due to degradation effects, or due to a combination of both processes [14].

For a constant area of a pure solid dissolving into a pure solvent, dissolution may be described by the Noyes-Whitney equation (Eq. (1)), where: M is the mass remaining to be dissolved; A is the surface area of the solid exposed to the dissolution medium; C_s is the saturation concentration of drug in the medium; C is the concentration of drug in the medium at time t; and, k is the dissolution constant.

$$\frac{\mathrm{d}M}{\mathrm{d}t} = -kA(C_\mathrm{s} - C) \tag{1}$$

However in 'real' systems, the application of this model may be complicated by the presence of additional excipients that modify the characteristics of the dissolution medium within the time scale of the experiment and by variations in the shape of the dissolving solid. This is particularly true for dosage forms with modified or sustained release properties and, as a result, in addition to the expressions for zero-order and first-order release, several alternative mathematical approaches [15] have been proposed as possible means of describing the controlled-release properties of such systems; these are summarised below.

(i) Zero-order release:

$$\frac{M_\mathrm{t}}{M_\infty} = kt \tag{2}$$

(ii) First-order release:

$$\ln\left(1 - \frac{M_\mathrm{t}}{M_\infty}\right) = -kt \tag{3}$$

(iii) The cube-root equation, proposed by Hixson and Crowell [16], models drug release from systems with dissolution-rate limitations; it is applicable to systems that dissolve isotropically:

$$\sqrt[3]{\left(\frac{1 - M_\mathrm{t}}{M_\infty}\right)} = -\mathrm{kt} \tag{4}$$

Table 3

Correlation coefficients R (±SD; $n = 5$) and mean standard errors MSD (mean±SD; $n = 5$) for the fitting of the profiles for the release of triclosan from chitosan microsheres to the mathematical models

Model	Initial phase		Terminal phase		Overall	
	R	MSE	R	MSE	R	MSE
Zero-order	0.988 (±0.004)	0.015 (±0.002)	0.956 (±0.007)	0.04 (±0.01)	0.914 (±0.007)	0.086 (±0.003)
First-order	0.994 (±0.002)	0.014 (±0.003)	0.972 (±0.007)	0.08 (±0.02)	0.960 (±0.007)	0.116 (±0.004)
Hixson and Crowell	0.992 (±0.003)	0.005 (±0.001)	0.967 (±0.007)	0.021 (±0.004)	0.947 (±0.008)	0.035 (±0.001)
Higuchi	0.999 (±0.001)	0.0021 (±0.0007)	0.966 (±0.007)	0.04 (±0.01)	0.963 (±0.005)	0.051 (±0.002)
Baker and Lonsdale	0.999 (±0.001)	0.0004 (±0.0002)	0.975 (±0.008)	0.011 (±0.003)	0.979 (±0.004)	0.010 (±0.001)

Initial phase, 5–60 min; terminal phase, 90–480 min.

(iv) The Higuchi square root of time model [17] has been derived from Fick's first law of diffusion and is suited for the modelling of drug release from a homogeneous planar matrix, assuming that the matrix does not dissolve:

