Chlorhexidine-containing mucoadhesive polymeric compacts designed for use in the oral cavity: an examination of their physical properties, *in vitro/in vivo* drug release properties and clinical acceptability

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This study describes the formulation, physicochemical and mucoadhesive properties and in *in vitro/in vivo* release of chlorhexidine from mucoadhesive, polymeric compacts, designed for application within the oral cavity. Compacts were prepared by direct compression of mixtures containing 100 mg sodium carboxymethylcellulose (NaCMC), 25 mg hydroxyethylcellulose (HEC)/75 mg polyacrylic acid (PAA) and 75 mg HEC/25 mg PAA. The mechanical and mucoadhesive properties of the drug-loaded compacts were examined using a texture analyzer in compression and tension modes, respectively. Evaluation of mucoadhesion was performed using a mucin-coated gauze substrate. *In vitro* release of chlorhexidine was performed under sink conditions (phosphate buffered saline, pH 7.0, 37 °C) using a Caleva 7ST dissolution apparatus. Salivary chlorhexidine levels were determined following intra-oral placement of drug-containing formulations. Quantification of the mass of chlorhexidine released both *in vitro* and *in vivo* was performed using HPLC with ultraviolet detection. Furthermore, the *in vivo* acceptability of the various polymeric compacts was assessed in volunteers using standard questionnaires. Compacts composed of HEC/PAA exhibited greater *in vivo* retention than those composed of NaCMC. Compacts composed of 25 mg PAA and 75 mg HEC displayed greatest patient acceptability. Introduction of chlorhexidine into these compacts did not significantly compromise either the work required for compact fracture or the *in vitro* mucoadhesion. Controlled release of chlorhexidine from these compacts was observed both *in vitro* and *in vivo*, the concentration of chlorhexidine in saliva exceeding the minimum inhibitory concentration of the common oral pathogens over the study period. In light of the patient acceptability and *in vivo* performance, it is suggested that the compact composed of 25 mg PAA/75 mg HEC containing 10 mg chlorhexidine offers considerable promise for use as an antimicrobial agent in the oral cavity.

Introduction

The systemic delivery of drugs can be associated with a number of adverse outcomes including toxicity, systemic side-effects, drug interactions and, in the case of antibiotics, the development of resistant strains and superimposed infections. Consequently, controlled release formulations are rapidly gaining importance in drug therapy as alternatives to conventional systemic dosage forms. Local delivery systems avoid many potential problems by limiting the drug to its target site with little or no systemic uptake. Controlled release formulations provide pre-programd delivery of the drug at a defined rate and for a defined period, established to meet a specific therapeutic need. The systems are designed to minimize the patient's intervention and optimize compliance with prescribed regimens [1, 2]. The use of controled drug delivery in the oral cavity, particularly in the treatment of periodontal disease, has increased rapidly in recent years [2–6]. The success of such treatments is intrinsically dependent on the physical

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properties of the formulation. Ideally such systems should show controled release of the drug, exhibit retention at the site of action for the desired period of time, be biodegradable, non-toxic, comfortable and non-irritant [2, 6]. Retention of such systems in the mouth can prove difficult both in the periodontal pocket, where crevicular fluid will naturally flush out pocket contents, and in the oral cavity exposed to salivary flow and natural shearing stresses during mastication and speech [7]. Retention of these formulations can be improved through interactions between the dosage form and the epithelial/tooth surfaces by means of interfacial forces in a process termed mucoadhesion [8]. There have been several reports of the use of mucoadhesive formulations for the treatment of disorders of the oral cavity. For example, Jones *et al*. [2, 3, 6] described the formulation, physicochemical properties and the clinical performance of novel mucoadhesive semi-solid formulations for the treatment of periodontal disease. The same authors reported the successful clinical application of chemically-related formulations for the treatment of gingivitis [5].

