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Statistical optimisation of the mucoadhesivity and characterisation of multipolymeric propranolol matrices for buccal therapy

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Abstract

A Box–Behnken experimental design was employed to optimise a polymeric blend for the preparation of propranolol HCl matrices with maximum mucoadhesivity and was thereafter modified for achieving controlled drug release. The quantitative effects of the polymers used i.e. poly(acrylic acid) (PAA) and poly(vinyl pyrrolidone) (PVP) on mucoadhesion could be predicted using polynomial equations. A formulation of 20% PAA, 20% CMC and 20% PVP was identified for maximising mucoadhesivity and obtaining a controlled drug release profile. Reproducibility of the optimal formulation in terms of mucoadhesivity and controlled drug release was confirmed. The optimal formulation was characterised in terms of mucoadhesivity, release kinetics, swelling/erosion, hydration dynamics and surface pH. From the model fitting analyses, drug release was found to be diffusion, polymeric relaxation and erosion based with the former two being more dominant over erosion. This was in agreement with the erosion and swelling studies which showed swelling and erosion occurring in the tablet matrix. Textural profiling showed initial rapid hydration, which could be beneficial for enhanced mucoadhesivity. Surface pH of the multipolymeric matrices was similar to salivary pH and did not show extremes in changes over the test period. The optimal preparation of multipolymeric propranolol matrices identified in this study shows potential for buccal administration.

Keywords: Mucoadhesive; Controlled drug release; Multipolymeric; Propranolol; Buccal; Experimental design

1. Introduction

The buccal route for drug administration has been associated with numerous advantages over peroral administration. These include an avoidance of both hepatic and intra-alimentary canal metabolism (Senel and Hincal, 2001); it is not influenced by potential variation in gastric emptying rates (Kaus et al., 1999) or the presence of food (Lippert et al., 1998). Furthermore, the non-keratinized epithelia is relatively permeable to drugs and this route is also associated with better patient compliance (Singh and Ahuja, 2002). Some classes of drugs that may benefit from buccal administration include antihypertensives, hypoglycemics and antiretrovirals. Propranolol HCl (PHCl), a β-blocker, used in the treatment of various cardiovascular disorders (Corbo et al., 1990) is an ideal model drug for incorporation into a controlled release buccal formulation due to its short half-life (3–6 h), low molecular weight and its extensive and highly variable first pass metabolism following oral administration (Gomeni et al., 1997).

Mucoadhesive polymers are pivotal in the development of buccal delivery systems. These polymers enable retention at the buccal mucosal surface so providing intimate contact between the dosage form and the absorbing tissue (Adriaens et al., 2003). Increasing the retention time of the dosage form is therefore essential in the development of these systems and it has been shown to increase with an increase in the mucoadhesivity of the system (Yun et al., 1999; Yong et al., 2001). Maximizing the mucoadhesivity of these systems therefore remains an important goal in the development of mucoadhesive drug delivery systems. In addition to mucoadhesivity, a controlled release of the drug from the dosage form is also desirable. The potential advantages of this concept include minimisation of drug related side effects and improved patient compliance (Bromberg et al., 2001).

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The identification of polymeric systems and technologies to optimize both the mucoadhesivity and controlled drug release kinetics of a buccal system remains an important goal and challenge. Homopolymeric systems for controlled release buccal delivery have been widely investigated and characterized in the literature (Minghetti et al., 1998; Alur et al., 1999). However, with homopolymeric systems, a polymer that has good mucoadhesivity may not necessarily have good controlled drug release behaviour and vice versa. For example, in a recent study by Perugini et al. (2003), a homopolymeric system of chitosan glutamate displayed excellent mucoadhesivity but was unable to provide controlled drug release. Poly-lactide-*co*-glycolide (PLGA) on the other hand was a poor mucoadhesive but was ideal for prolonging drug release.