$$\left(\frac{M_t}{M_\infty}\right)^2 = kt \tag{5}$$

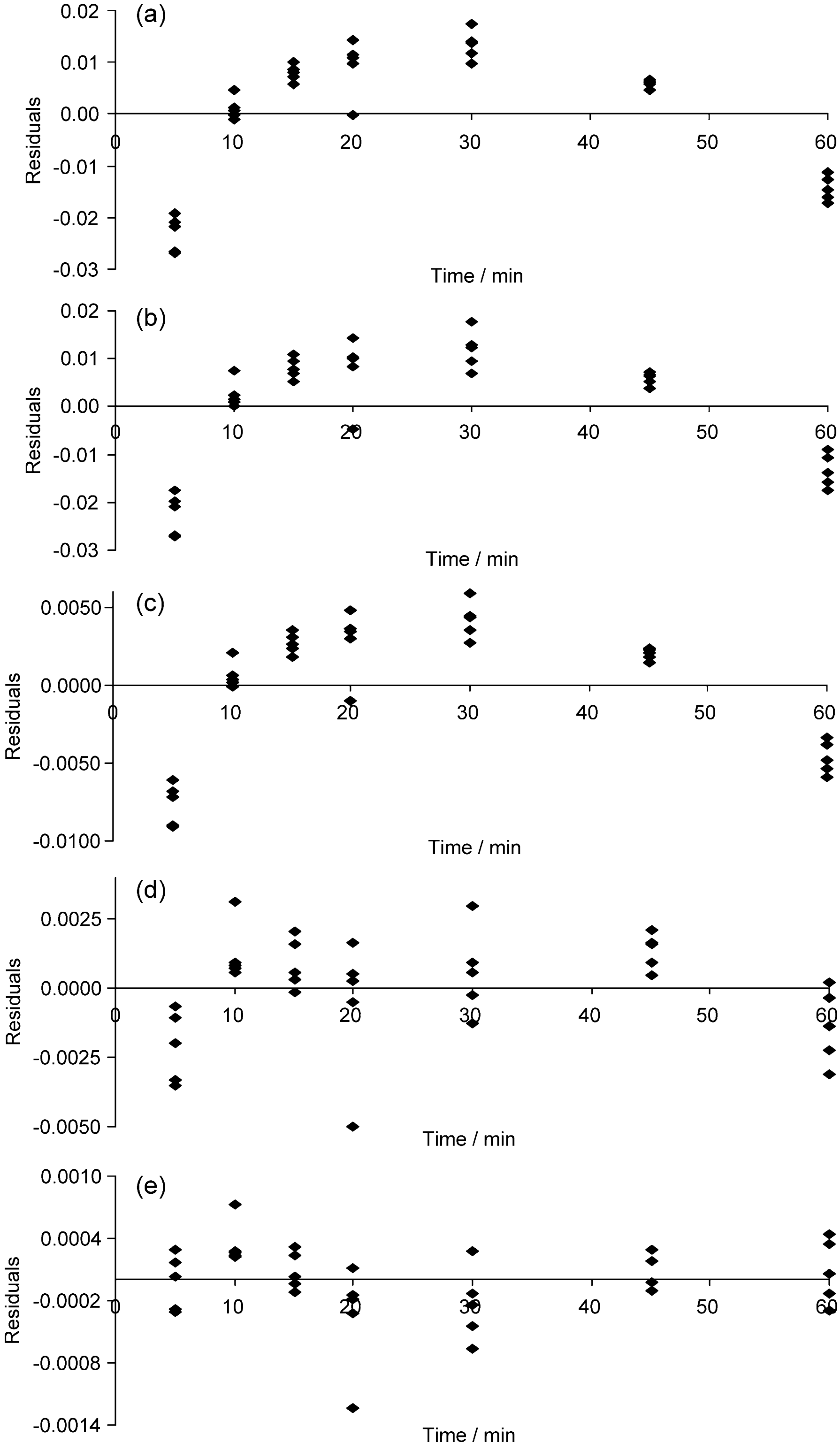

Fig. 9. Plot of residuals ($n=5$) for the initial phase of triclosan release from chitosan microspheres: fitted to (a) zero-order model; (b) first-order model; (c) cube-root of time model; (d) Higuchi model; and (e) Baker and Lonsdale model.

Table 4
Correlation coefficients, *R*, and mean standard errors, MSE, for the fitting of the triclosan release profiles of glycerol-suspended microspheres (Carbopol, polycarbophil, Gantrez and chitosan) to the mathematical models

Model	Carbopol		Polycarbophil		Gantrez		Chitosan	
	R	MSE	*R*	MSE	*R*	MSE	*R*	MSE
Zero-order	0.996	0.022	0.999	0.010	0.995	0.021	0.948	0.071
First-order	0.995	0.063	0.982	0.114	0.978	0.080	0.979	0.088
Hixson Crowell	0.999	0.005	0.991	0.021	0.986	0.018	0.970	0.028
Higuchi	0.999	0.007	0.980	0.054	0.963	0.047	0.981	0.038
Baker and Lonsdale	0.992	0.012	0.958	0.022	0.945	0.015	0.991	0.007

(v) The Baker and Lonsdale equation [18] models drug release from diffusion-rate-limiting matrixes of spherical shape:

$$\frac{3}{2}\left[1-\left(1-\frac{M_t}{M_\infty}\right)^{2/3}\right]-\frac{M_t}{M_\infty}=kt \tag{6}$$

As described previously [15,19], correlation coefficients and standard errors for the linear regression may be used as a means of comparing the 'quality of fit' to the different models. For the calculation of these parameters, only drug release at $>10\%$ (i.e. ≥ 5 min) was considered. This strategy was adopted to avoid any complications due to 'non-steady state' behaviour, typically exhibited within the first few minutes of a dissolution experiment.