It is accepted that the physical state of the bioadhesive polymeric constituent within mucoadhesive formulations directly affects the nature of the interaction within the biological substrate and, indeed, this property is a determinant of the clinical performance of such systems [8]. Accordingly, it is acknowledged that for a given bioadhesive polymer, formulations containing a low water content (e.g. polymeric films and compacts) will provide greater bioadhesion when compared to systems that are more highly hydrated, e.g. gels [2, 8, 9]. There have been reports on the formulation and clinical use of mucoadhesive compacts. For example, Ponchel *et al*. [10] described the physicochemical factors that influenced bioadhesion of a metronidazole bioadhesive tablet, whereas, Iscan *et al*. [11] described the pharmacokinetic properties of a captopril-containing mucoadhesive compact following application to the buccal cavity. However, the use of mucoadhesive compacts for the controled delivery of therapeutic agents for the prevention/treatment of conditions of the oral cavity has received comparatively little attention. Therefore, the aims of this study were to examine the physicochemical and mucoadhesive properties of mucoadhesive compacts, to evaluate the clinical acceptability of these systems and finally, to examine the *in vitro* and *in vivo* release of an active agent from these systems. Selection of the polymeric formulations was performed to provide a range of physicochemical, mucoadhesive and drug release properties whereas chlorhexidine was chosen as the candidate agent due to its known anti-plaque and anti-fungal activity.

Materials and methods

Chemicals

Hydroxyethylcellulose (Natrosol 250-HHX-Pharm) and Carbopol 974P were gifts from Aqualon Ltd. (Warrington, U.K.) and B.F. Goodrich Company (Cleveland, Ohio, USA), respectively.

Sodium carboxymethylcellulose (medium viscosity) and mucin (crude porcine gastric) were purchased from the Sigma Chemical Co., St. Louis, PA, USA.

Chlorhexidine, as the diacetate salt, was a gift from Degussa, Cheshire, U.K.

All other chemicals were purchased from BDH Chemicals Ltd. (Gillingham, Dorset, U.K.) and were of AnalaR, or equivalent, quality.

Manufacture of mucoadhesive compacts

Mucoadhesive compacts were individually manufactured by mixing polyacrylic acid and hydroxyethylcellulose (in mixtures of either 25 : 75 mg or 75 : 25 mg) using a mortar and pestle. A defined mass of the polymeric mixture (100 mg) was transferred to a Carver press and compressed for 5 min at a pressure of 10 tonnes. In a similar fashion, compacts composed of sodium carboxymethylcellulose (100 mg) were prepared. Chlorhexidine containing compacts composed of polyacrylic acid and hydroxyethylcellulose were prepared by mixing 25 mg polyacrylic acid, 75 mg of hydroxyethylcellulose and 5, 10 or 20 mg of chlorhexidine, as the diacetate. Once more, these mixtures were compressed for 5 min at a pressure of 10 tonnes. All compacts were stored at room temperature for at least 1 day prior to analysis.

Assessment of the clinical acceptability and performance of the mucoadhesive compacts

The clinical acceptability and performance of chlorhexidine-devoid mucoadhesive compacts were examined using ten subjects with ethical approval from the Queen's University of Belfast. Each subject was given one bioadhesive compact (of each formulation) and asked to attach the compact to the alveolar mucosa above an upper lateral incisor. The subjects were reassured of the biocompatibility of the formulations. The subjects were asked to record the time at which the patch was attached and the time at which detachment occurred. Furthermore, the acceptability of the various bioadhesive compact formulations was assessed using a questionnaire in which the ease of attachment, the effects of the bioadhesive compacts on oral function, the sensory perception of the bioadhesive compacts and the awareness of the presence of the compacts were recorded.

Measurement of the mechanical properties of compacts

The work of failure of the various mucoadhesive compacts was determined using a Stable Micro Systems texture analyzer (TA-XT2) in compression mode. Each compact was placed onto a platform underneath the analytical probe (2 mm diameter, stainless steel). The analytical probe was then depressed into the sample at a defined crosshead speed (1 mm s^{-1}) until fracture of the compact resulted. The work required to fracture each compact was determined from the area under the force-distance curve. In all cases, the mechanical properties of at least six replicates of each formulation were examined.