To overcome the limitations of homopolymeric systems, the use of polymeric blends in many pharmaceutical preparations, especially in controlled drug delivery (Tan et al., 2001) and mucoadhesive systems (Betageri et al., 2001; Khoo et al., 2003; Perioli et al., 2004; Owens et al., 2005), are being investigated. For example, bilayered (Remunan-Lopez et al., 1998), multilayered (Perugini et al., 2003) and wafer systems (Bromberg et al., 2001) have been initiated to overcome the limitations of homopolymeric systems. However, the preparation involves complex processing and higher costs of production. The identification of ideal polymeric combinations in a monolayered system may achieve both optimal controlled drug release and mucoadhesivity with simpler processing and lower costs. In addition to the inherent physicochemical properties of individual polymers, complexation between polymers has also been shown to modulate drug release (Pillay and Fassihi, 1999). Thus, polymeric blending in delivery systems may allow for polymeric complexation that may lead to phase transitions within the dosage form structure, alter influx/efflux of water mobility and also alter the hydration dynamics of the system all of which can simultaneously regulate drug release and mucoadhesion. Optimisation by means of statistical experimental design methodologies have been successfully applied in the literature for the formulation of controlled release preparations (Hamed and Sakr, 2001; Kramar et al., 2003). However, to date, while mucoadhesivity is an important prerequisite for an optimal formulation for prolonged delivery via the buccal route, few experimental studies (if any) have used statistical optimisation to identify a formulation with an ideal polymeric blend for maximum mucoadhesion. The aim of this study was therefore to use an experimental design to identify optimal polymeric combinations for a propranolol matrix preparation with maximum mucoadhesion. In addition to identifying an optimal polymeric blend, the use of experimental designs will also identify and quantify the possible main and interaction effects of polymers on mucoadhesion. Also, another aim was to undertake a detailed physicochemical/mechanical characterisation of the optimal multipolymeric matrix formulation once optimised for mucoadhesion and controlled drug release in terms of release kinetics, swelling and erosion properties, hydration dynamics, and surface pH. A more detailed physicochemical/mechanical characterisation and mechanistic understanding of multipolymeric propranolol matrices is essential for optimisation of this system.

2. Materials and methods

2.1. Materials

Propanolol HCl (PHCl) was purchased from Frankel Chemicals (SA). Poly(acrylic acid) 2100 (PAA); carboxymethylcellulose (low viscosity) (CMC); poly(vinyl pyrrolidone) (MW 40,000) (PVP) and mucin were purchased from Sigma–Aldrich (UK) and used as received. Other excipients used to prepare the mucoadhesive tablets were of standard pharmaceutical grade and all chemical reagents used were of analytical grade.

2.2. Methods

2.2.1. Preparation of multipolymeric tablet matrices

Flat-faced tablets (300 mg, 10 mm in diameter, 2.8–3 mm in thickness) were prepared using a Carver Press (Beckman, Scotland). Compaction pressures ranging from 2 to 5 MPa were used in order to produce a suitable tablet hardness within a range of 70–90 N. These parameters hence ensured that a friability of <1% was maintained (BP, 2002). Each batch formulated comprised of different polymeric blends, magnesium stearate (1%) and dicalcium orthophosphate (accordingly adjusted to achieve a mass of 300 mg).

2.2.2. Experimental design approach

A Box–Behnken experimental design was employed in this study to statistically optimise the polymeric blends of a PHCl matrix preparation for maximum mucoadhesivity. Response surface methodologies, such as the Box–Behnken and central composite designs, model possible curvature in the response function (Zaghloul et al., 2001; Dayal et al., 2005). The Box–Behnken design was specifically selected since it requires fewer treatment combinations than a central composite design in cases involving three or four factors. The Box–Behnken design is also rotable and contains statistical "missing corners" which may be useful when the experimenter is trying to avoid combined factor extremes. This property prevents a potential loss of data in those cases.

Generation and evaluation of the statistical experimental design were performed with the Microsoft Excel 2002 Add-In, Essential Regression and Experimental Design software Version 2.2 (USA). The studied factors were percentages of PAA, CMC and PVP in the formulation; as these polymers and the level settings used were found to have a significant effect on mucoadhesion and drug release of the matrices in preliminary investigations. The response variables was the maximum detachment force (MDF). A design matrix comprising of 16 experimental runs was constructed. An interactive second order polynomial model was utilised to evaluate both the response variables:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_1X_1 + b_5X_2X_2 + b_6X_3X_3 + b_7X_1X_2 + b_8X_1X_3 + b_9X_2X_3 \quad (1)$$

where b_0–b_9 are the regression coefficients, X_1, X_2, X_3 are the factors studied and Y is the measured response associated with each factor level combination. Stepwise forward and backward regression produced a model containing only the significant

Table 1
Independent variables: factors and levels for the Box–Behnken design

Coding	Factor	High level	Intermediate level	Low level
Independent variables				
X_1	PAA	20	10	0
X_2	CMC	20	10	0
X_3	PVP	20	10	0
Coding			Response	
Dependent variables				
Y1			Maximum detachment force (MDF)	

terms. The resulting equation was also subjected to a lack-of-fit statistical evaluation and model simplification at a 95% significance level. Table 1 summarises the factors and their levels and Table 2 summarises the design matrix with the experimental runs, factor levels and combinations and the measured response i.e. MDF.

For all optimisation procedures the Solver function in the Essential Regression and Experimental Design software, which incorporated the Generalised Linear Gradient Algorithm (GRG-2 algorithm), was used.