For the release of triclosan from particles in free aqueous suspension, the modelling could only be performed meaningfully for chitosan, as the other polymers microspheres were witnessed to release the drug within a very brief timescale. The regression analysis was performed for the entire profile (from 5 to 480 min) and also, separately, for both the initial phase (5–60 min) and the terminal phase (90–480 min) of drug release (Table 3). The release data were seen to fit all models well ($R > 0.91$); the 'quality of fit' was generally better for the modelling of the initial phase ($R \geq 0.99$). To gain further insight into the 'quality of fit', a graphical analysis of the residuals was performed, whereby the residuals for each release profile of the linear regression were plotted as a function of time (Fig. 9). For the fits to the *zero-order*, *first-order* and the *cube root of time* models, the plots of residuals revealed very clear trends, indicating that, for these models, there is a departure of experimental data from the values predicted by the models. For the *Higuchi* model, such a non-random cyclic pattern is much less pronounced but still present and, although the latter model gave a very good correlation ($R = 0.999$), it was also rejected. For the *Baker and Lonsdale* model, the residuals were found to be scattered randomly around zero, suggesting that, in this case, the experimental data did not depart markedly from the theoretical values. Moreover, the absolute values of the residuals are an order of magnitude lower than those characterising the other models; the same model gave consistently the best correlation coefficient and the smallest mean standard error for all release phases tested. However, it is noted that for the terminal and overall-release phases, the fit was not as good as for the initial phase; it is likely that this arises from a change in the shape of the microspheres; polymer swelling may result in the formation of an outer gel diffusion layer that impedes the outward transport of drug from the matrix.

Table 4 summarises the correlation coefficients (*R*) and the mean standard errors (MSE) calculated for the fitting of the experimental data for the release of triclosan from microspheres in a non-aqueous paste to the different models. As the modelling was only performed in the range of 10–80% drug release, only 4 time points could be considered for Carbopol or polycarbophil, 5 for Gantrez and 8 for chitosan. For Gantrez and polycarbophil, the best correlation was obtained for the *zero-order* model ($R = 0.995$ and 0.999, respectively). For Carbopol, a very good correlation was achieved for all models considered ($R > 0.99$); the best fits was obtained for the *Hixson and Crowell* and for the *Higuchi* models ($R = 0.999$). For microspheres of this polymer, the correlation coefficient for the fitting to the *zero-order* model (0.996) was similar to that for those prepared from Gantrez (0.995). Assuming zero order kinetics for the release of triclosan from Carbopol, polycarbophil and Gantrez microspheres, statistical analysis revealed that the values obtained for the release constants, *k*, were not significantly different (one-way analysis of variances; Tukey's test; 95% confidence level): 3.93 ± 0.58, 3.67 ± 0.46 and 3.96 ± 0.63%/min.

The *Baker and Lonsdale* model was confirmed as the most appropriate for describing the release behaviour of chitosan microspheres. As this describes release from a diffusion-rate-limiting spherical matrix it might be expected to be most appropriate for this system. The release rate constants, *k*, and the time required for the release of 50% of the drug ($M_t/M_\infty = 1/2$) were determined for both the release of triclosan from microspheres in free aqueous suspension (aq) and for that from a non-aqueous paste (n-aq):

$$k_{aq} = (3.13 \pm 0.32) \times 10^{-4}\%/\text{min},$$

$$k_{n-aq} = (2.94 \pm 0.58) \times 10^{-4}\%/\text{min}$$

$t_{1/2(\mathrm{aq})} = (177.1 \pm 18.6)$ min,

$t_{1/2\mathrm{n-aq}} = (193.1 \pm 35.5)$ min

Statistical analysis (two-sample *t*-test; 95% confidence level) revealed that the differences were not significant.