Examination of the mucoadhesive properties

The mucoadhesive properties of the various bioadhesive compacts were determined using a Stable Micro Systems texture analyzer (TA-XT2) in tensile mode in association with a mucin substrate. Initially, the mucin substrate was prepared by soaking a sheet of gauze overnight in an aqueous mucin dispersion (20% w/w). The mucin-soaked gauze was then inserted within a Perspex ring clamp and the clamp attached to the base of the texture analyzer. The compact was then attached horizontally to an analytical probe which was, in turn, attached to the vertical arm of the texture analyzer. The arm was lowered until intimate contact between the two substrates occurred, at which point a downward pressure (0.1 N) was applied for a defined period (10 s). Following this, the analytical probe was retracted at a crosshead speed of $1\ \mathrm{mm\ s^{-1}}$ until separation of the two substrates occurred. This process was then repeated to examine the ''restick'' of the compacts. In all cases, the work required to separate the two substrates was determined from the area under the resultant force-distance plot. In all cases, the mucoadhesive properties of at least six replicates were examined.

Examination of the *in vitro* release of chlorhexidine

The release of chlorhexidine from the bioadhesive compacts composed of polyacrylic acid (25 mg) and hydroxyethylcellulose (75 mg) and containing a range of masses of chlorhexidine (5, 10, 20 mg, as the diacetate) was determined $(n = 6)$ using a Caleva 7ST dissolution apparatus in conjunction with paddle stirrers, as previously reported [2, 6]. In brief, the compacts were attached to metal supports and lowered into the 1L dissolution vessels containing dissolution medium (phosphate buffered saline, pH 7.0 at 37 °C). The medium was stirred at a constant rate $(60 \pm 1\ \mathrm{rev\ min^{-1}})$ and, at pre-determined intervals, samples of dissolution fluid (5 mL) were removed and an equal volume of fresh, pre-warmed dissolution fluid replaced into the dissolution vessels. The mass of chlorhexidine in the samples of dissolution fluid were analyzed by HPLC using a previously published method [12] with reference to a previously constructed calibration curve $(r > 0.99)$.

Examination of the *in vivo* release of chlorhexidine

The *in vivo* release of chlorhexidine from a compact composed of 25 mg polyacrylic acid, 75 mg hydroxyethylcellulose and 10 mg of chlorhexidine, as the diacetate, was investigated using five subjects. Each subject was given one bioadhesive compact and instructed to place the dosage form on the alveolar mucosa, above the lateral incisor. At defined time intervals (15, 30, 45, 60, 120, 180 and 240 min), patients were supplied with and instructed to thoroughly rinse their mouths with a known volume of deionized water (10 mL). The rinses were collected, diluted when required, centrifuged (14 000 g for 15 min), filtered using a clarifying (0.7 μm) filter and the mass of chlorhexidine quantified by HPLC as previously described [12].

Statistical analysis

The effect of compact formulation on the residence time within the oral cavity was statistically examined using a Kruskal–Wallis test, individual differences between ranked scores being statistically evaluated using Nemenyi's test. The effects of each formulation on ease of attachment (straightforward, some difficulty, very difficult), acceptability (comfortable, reasonably comfortable, uncomfortable), recorded problems concerning speech, eating, bad taste, consciousness of the presence of the compact (continually, occasionally, not at all) were statistically compared using χ^2 analysis. Individual differences between categories were examined using *post hoc* tests. The effect of chlorhexidine content on the work of failure of compacts composed of polyacrylic acid and hydroxyethylcellulose was statistically examined using a one-way ANOVA, whereas the effects of chlorhexidine content and number of attachments (one or two) on the force of detachment of the compact from the mucin-coated substrate were statistically evaluated using a two-way ANOVA. The effect of chlorhexidine content on the mass of chlorhexidine released *in vitro* at each time point was evaluated using a one-way ANOVA. Post hoc comparisons of individual means were performed using Tukey's Honestly Significant Difference test. Finally, patient differences in the mass of chlorhexidine released (*in vivo*) were statistically characterized using Friedman's test, in association with Nemenyi's test to identify specific patient differences. In all analyses, $p < 0.05$ was accepted to denote significance.

Results

The effect of formulation composition on the median residence time of mucoadhesive compacts within the oral cavity is shown in Table I. As may be observed the lowest residence time was associated with the compact composed of sodium carboxymethylcellulose whereas, compacts composed of PAA and HEC exhibited statistically similar residence times, the magnitudes of which were significantly greater than that associated with sodium carboxymethylcellulose.