2.2.3. Evaluation of the multipolymeric PHCl matrices

2.2.3.1. Mucoadhesivity. Mucoadhesivity was measured using a Lutron Digital force gauge (FG5000A, Korea). A petri dish containing mucin (30% w/w), was placed in a thermostatically controlled water bath (37.0 ± 0.5 °C). The mucoadhesive tablet was attached to one side of a double-sided metal disk using cyanoacrylate adhesive. Experimental parameters for MDF measurements were set as identified and optimised in a previous study (Munasur et al., 2002). The tablet surface was hydrated with 15 μL phosphate buffered saline (PBS) pH 6.8 for 3.5 min. The double-sided disk containing the tablet was then attached to the Lutron force gauge via a non-elastic connector and brought into contact with the mucin. After 5 min the tablet surface was separated from the mucin (15 mm/min), using a cross-head pulley until a peak detachment force was obtained. The mean ± S.D. of 10 individual replicates were expressed as the force required to separate the tablet from the mucin (maximum detachment force (MDF)). As a control, the mucoadhesion experiments were conducted on tablet matrices containing PHCl, magnesium stearate and dicalcium orthophosphate only (i.e. matrices containing no mucoadhesive polymers) and the blank values for each formulation were subtracted from the test values.

Table 2
Experimental matrix for polymer levels and results obtained for MDF measurements

Experiment number	PAA level (%m/m)	CMC level (%m/m)	PVP level (%m/m)	Response 1 MDF (mN)
1[a]	10	10	10	640
2[a]	10	10	10	730
3	10	0	20	880
4	10	20	0	300
5	0	10	0	400
6	10	0	0	540
7[a]	10	10	10	383
8	0	0	10	270
9	10	20	20	818
10	20	10	20	740
11[a]	10	10	10	630
12	20	0	10	330
13	20	20	10	570
14	20	10	0	380
15	0	20	10	420
16	0	10	20	360

[a] Center point measurement.

2.2.3.2. Assay and in vitro drug release studies. Ten tablets were weighed and subsequently powdered using a mortar and pestle. Powder equivalent to the mass of one tablet was quantitatively transferred into a volumetric flask containing PBS pH 6.8. Following sonication, the sample was filtered (Millipore® Filter, 0.45 μm), suitably diluted and analysed at a λ max of 288 nm (UV-1650 PC, Shimadzu, Japan). For each batch, the assay procedure was performed in triplicate.

In vitro drug release studies were performed on all tablet matrix formulations using the USP 24 Method (Apparatus II, PBS pH 6.8, 500 mL, 25 rpm, 37 ± 0.5 °C) (Erweka DT6R, Germany). At the end of the predetermined time intervals (e.g. 0.25, 0.5, 0.75, 1, 2, 3, 4, 6 and 8 h), aliquots (5 mL) were removed from each dissolution vessel and filtered through 0.45 μm Millex® filters. An equal volume of drug-free medium (5 mL) to that of the aliquot removed was replaced into each dissolution vessel, to maintain a constant volume of medium during the dissolution test. The percentage drug released at each time point was quantified by ultraviolet spectroscopy at a λ max of 288 nm (UV-1650 PC, Shimadzu, Japan) with a total of three replicate determinations for each batch.

2.2.3.3. Kinetic analysis of drug release profiles and model fitting. Kinetic analysis of the drug release data was performed using Win Nonlin Version 3.1 (Pharsight, CA) and was based on non-linear regression. In all least squares analyses, the Guassian–Newton (Levenberg–Hartley) approach was adopted. The Power Law expression together with its geometry-independent form (Peppas, 1985) as well as the Hopfenberg model (Hopfenberg, 1976), a geometry dependent equation, were applied to the drug release data.

2.2.3.4. Swelling and erosion studies. Erosion and swelling of the tablet matrices were determined under conditions identical to those described for the dissolution testing. Water uptake and mass loss were determined gravimetrically according to the following equations, using a modified method as prescribed by Durig and Fassihi (2002).

$$\text{Degree of swelling (water uptake)} = \frac{\text{wet weight} - \text{original dry weight}}{\text{original dry weight}} \quad (2)$$

$$\text{Erosion (\%mass loss)} = \frac{\text{original weight} - \text{remaining dry weight}}{\text{original weight}} \times 100 \quad (3)$$

At predetermined time intervals of 1, 2, 4, 6 and 8 h the hydrated tablet matrices were carefully removed from the dissolution vessels and lightly patted with tissue paper to remove excess surface water. After determining the wet weight, the tablets were dried at 40 °C until constant mass.

2.2.3.5. Textural profile analysis. The textural profile analysis studies were undertaken using a 25 kg load cell (Texture Analyser XT2ί, Stable Micro Systems, UK). The test parameters for all experimental studies were set as follows: a maximum force of 40 N, trigger force of 0.1 N, pre-test and post-test speeds of 2 mm/s and a test speed of 1 mm/s. Data were captured at 200 points per second via the Texture Expert for Windows software, Version 1.20. All measurements of probe displacement (mm) were conducted at a constant force of 5 N. Tablets were placed in buffer medium pH 6.8, maintained at a temperature of 37 °C for the duration of the study. Samples were removed in triplicate at predetermined time intervals and subjected to textural analysis. The data are presented as peripheral hydration zones (mm) versus hydration time.