4. Conclusions

Triclosan-loaded microspheres of four mucoadhesive polymers, Carbopol, polycarbophil, chitosan and Gantrez, were prepared. The loading efficiencies for Carbopol, polycarbophil and Gantrez, were of the order of 30% whereas that for chitosan was ca. 70%. Triclosan-loaded microspheres prepared from chitosan has been shown to exhibit controlled-release behaviour over extended time periods; the kinetics of the release have been shown to obey the *Baker and Lonsdale* model appropriate for diffusion-controlled spherical matrices. These will therefore be suitable for taking forward for in vitro bioadhesion studies followed by in vivo evaluation.

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References

[1] D. Steinberg, M. Friedman, Dental drug-delivery devices: local and sustained-release applications, Crit. Rev. Therap. Drug Carrier Syst. 16 (1999) 425–459.
[2] L. Krowszynski, Extended-release Dosage Forms, CRC Press, Boca Raton, FL, 1987.
[3] J.R. Robinson, Sustained and Controlled Release Drug Delivery Systems, Marcel Dekker, New York, 1978.
[4] L. Yang, P. Alexandridis, Physicochemical aspects of drug delivery and release from polymer-based colloids. Current opinion, Colloid Interf. Sci. 5 (2000) 132–143.
[5] A. Ahuja, R.K. Khar, J. Ali, Mucoadhesive drug delivery systems, Drug Dev. Ind. Pharm. 23 (1997) 489–515.
[6] J.D. Smart, Drug delivery using buccal adhesive systems, Adv. Drug Deliv. Rev. 11 (1993) 253–270.
[7] D. Patel, A.W. Smith, N. Grist, P. Barnett, J.D. Smart, An in vitro mucosal model predictive of bioadhesive agents in the oral cavity, J. Contr. Rel. 61 (1999) 175–183.
[8] S. Kockisch, G.D. Rees, S.A. Young, J. Tsibouklis, J.D. Smart, A direct-staining method to evaluate the adhesion of polymers from aqueous dispersion onto oral mucosal cells, J. Contr. Rel. 77 (2001) 1–6.
[9] S. Kockisch, G.D. Rees, S.A. Young, J. Tsibouklis, J.D. Smart, Polymeric microspheres for drug delivery to the oral cavity: an in vitro evaluation of mucoadhesive potential, J. Pharm. Sci. 92 (2003) 1614–1623.
[10] S. Kockisch, G.D. Rees, S.A. Young, J. Tsibouklis, J.D. Smart, In-situ evaluation of drug-loaded microspheres on a mucosal surface under dynamic test conditions, Int. J. Pharm. 276 (2004) 51–58.
[11] H.N. Bhargava, P.A. Leonardm, Triclosan: applications and safety, Am. J. Infect. Cont. 24 (1996) 209–218.
[12] J.E. Creeth, P.J. Abraham, J.A. Barlow, D. Cummins, Oral delivery and clearance of antiplaque agents from triclosan-containing dentifrices, Int. Dent. J. 43 (1993) 387–397.
[13] R.J. Gilbert, P.E.O. Williams, The oral retention and antiplaque efficacy of triclosan in human volunteers, Br. J. Clin. Pharm. 23 (1987) 579–583.
[14] H. Kawaguchi, Functional polymer microspheres, Prog. Polym. Sci. 25 (2000) 1171–1210.
[15] A. Li Wan Po, L.P. Wong, C.A. Gilligan, Characterisation of commercially available theophylline sustained- or controlled-release systems: in vitro drug release profiles, Int. J. Pharm. 66 (1990) 111–130.
[16] A.W. Hixson, J.H. Crowell, Dependence of reaction velocity upon surface and agitation. I. Theoretical consideration, Ind. Eng. Chem. 23 (1931) 923–931.
[17] T. Higuchi, Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices, J. Pharm. Sci. 52 (1963) 1145–1149.
[18] R.W. Baker, H.K. Lonsdale, Controlled release: mechanisms and rates in: A.C. Tanquary, R.F. Lacey (Eds.), Controlled Release of Biologically Active Agents, Plenum Press, New York, 1974, pp. 15–71.
[19] J.D. Smart, M.S. Barnes, M.J. Norris, An in vitro comparison of controlled release aminophylline tablets: Phyllocontin Continus and Pecram, J. Pharm. Pharmacol. 44 (1992) 623–625.