Table II displays the patient assessments of the performance of the various blank compacts (devoid of drug). There were no significant differences in the ease of

TABLE I The effect of formulation composition on the median and range residence time of mucoadhesive compacts

Formulation composition	Median and range (in parentheses) residence time (min)
75 mg PAA/25 mg HEC	316 (180–550)
25 mg PAA/75 mg HEC	309 (225–490)
Sodium CMC (100 mg)	137 (90–240)

PAA, polyacrylic acid; HEC, hydroxyethylcellulose; sodium CMC, sodium carboxymethvlcellulose.

TABLE II The effect of formulation composition on the clinical acceptability of the mucoadhesive compacts

Formulation	Number of responses (patients)											
	Ease of attachment			Recorded problems concerning			Degree of comfort			Patient awareness		
	Straight-forward	Some difficulty	Very difficult	Speech	Eating	Bad taste	Comfortable	Reasonably comfortable	Uncomfortable	Continually	Occasionally	None
75mg PAA/ 25 mg HEC	8	2	0	0	0	2	0	8	5	5	5	0
25mg PAA/ 75 mg HEC	9	1	0	0	0	0	7	3	0	2	4	4
Na CMC (100 mg)	10	0	0	0	0	8	0	4	6	7	3	0

PAA, polyacrylic acid; HEC, hydroxyethylcellulose; Na CMC, sodium carboxymethylcellulose.

attachment of the three bioadhesive compacts. Furthermore, patients reported no problems concerning speech and eating during the period of attachment. However; patients complained that the compacts composed of sodium carboxymethylcellulose (100 mg) and, in addition, PAA (75 mg)/HEC (25 mg) presented a bad taste (8/10 and 2/10 patients, respectively). No taste problems were associated with the compact composed of PAA (25 mg)/HEC (75 mg). The composition of the bioadhesive compacts significantly affected performance in terms of comfort. Compacts composed of PAA (25 mg)/HEC (75 mg) were perceived by patients to be more comfort-able than the other candidate formulations under examination. However, there was no difference in the performance of compacts composed of sodium carboxymethylcellulose (100 mg) and PAA (75 mg)/HEC (25 mg) in this respect. Furthermore, the composition of the bioadhesive compact significantly affected the patients' awareness of the presence of the compact *in vivo*. Interestingly subjects had a greater awareness of the presence of bioadhesive compacts composed of either sodium carboxymethylcellulose or PAA (75 mg)/HEC (25 mg) than compacts composed of PAA (25 mg)/HEC (75 mg).

Due to their acceptable residence time within the oral cavity and performance, in terms of patient acceptability, the physicochemical and *in vitro*/*in vivo* drug release properties of chlorhexidine-containing compacts composed of PAA (25 mg)/HEC (75 mg) were further examined. The effect of chlorhexidine content (0, 5, 10 or 20 mg, as the diacetate) on the work required to fracture bioadhesive compacts composed of PAA (25 mg) and HEC (75 mg) is shown in Table III. As may be observed the work required to fracture compacts containing 0, 5 and 10 mg chlorhexidine was statistically similar. Conversely, compacts containing 20 mg chlorhexidine were not as mechanically robust (lower work of fracture) as those containing lower concentrations of this antimicrobial agent. The mucoadhesive properties of compacts composed of PAA (25 mg)/HEC (75 mg) and containing a range of masses of chlorhexidine (5, 10 and 20 mg as the diacetate) are presented in Table IV. From this, it may be observed that increasing the concentration of chlorhexidine did not significantly affect either the force or work required to overcome the adhesive bond between the two substrates. Furthermore, the adhesion of the compacts to the mucin-coated substrate was statistically similar following initial attachment to the substrate and following restick, i.e. reattachment.

TABLE III The effects of chlorhexidine content on the work required to fracture mucoadhesive compacts containing 25 mg polyacrylic acid and 75 mg hydroxyethylcellulose

	Chlorhexidine content (mg)			
	0	5	10	20
Work done (Nmm)	3.51 ± 0.22	3.43 ± 0.38	3.49 ± 0.38	2.22 ± 0.19

The effect of chlorhexidine loading (5, 10, 20 mg, as the diacetate) on the resultant release from compacts *in vitro* is graphically illustrated in Fig. 1. The mechanism of chlorhexidine release from these systems was evaluated by fitting the data generated from these release studies to the general release equation [13, 14] using logarithmic transformations and least squares regression analysis, as described below:

$$\ln \frac{M_t}{M_\infty} = \ln k + n \ln t$$

where M_t is the amount of drug released at time t, M_∞ is the total drug content, k is a constant incorporating structural/geometrical characteristics of the compact, n is the release exponent from which the mechanism of drug release may be elucidated.