2.2.3.6. Surface pH evaluation. Tablets were placed in glass tubes and allowed to swell in contact with 1 mL of phosphate buffered saline (pH 6.8). The surface pH was noted by bringing a glass micro-electrode (Mettler Instrumente, Germany) near the surface of tablet matrices and allowing it to equilibrate for 1 min. Thereafter surface pH measurements were recorded at predetermined time intervals of 0, 1, 2, 4, 6 and 8 h. These studies were performed in triplicate.

3. Results and discussion

3.1. Formulation optimisation

3.1.1. Fitting of mucoadhesion data to the model

Based on the experimental design, the factor combinations yielded different mean maximum detachment forces. Table 2 summarises the experimental runs, their factor combinations and the levels of experimental units used in the study as well as the bioadhesive forces obtained for each factor combination. In order to determine the levels of factors which yielded optimal mucoadhesivity, mathematical relationships were generated between the dependent and independent variables. Using the software described earlier, the model was fitted to the data. Repeated backward stepwise regression was used to eliminate the insignificant effects and to generate the equation for the response parameter (MDF). The regression equation together with the statistically significant coefficients and the regression significance generated for the response variable from the above procedure is presented in Table 3.

The initial model was refined to include in the model only those terms for which the level of significance was below or equal to $p \leq 0.05$. Statistical testing (ANOVA) indicated that the regression model obtained was statistically significant ($p = 0.003$). The lack of fit error was statistically insignificant ($p = 0.359$) further indicating good model fitting.

Table 3
Regression equation, significant coefficients, terms and regression significance of the MDF model

Coefficient	Numerical value	p-Value
b_0	362.50	0.000103
b_1	1.315	0.00387
b_2	−1.814	0.01487
b_3	30.25	0.005216
Regression significance		0.003
Lack of fit error significance		0.359

Model generated: MDF = $b_0 + b_1$ PAA PVP + b_2 PAA PAA + b_3 PAA.

3.1.2. Examination of the mucoadhesion model coefficients and response surface plots

Using backward elimination, the statistically significant mathematical model in Table 3 was generated. The resultant equation which represents the quantitative effect of the formulation parameters on the maximum detachment force is given below:

$$\mathrm{MDF} = 362.50 + 1.315\,\mathrm{PAA\,PVP} - 1.814\,\mathrm{PAA}^2 + 30.25\,\mathrm{PAA} \quad (4)$$

Fig. 1a and b illustrate the corresponding response surface and contour plots of the model compiled in Table 3. The above model and Fig. 1a show that only PAA had a significant main positive effect on the MDF ($p < 0.05$). Generally, the interaction of PAA with the mucin is brought about via hydrogen bonding, especially with the glycoprotein predominant in the mucous layer resulting in adhesion to the mucin (Solomonidou et al., 2000). This observation suggests that an increase in the PAA content resulted in a corresponding increase in the number of carboxylic groups, thereby enhancing the hydrogen bonding capacity of the tablet which subsequently produced a profoundly higher binding potential of the two surfaces. An increase in mucoadhesivity with an increase in PAA content is consistent with findings in the literature (Peh and Wong, 1999). However, an increase in PAA content beyond an optimal threshold level resulted in a decrease in the MDF as represented by the negative quadratic affect of PAA ($p < 0.05$). Other studies have also shown that exceeding the critical concentration of a polymer decreases mucoadhesion significantly (Bremecker, 1980; Gurny et al., 1984)). The findings in this study with PAA may be rationalized by the possibility that in a high concentrated environment of PAA, the coiled molecules become solvent poor. As a result, the macromolecules approached the dimension of an unperturbed state, and the available chain length for penetration decreases (Gandhi and Robinson, 1994).

While PVP did not have a significant main effect, its interaction effect with PAA had a significant positive effect on mucoadhesivity ($p < 0.05$). This observation can be attributed to the potential occurrence of an interaction effect of the two polymers at the corresponding factor levels, thereby suggesting that each polymer tends to modify the effect of another towards the MDF.

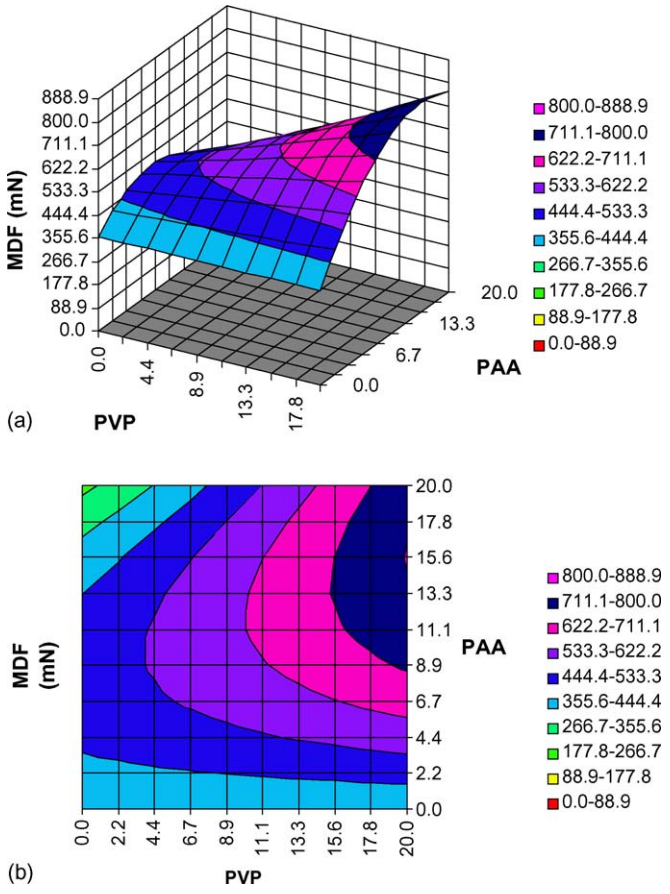

Fig. 1. (a) Response surface plot illustrating the influence of PAA and PVP on MDF values. (b) Contour plot illustrating the relationship between various levels of PAA and PVP to attain fixed values of MDF.

3.1.3. Prediction of the optimal mucoadhesion formulation and validation of the model

Optimisation (Essential Regression, USA, 1997) was used in order to predict a formulation with maximal mucoadhesion from the model generated (Eq. (4)). An optimal MDF value of 803 mN for a formulation comprising of PAA (15.6%) and PVP (20.00%) was predicted. A batch of tablets was therefore prepared using this identified formulation and its mucoadhesivity was measured. A mean value of 897 ± 154.34 mN ($n = 10$) was obtained for this tablet matrix. Statistical analysis using a *t*-test showed no significant differences ($p = 0.086$) ($p > 0.05$) between the predicted (803 mN) and experimental (897 mN) values, hence validating the model generated in this study.

3.1.4. In vitro drug release profile of the optimal MDF formulation and modification to achieve a desired controlled release profile

In addition to mucoadhesivity, controlled drug release from the preparation was also a prerequisite for this formulation. The optimal mucoadhesive formulation generated above (15.6% PAA and 20% PVP) was subjected to *in vitro* dissolution testing to assess its drug release profile. From the dissolution profile obtained (Fig. 2) it was evident that while drug release rate was controlled, only 31.51 ± 2.66% PHCl was released at the end of 8 h. The reason for this extremely retarded drug release observed

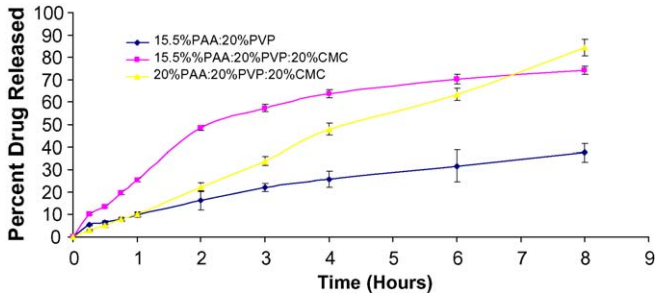

Fig. 2. A comparison of *in vitro* drug release profiles from various PAA/PVP/CMC tablet matrices.

in this formulation may be attributed to the three-dimensional network structure that could be produced by complex formation between drug and the various polymers, following penetration of dissolution medium (pH 6.8) into the tablet matrix (Tan et al., 2001). Though the pH value of the dissolution medium was higher than the critical pH for complexation, the pH value inside the polymer matrix could be low enough for the complexation owing to the acidity of PAA (Gurny et al., 1984). As a result, PHCl may have been tightly held in the matrix in the initial dissolution stage. While the optimal formulation identified from the model generated was capable of maximizing mucoadhesivity, the drug release was considered too retarded. A formulation with an appropriate controlled release profile with at least 80% drug release over an 8 h period was desired for the purpose of this study. Hence, modifications to the polymeric content of the optimal MDF formulation i.e. 15.6% PAA and 20% PVP (Formulation A) was attempted to obtain the desired controlled release profile.

Since preliminary studies showed that CMC provided faster drug release than PVP and PAA, its inclusion at a 20% level was considered (Formulation B). Fig. 2 clearly shows that CMC improved the drug release profile as a faster drug release was obtained with Formulation B than with Formulation A. The incorporation of CMC may have altered the structural properties of the tablet matrix by creating an increased porosity in the tablet, thus allowing more rapid penetration of the dissolution medium (PBS, pH 6.8) into the tablet which facilitated the drug release behaviour. Although drug release was faster, the total percentage drug released at the end of 8 h was less than 80%. Formulation C examined the effect of maintaining all three polymers at a concentration of 20%. An increase in the concentration of PAA from 15.6% to 20% led to an initial decrease in the amount of drug released for the first 6 h as compared to Formulation B. However, the amount released at the end of 8 h was greater than 80%. The dramatic increase in swelling of this preparation after the sixth hour as discussed in Section 3.2.2 correlates with the increased drug release after the sixth hour as compared to Formulation B. Therefore, for the purposes of this study, Formulation C was considered most suitable for enhancing drug release; however it was also important to ensure that Formulation C did not adversely affect the MDF of the original formulation optimised via the experimental design.