In each of the compacts under investigation the release exponents, both *in vitro* and *in vivo*, were significantly greater than 0.5 but significantly lower than 1.0, indicative of an anomalous mechanism of release.

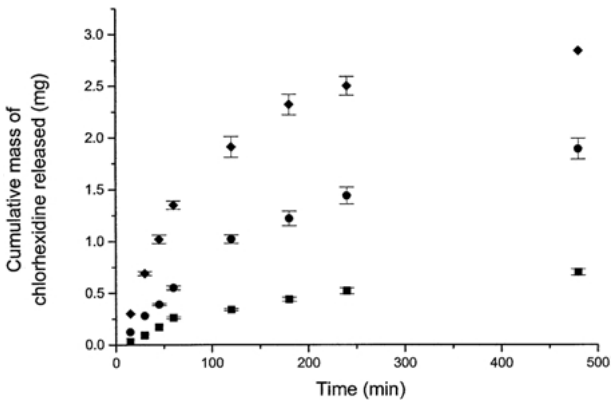

Figure 1 The effect of drug concentration on the mean (± sd) cumulative mass of chlorhexidine released *in vitro* from mucoadhesive compacts composed of 25 mg polyacrylic acid, 75 mg hydroxyethylcellulose and 5 mg (squares), 10 mg (circles) and 20 mg (diamonds) chlorhexidine (as the diacetate).

TABLE IV The effects of chlorhexidine concentration on the mean (± sd) force and work required to overcome the mucin/formulation bond following initial adherence and restick of formulations containing 25 mg polyacrylic acid and 75 mg hydroxyethylcellulose

Chlorhexidine content (mg)	Force required to overcome the mucin/formulation bond		Work required to overcome the mucin/formulation bond	
	Initial adherence	Restick	Initial adherence	Restick
0	0.09 ± 0.02	0.11 ± 0.02	0.08 ± 0.01	0.12 ± 0.02
5	0.08 ± 0.01	0.12 ± 0.02	0.07 ± 0.01	0.10 ± 0.01
10	0.07 ± 0.01	0.11 ± 0.01	0.07 ± 0.01	0.12 ± 0.02
20	0.08 ± 0.01	0.11 ± 0.01	0.07 ± 0.01	0.11 ± 0.01

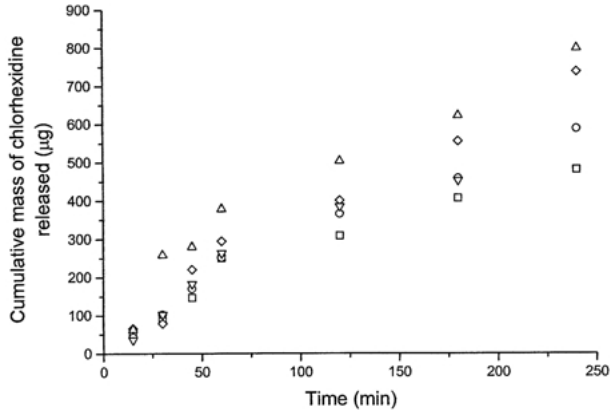

Figure 2 The cumulative mass of chlorhexidine released into salivary following attachment of a compact composed of 25 mg Polyacrylic acid, 75 mg hydroxyethylcellulose and 10 mg chlorhexidine (as the diacetate) to the alveolar mucosa in five volunteers.

Increasing chlorhexidine content was observed to significantly increase the mass of drug released at each sampling period.

The *in vivo* release of chlorhexidine from a bioadhesive compact formulation composed of PAA (25 mg)/HEC (75 mg) and containing 10 mg chlorhexidine, in five subjects is graphically portrayed in Fig. 2. Following application of the general release equation, the mechanism of release of chlorhexidine from the compacts *in vivo* was anomalous, akin to the release mechanism observed *in vitro*.