The MDF value for Formulation C was therefore determined and compared to the MDF value of the optimal MDF formulation

(Formulation A). The MDF values of Formulations A and C were found to be 897 ± 154.34 mN ($n = 10$) and 792 ± 167.25 mN ($n = 10$), respectively. Statistical analysis using a two-sample, t-test showed no significant difference ($p = 0.092$) ($p > 0.05$) between the two formulations. Clearly, the formulation with an improved drug release profile did not compromise the optimal mucoadhesivity achievable. Hence, a formula comprising of PAA (20%), CMC (20%) and PVP (20%) was identified as being capable of providing both enhanced mucoadhesivity and an optimal controlled release profile for the purposes of this study. The use of an experimental design to optimise the mucoadhesivity of the formulation first and further polymeric modifications to obtain a desired controlled release profile was successful in identifying a formulation with both maximal mucoadhesivity and controlled drug release.

3.1.5. Reproducibility study

This study was undertaken to confirm the reproducibility of the drug release and mucoadhesivity properties of the optimal formulation identified. An additional two batches (B and C) comprising of PAA (20%), CMC (20%) and PVP (20%) were prepared and the following studies were undertaken.

3.1.5.1. Quality control of mucoadhesive matrix tablets. The hardness values obtained for formulations A–C were 96 ± 15.26, 94.89 ± 10.54 and 94.52 ± 5.10 N, respectively. Friability determinations for the three formulations complied with the specifications of less than 1% and were 0.35%, 0.48% and 0.83%, respectively. The assay measurements for these formulations also complied with the stipulated regulatory specifications of 95–105%, being $99.54 \pm 0.23\%$, $101.37 \pm 0.06\%$ and $98.13 \pm 0.66\%$, respectively. The optimal formulation was therefore reproducible in terms of hardness, friability and drug uniformity.

3.1.5.2. Mucoadhesivity measurements. The MDF measurements obtained for the three formulations were 792 ± 167.25, 744 ± 132.09 and 799 ± 107.75 mN, respectively. Statistical analysis using the paired *t*-test showed that these formulations were similar ($p > 0.05$) (A versus B: $p = 0.41$; B versus C: $p = 0.161$; A versus C: $p = 0.45$).

3.1.5.3. In vitro drug release studies. The *in vitro* drug release profiles of the three formulations are illustrated in Fig. 3. The profiles appeared to be almost super-imposable. In order to confirm the similarity of these dissolution profiles, the similarity factor were used. The *similarity factor* denoted as f_2 (Moore and Flanner, 1996), directly compares the similarity between percentage drug dissolved per unit time for a test and reference product. The *similarity factor* (f_2) is a logarithmic transformation of the sum-squared error of differences between the test T_j and reference product R_j over all time points:

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{N} \right) \sum_{j=1}^{n} |R_j - T_j|^2 \right]^{-0.5} \right\} \times 100 \quad (5)$$

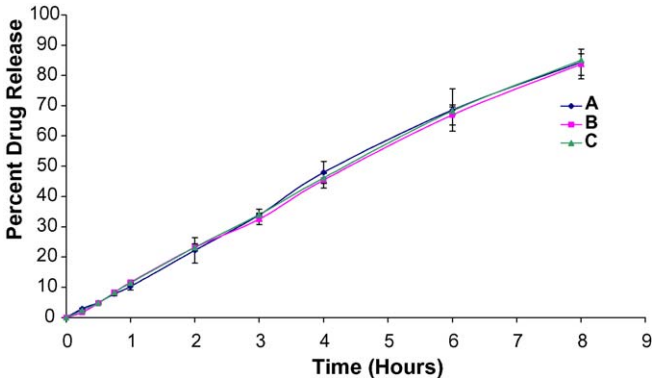

Fig. 3. Reproducibility of *in vitro* drug release profiles.

In general, f_2 values higher than 50 (50–100) show similarity of the dissolution profiles. The calculated f_2 value obtained in this study for A versus B, B versus C and A versus C were 91.69, 95.70 and 95.74, respectively. These findings suggest that the *in vitro* drug release profiles investigated were therefore similar.

Based on the results obtained in the various tests namely hardness, friability, assay measurements, MDF and drug release studies, it was found that the optimal formulation identified was reproducible in terms of quality control, mucoadhesivity and dissolution.

3.2. Characterisation of the optimal formulation

The formulation identified for optimal mucoadhesivity and drug release (Formulation C) was then subjected to a detailed characterisation in terms of release kinetics, swelling/erosion, hydration dynamics and surface pH.

3.2.1. Kinetic analysis of drug release profiles and model fitting

Table 4 provides a summary of the model fitting and statistical parameters for release kinetics of the optimal formulation. The Akaike Information Criterion (AIC) is a measure of the goodness of fit of a particular model based on the maximum likelihood. When comparing several models for a given set of data, the model associated with the smallest value of AIC is regarded as giving the best fit out of that set of models and is calculated as follows:

$$\mathrm{AIC} = N_\mathrm{d} \ln \mathrm{SSR} + 2P \quad (6)$$

where N_d represents the number of data points, SSR the sum of squares and P denotes the number of parameters used in the model. In addition, the Schwartz Bayesian criteria (SBC) was also used as a confirmatory indicator of the soundness of statistical and experimental interpretation (Costa and Lobo, 2001).

The relatively low values of AIC and SBC for all three models indicate that the drug release can be described by all three models. The drug release kinetics may be best described by Model 1, followed by Model 2 and then Model 3. Model 1 produced an *n*-value of 0.9467, confirming the closeness to attainment of ideal zero-order drug release. The non-Fickian release behaviour here may suggest that the release of PHCl was controlled by

Table 4
Drug release kinetic data derived from various mathematical models

Model	k_1	k_2	k_2/k_1	n	AIC	SBC
$(M_t/M_\infty) = k_1 t^n$ (Model 1 = Power law)	0.189	–		0.947	−57.922	−58.620
$(M_t/M_\infty) = k_1 t^n + k_2 t^{2n}$ (Model 2 = Derivative of Power law)	1×10^{-6}	0.119	119000	0.473	−54.922	−57.467
$(M_t/M_\infty) = 1 - (1 - k_1 t)^n$ (Model 3 = Hopfenberg Model)	0.068	–		2	−48.751	−49.599

a combination of diffusion of the drug from the matrix and also perhaps the three-dimensional network structure which was produced by polymer complex formation following water penetration into the tablet. On the basis of the application of the geometry-independent expression (Model 2), it became apparent that through separation of the release constant into Fickian and relaxational components, matrix relaxation was predominant, as supported by the k_2/k_1 ratio (=119000). Using an n-value of 2 in the Hopfenberg model (Model 3) a k_1 value of 0.068 was obtained. As k_1 incorporated the erosion constant k_0, this provided an indication that while erosion did occur to some extent, the mechanism of drug release was not purely erosion dominant. Therefore, diffusion and polymer relaxation were predominantly responsible for drug release followed by erosion from the multipolymeric tablet matrices formulated.

3.2.2. Swelling and erosion studies

To obtain further evidence for the observed drug release mechanism attributed to the polymeric blend, additional swelling, erosion and textural analysis studies were conducted. Fig. 4 shows that an initial increase in swelling occurred i.e. swelling degree increased from 0 to 50, followed by a dramatic increase to 300 after the sixth hour. The matrix core was completely hydrated after 6 h and hence support the rapid swelling due to the high diffusivity of the matrix. The contribution of matrix erosion towards drug release was also observed to play a role (Fig. 4). A possible advantage of the erosive behaviour as displayed by this matrix formulation, is that this tablet would not require retrieval after delivery of the drug (Martin et al., 2003). The results obtained strongly suggested a definite contribution of swelling and polymer erosion on the drug release mechanism. The data obtained is in agreement with the kinetic analysis obtained in the previous section.

3.2.3. Textural profile analysis

An examination of the hydration rates of the multipolymeric tablet matrices, can also be helpful to explore the mechanism underlying drug release and mucoadhesion. Fig. 5 provides an indication of the hydration dynamics of the statistically optimised multipolymeric tablet matrix up to 2 h. It was observed that initial rapid hydration occurs, followed by a decline probably due to the onset of matrix erosion. Despite the fact that erosion of the matrix ensued after 0.5 h ($k_1 = 0.068$), it was apparent that matrix relaxation ($k_2 = 0.119$) was still predominant (Table 4). The initial rapid hydration of the tablet may be beneficial for an enhanced mucoadhesivity and the faster drug release obtained with the multipolymeric system.