Discussion

The antimicrobial agent chlorhexidine has been successfully employed as an anti-plaque agent for almost 50 years, the success of which may be accredited to both the potent antimicrobial activity and, in addition, the retention characteristics in the oral cavity following application using conventional dosage forms, e.g. mouth washes [15–17]. Unfortunately, the prolonged use of this antimicrobial agent as a mouthwash within the oral cavity is associated with several problems including disagreeable taste and discoloration of the surface of the teeth [18, 19]. These complications are due in part to the high concentrations of chlorhexidine that are presented to the hard and soft surfaces of the oral cavity from these dosage forms. Therefore, it has been suggested that these problems may be reduced by the use of a chlorhexidine controlled release delivery system in which the surfaces of the oral cavity are exposed to dramatically lower concentrations of this therapeutic agent for prolonged periods [14].

It is accepted that the successful treatment of disorders of the oral cavity using topical dosage forms is a difficult process [6, 20]. This difficulty arises from both the wide range of stresses to which the dosage form will be exposed and the poor residence time of the dosage form/therapeutic agent at the required site [4]. In combination, these factors limit both the concentration at, and the time of contact of the therapeutic agent with, the proposed site of action. One method that has been proposed to correct this problem is the use of mucoadhesive formulations. Such systems have been shown to physically interact with a biological substrate [8]. Within the oral cavity, the interaction of these formulations is facilitated by the mucin layer that coats both the hard and soft tissues and, accordingly, under these circumstances, the process is referred to as mucoadhesion [8]. The use of mucoadhesive systems within the oral cavity for the treatment of local disorders has been the focus of several studies. For example, Collins and Deasy [21] described the formulation of a multilayered tablet containing cetylpyridinium chloride that maintained super-inhibitory concentrations of this antimicrobial agent in the saliva for greater than 3 h. More recently, Jones *et al.* [5] described the formulation, characterization and clinical efficacy of mucoadhesive, flurbiprofen-containing semi-solids for the treatment of gingivitis. Furthermore, the same authors described the physicochemical, rheological/mechanical and mucoadhesive properties of tetracycline-containing semi-solids and their clinical efficacy for the treatment of periodontal disease [6, 20].

Several hydrophilic polymers have been reported to possess mucoadhesive/bioadhesive properties [8]. Examples of these include polyacrylic acids [22, 23] and celluloses [24], chitosan [25, 26] and co-polymers of methylvinylether and maleic anhydride [27, 28]. In particular, it has been reported that the state of the mucoadhesive polymeric components directly affects the resultant mucoadhesive properties of the dosage form [5, 6, 8]. Consequently, greater mucoadhesive properties may be achieved whenever the mucoadhesive polymer is presented to the mucosal substrate in a solid (non-hydrated) state. The importance of the physical state of the mucoadhesive polymer on the rheological and mucoadhesive properties of semi-solid dosage forms has been examined by the authors [3–6, 20]. Furthermore, many studies have illustrated that the bioadhesive character of mucoadhesive drug delivery formulations decreases with increasing formulation water content [9, 29, 30]. Therefore, maximum mucoadhesion is frequently exhibited whenever mucoadhesive polymers are formulated as solid systems (compacts and solvent cast

films). One major advantage associated with solid compacts is the greater ease of manufacture and accordingly, this formulation platform was employed in this study. However, despite their proposed usage within the oral cavity, there is a paucity of information concerning both the *in vivo* release of therapeutic agents from bioadhesive compacts and, importantly, the acceptability of these delivery systems to the patient. Therefore, this study uniquely examined both of these aspects, and as a result, provides a further insight as to the performance of bioadhesive compacts as drug delivery systems for use in the oral cavity.

The patient acceptability of the various compacts was dependent on the nature of the formulation. Whilst there were no differences in the ease of attachment of the various compact formulations to the oral mucosa, differences in the patient acceptability were observed between formulations composed of sodium carboxymethylcellulose and those containing hydroxyethylcellulose (75 mg) and polyacrylic acid (25 mg). For example, formulations composed of either sodium carboxymethylcellulose or HEC (25 mg)/PAA(75 mg) exhibited greater interference with oral performance (speech) and furthermore patients reported a greater awareness of the presence of these systems, in comparison to the other compact system under examination in this study. Following attachment it is important that the compact hydrates to form a lubricious (gel) surface, which, in so doing, will decrease the modulus (and increase the comfort) of the dosage form. Therefore, the hydration properties of the various compacts may be partly responsible for the observed differences in patient acceptability. In this respect, the compact composed of HEC (75 mg) and PAA (25 mg) may possess the most appropriate hydration properties. Compacts composed of PAA alone were not examined in this study due to the possibility of mucosal damage resultant from the highly acidic properties of this polymer.

Interestingly, significant differences in the residence time of formulations composed of sodium carboxymethylcellulose and those containing hydroxyethylcellulose and polyacrylic acid (independent of the ratios of these components) were observed. The residence times of compacts composed of HEC and PAA were significantly greater that that for the compact composed of sodium carboxymethylcellulose; however, the ratio of HEC to PAA was not significant in this respect. Whilst, both sodium carboxymethylcellulose and polyacrylic acid have been reported to be strongly bioadhesive *in vitro* [31], several studies has reported that the mucoadhesive properties of polyacrylic acid are superior to those of sodium carboxymethylcellulose. For example, using an *in vitro* chicken pouch model to simulate the oral environment, Wong *et al*. [32] ranked the mucoadhesive properties of polymers as:

Carbopols (polyacrylicacid) > gelatin >
sodiumcarboxymethylcellulose >
hydroxypropylmethylcellulose >
alginic acid, Eudragits and chitosan.

Similarly, Cvetkovic *et al*. [33] reported that the mucoadhesive properties of polyacrylic acid were greater than those of sodium carboxymethylcellulose, as evaluated using an *in vitro* modified intestinal perfusion technique. The results obtained in the current study are therefore in accordance with the above reports. However, it must be highlighted that in this study the *in vivo* residence (a measure of mucoadhesion) was examined and therefore, this is one of the few studies that have comparatively described the clinical mucoadhesive properties of polymeric systems. The agreement between the current *in vivo* study and those *in vitro* studies reported by Wong *et al*. [32] and Cvetkovic *et al*. [33] illustrate the potential usefulness of appropriately designed *in vitro* mucoadhesive methods. Interestingly, in compacts containing HEC and PAA, it would be expected that as the mass of PAA (a strong mucoadhesive) increases, the mucoadhesive properties would similarly increase. However, in this study the *in vivo* residence of compacts composed of either HEC 75 mg/PAA 25 mg or HEC 257 mg/PAA 75 mg were statistically similar. Assuming that the distribution of PAA was homogeneous in each compact (and hence the mass of PAA at the surface of the two formulations differed), this would suggest that in these compacts the presence of HEC, a moderately mucoadhesive polymer, may modify the hydration properties of PAA and, in so doing, affect the subsequent mucoadhesion (and hence retention). This study has therefore highlighted the importance of formulation design on the subsequent *in vivo* behavior (residence) of mucoadhesive dosage forms.

Due to the greater acceptability and appropriate residence time within the oral cavity, the formulation containing HEC 75 mg and 25 mg PAA was selected for further examination as a vehicle for the delivery of chlorhexidine. In particular, the effect of chlorhexidine loading on *in vitro* mucoadhesion, mechanical properties and chlorhexidine release, both *in vitro* and *in vivo*, was examined. The mechanical properties of compacts either devoid of, or containing 5 or 10 mg chlorhexidine were statistically similar, however, incorporation of 20 mg of this therapeutic agent significantly decreased the work required to fracture the compacts. Therefore, at the highest loading, chlorhexidine interfered with the compaction properties of HEC and PAA. The clinical consequences of the effects of chlorhexidine (20 mg) on the mechanical properties are uncertain, however, it is important to remember that ideally compacts designed for use in the oral cavity should be resistant to fracture. Therefore, in this respect, compacts containing up to 10 mg of chlorhexidine would be more suitable for clinical application than compacts containing 20 mg, or greater, of this therapeutic agent.

Conversely, the chlorhexidine content of the mucoadhesive compact did not significantly affect the resultant *in vitro* mucoadhesion, i.e. both the force and work required to overcome the bond between mucin and the compact. Interestingly, the mucoadhesive properties of the compacts were significantly greater following reattachment (restick). Few studies have considered the mucoadhesive properties of compacts following successive attachments; however, information is available concerning the restick properties of mucoadhesive films. For example, Woolfson *et al*. [9] described the ability of films composed of polymethylvinylether-co-

maleic anhydride and polyvinylpyrrolidone to restick; however, the mucoadhesive properties of the film were reduced upon subsequent attachments. Therefore, the results from this current study are particularly relevant as the ability to effectively restick allows the patient to reattach the compact under circumstances in which the original location of attachment was either incorrect of sub-optimal.