3.2.4. Surface pH evaluation

While PAAs are amongst some of the most extensively studied mucosal adhesives, a possible drawback of their incorporation is very low pH values at high concentrations of carboxyl groups (Smart, 1993). Since *in vivo* studies by Bottenberg et al. (1991) have demonstrated that a low surface pH caused damage to a contacting mucosal surface, it was therefore important in the present study to determine if any extreme surface pH changes occurred with the multipolymeric matrix tablet developed. The surface pH values obtained during 0–8 h ranged between 6.62 and 6.83 (Fig. 6). A possible explanation for the higher surface pH readings, despite the presence of a high concentration of PAA (20%), can be attributed to the inclusion of other polymers in the system. The results also indicated that while there was a relatively small increase in the pH from 6.62 at 0 h to 6.83 at 8 h, the increase in pH was within an acceptable range. These results therefore suggested that the polymeric blend identified was suited for oral application owing to the acceptable pH mea-

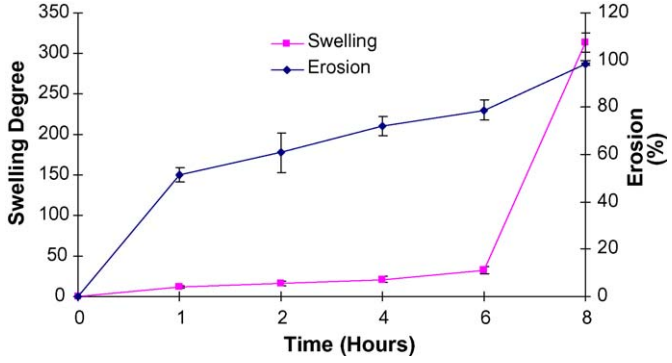

Fig. 4. Correlation of swelling and erosion profiles of multipolymeric PHCl matrices.

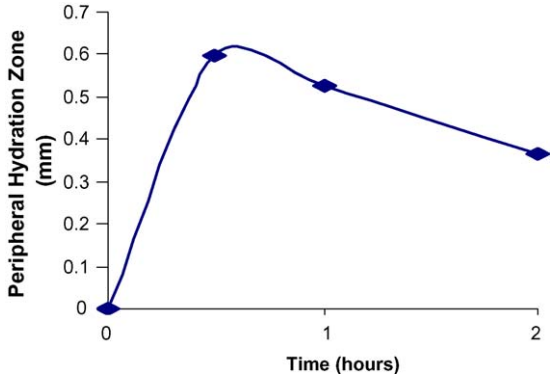

Fig. 5. Hydration dynamics of the optimised multipolymeric PHCl matrices.

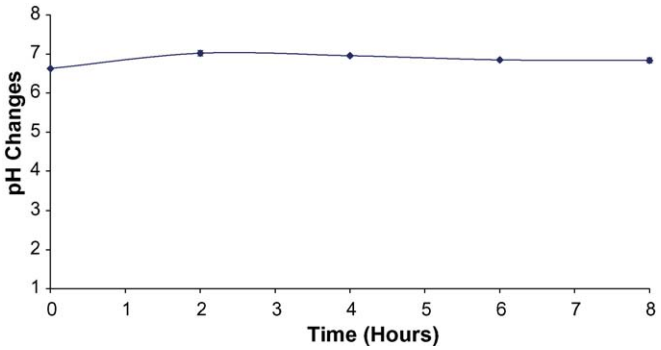

Fig. 6. Surface pH changes of the optimised PHCl matrices PBS pH 6.8.

sured. Furthermore, this pH was within the range of 5.8–7.1 for saliva in mouth (de Vries et al., 1991).

4. Conclusions

The aim of this study was to identify an optimal polymeric combination to prepare a PHCl matrix tablet with maximum mucoadhesivity. A Box–Behnken design was used for this purpose. An optimal formulation comprising of PAA (15.6%) and PVP (20%) was identified for providing a maximal MDF of 897 mN. However, the cumulative amount drug released at the end of 8 h was too low. Further modifications to this polymeric combination was attempted to enhance drug release over an 8 h period. An optimal polymeric blend of PAA (20%), CMC (20%) and PVP (20%) displayed a desired controlled release profile with 10.27% in the first hour and 84.37% drug released at the end of 8 h. Also, an MDF value of 792 mN was displayed with this formulation. It was further found that the MDF obtained for the modified formulation was statistically similar to that of the MDF model, and it also additionally exhibited a desirable controlled drug release profile. A precise polymeric combination of PAA (20%), CMC (20%) and PVP (20%), was therefore identified as the formulation providing both an enhanced mucoadhesive and controlled drug release. Reproducibility of the optimal formulation in terms of mucoadhesivity and controlled drug release was confirmed. The newly optimised tablet matrices were subsequently characterised in terms of drug release kinetics, swelling/erosion, hydration dynamics and surface pH. A kinetic evaluation of the drug release profile suggested that the mechanism of drug release was anomalous, i.e. controlled by a combination of diffusion, polymeric relaxation and erosion. The data obtained from the swelling/erosion study were in agreement with the kinetic analyses and showed that both swelling and erosion occurred. Textural profiling showed initial rapid hydration of the matrices which was considered beneficial for enhancing mucoadhesivity. Surface pH measurements confirmed that the pH was within salivary pH conditions and did not display extreme pH changes during a period of 8 h. Multipolymeric matrices proved successful in optimising mucoadhesivity and controlled release of PHCl for buccal application. Furthermore, characterisation of this newly identified formulation provided useful mechanistic insight with regards to the observed mucoadhesive and controlled drug release properties.

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