The release of therapeutic agents from pharmaceutical dosage forms is a determinant of the resultant clinical performance. With respect to mucoadhesive dosage forms that are designed for the treatment of oral disorders, it is important that the therapeutic agent is released at the required site for a prolonged period. In so doing, a lower mass of therapeutic agent is required and, in addition, a reduced number of applications of the dosage form will be required, In the current system, the mass of chlorhexidine released for the candidate compact (25 mg PAA/ 75 mg HEC) increased as a function of drug loading. Therefore, it was possible to increase the release of chlorhexidine by increasing the drug loading from 5 to 10 to 20 mg. Following application of the generalized release equation (Peppas 1985), it was confirmed that the mechanism of drug release from these systems was not diffusion controled but anomalous. This release mechanism is frequently associated with hydrophilic systems in which polymer swelling and drug release occur simultaneously. For example, Jones *et al.* [2, 5, 6] described anomalous release of metronidazole, flurbiprofen and tetracycline from hydrophilic polymeric, mucoadhesive semi-solids and partially accredited the release profiles to the unique swelling properties of these systems. Over the period of examination (8 h), less than 20% of the original mass of chlorhexidine present in the compacts was released *in vitro*, further evidence of the controled release properties of these systems. Based upon the *in vitro* release of chlorhexidine from the compacts and remembering the effects of chlorhexidine loading on the mechanical properties of the compacts, a candidate formulation was chosen for clinical examination that offered maximal drug release and suitable mechanical properties (25 mg PAA, 75 mg HEC and 10 mg chlorhexidine, as the diacetate). The *in vivo* release of chlorhexidine within the oral cavity (examined from the concentration of chlorhexidine in saliva as a function of time) was anomalous ($0.5 < n < 1.0$) and is therefore in accordance with the pattern (mechanism) of drug release *in vitro*. The mass of chlorhexidine in the saliva was significantly lower than the corresponding mass of drug released *in vitro*. This may be accredited to both the lower rate of drug release from the compacts *in vivo* (due to the relatively low volume of saliva and unstirred nature of the oral environment) and, in addition, to the elimination of chlorhexidine from the saliva. Whilst the rate of drug release was not constant (i.e. not zero order), the concentration of chlorhexidine within the saliva exceeded the minimal inhibitory concentration of several pathogens of the oral cavity (e.g. *Candida albicans*) over the period of examination (6 h). The excellent retention properties of chlorhexidine within the oral cavity have been documented in several studies [16, 17] and therefore, the contribution of these properties to the results observed in this study should be acknowledged. However, in light of the significant mass of chlorhexidine present in the oral cavity during the period of application of the medicated mucoadhesive compact, it may be assumed that the dosage form is primarily responsible for the appreciable salivary levels of chlorhexidine over the 6h sampling period.

In conclusion, this study has described the formulation, characterization and examination of the drug release properties of mucoadhesive compacts composed of either sodium carboxymethylcellulose or blends of polyacrylic acid and hydroxyethylcellulose and containing the antimicrobial agent, chlorhexidine. Greatest patient acceptability was recorded with compacts composed of polyacrylic acid (25 mg) and hydroxyethylcellulose (75 mg). Compacts composed of hydroxyethylcellulose (25, 75 mg) and polyacrylic acid (75 and 25 mg) exhibited greatest (and statistically similar) mucoadhesion *in vitro* and retention properties *in vivo*. A range of drug release rates were observed *in vitro* from compacts composed of 75 mg HEC and 35 mg PAA that were anomalous in nature and which may be readily controled by modification of the original chlorhexidine loading. Sustained release of chlorhexidine *in vivo* from a compact composed of 75 mg HEC, 25 mg PAA and 10 mg chlorhexidine was observed over the period of examination. Interestingly, inter-patient differences were observed concerning the mass of chlorhexidine released as a function of time, however, independent of this, super minimum inhibitory concentrations of chlorhexidine were recorded in the saliva at all sampling period. The general acceptability of the above systems, their excellent retention characteristics and, in addition, the prolonged *in vivo* release of active offers opportunities for the use of compacts in the topical treatment of conditions of the oral cavity.

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