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Comparing the Mucoadhesivity and Drug Release Mechanisms of Various Polymer-Containing Propranolol Buccal Tablets

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The aims were to compare the mucoadhesivity, controlled release properties, and release mechanisms of several polymeric systems of propranolol buccal tablets and to propose polymer(s) for formulation optimization. Mucoadhesivity differences in the polymer ranking between compacts and tablets were found. Mathematical models that best described the matrices were power law or a combination of the power law and Hopfenberg models. Poly acrylic acid (PAA), carboxymethyl cellulose (CMC), and poly ethylene glycol (PEG) in combination, were identified as suitable polymers for formulation optimization of a multipolymeric propranolol buccal tablet. Artificial neural networks were employed as a confirmatory approach to explicate that the selected polymers, in particular PAA, produced the most significant effect on the mean dissolution time and mucoadhesivity.

Keywords polymers; drug release kinetics; controlled release; artificial neural networks; dissolution; mucoadhesion

INTRODUCTION

The many advantages of controlled-release buccal delivery systems include, inter alia, minimization of drug-related side effects, improved bioavailability, improved patient compliance (Bromberg, Buxton, & Friden, 2001; Sudhakar, Kuotsu', & Bandyopadhyay, 2006), and avoidance of both hepatic and intra-alimentary canal metabolism and therefore improved bioavailability (Senel & Hincal, 2001; Singh & Ahuja, 2002). Propranolol HCl (PHCl), a β-blocker used widely in the treatment of cardiovascular disorders (Corbo, Lia, & Chien, 1990), is an ideal model drug for incorporation into a controlled-release buccal formulation due to its short half-life (3 to 6 hours), low molecular weight, and extensive and highly variable first-pass metabolism following oral administration (Gomeni, Bianchetti, Sega, & Morselli, 1997). While PHCl dosage forms are being investigated currently for buccal delivery (Akbari et al., 2004; Guyot & Fawaz, 2000; Remunan-Lopez et al., 1998), no commercially available preparations are available to date. Thus, studies that contribute to formulation optimization and a mechanistic understanding of the behavior of such systems are essential for ultimately improving drug therapy.

In addition to displaying controlled drug release profiles, such delivery systems need to display prolonged retention on the mucosa, that is, mucoadhesivity. Therefore, the selection of polymers to achieve both an optimal mucoadhesivity and a suitable controlled drug release profile is an important goal in formulation optimization. Several polymers, both natural and synthetic, have been investigated for providing mucoadhesivity (Salamat-Miller, Chittchang, & Johnston 2005). Due to a possible specific drug-polymer and/or drug mucin interaction (Hombreiro-Perez et al., 2003; Remunan-Lopez et al., 1998), a comparison of polymeric systems within a specific drug delivery system is essential in the identification of polymeric

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systems for both mucoadhesion and controlled release. A specific polymer may not simultaneously possess adequate mucoadhesivity and controlled release in a drug delivery system. For example, in a study by Perugini, Genta, Conti, Modena, & Davanetto (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. There is therefore also a need for studies to simultaneously compare the mucoadhesivity and controlled-release potential of polymers in a specific drug delivery system. The above comparative studies among several polymers would be beneficial both in terms of formulation optimization, as it would facilitate the judicious selection of polymer(s) for a controlled-release buccal delivery system, as well as provide further insight into mechanisms of mucoadhesion and drug release. A comparative evaluation of the kinetics and hydration dynamics of mucoadhesive, controlled-release, polymeric-containing tablets is currently lacking in the literature. Kinetic analysis of the dissolution data by mathematic modelling will allow for the prediction of mechanisms of drug release essential for formulation modification and also for predicting in vivo behavior. Drug release and hydration dynamics studies by textural profiling can also enable identification of the mechanical properties of the polymeric delivery system and as such its integrity, thereby indicating its suitability for retention and drug delivery in the oral cavity.

In lieu of the above, during formulation development, repetition of experiments is often hindered by numerous factors. Hence, when identifying specific input formulation variables, such as the polymer type that most significantly affects the performance of a formulation, artificial neural networks (ANNs) may provide an alternative and more robust mathematical approach to confirming such findings compared with conventional linear correlation techniques. ANNs are capable of generating nonlinear input-output mappings that could produce accurate confirmation or predictions of previous results with fast and sensitive computational time.

The aim of this study was therefore to compare the mucoadhesivity and controlled release properties of several polymeric systems of a propranolol HCl matrix buccal tablet and also to identify polymer(s) for future formulation optimization of such a system. ANNs was also employed as a confirmatory approach to explicate the polymer types that may produce the most significant effect on the formulation in terms of its mucoadhesivity and its ability to influence the drug release dynamics of the formulation. Tablets containing propranolol HCl and a range of natural and synthetic polymers were prepared and characterized in terms of mucoadhesivity, drug release mechanisms, and hydration dynamics.

MATERIALS AND METHODS

Materials

Poly(acrylic acid) 2100 (Sigma-Aldrich, UK); Carboxymethylcellulose (low viscosity) (Sigma-Aldrich, UK); Chitosan (MW 110 000) (Primex Ingredients, ASA, Norway); Eudragit® RS100 (Rohm Pharma, Germany); sodium alginate (BDH Laboratories, UK); pectin (Thomas Baker Chemicals, India); poly(vinyl pyrrolidone) (MW 40 000) (Sigma-Aldrich, UK); guar gum (Sigma-Aldrich, UK); polyethylene glycol 4000 (BDH Poole, England); propranolol HCl (Frankel Chemicals, SA); and mucin (Sigma-Aldrich, UK) were purchased and used as received. All other chemicals used were of analytical or reagent grade.

Methods

Preparation of Various Formulations

Both natural and synthetic polymers were investigated in this study and included the following: sodium alginate (ALG), carboxymethyl cellulose (CMC), chitosan (CHITO), Eudragit® RS100 (EUD), guar gum (GUAR), poly(acrylic acid) (PAA), pectin (PECT), poly(ethylene glycol) 4000 (PEG) and poly(vinyl pyrrolidone) (PVP). These individual polymers were specifically chosen since they are widely used in the literature for mucadhesivity and or controlled drug release formulations. Compacts and tablets were prepared, each containing a different polymer for comparison. The comparative data obtained in the study and the subsequent discussion apply to the molecular weights of the polymer specifically used in this study.

A preliminary screening procedure together with ANN optimization was employed to select three polymers for providing enhanced mucoadhesion and controlled drug release. Since prolonged retention is associated with higher mucoadhesivity values (Yong, Jung, Rhee, Kim, & Choi, 2001; Yun, Choi, Jung, & Kim, 1999), polymers with higher mucoadhesivity values in relation to each other were considered most suitable for enhanced mucoadhesion. High drug release initially is not desirable due to dose dumping, while overly retarded drug release is not desirable from a cost perspective. For the purposes of this study, a polymer combination most likely to provide a controlled drug release profile with less than 25% to 30% release in the first hour and at least 60% release by the fourth hour was considered appropriate. Therefore, polymers with release profiles showing potential for the above were chosen.

Preparation of Polymer Compacts. It was important to determine the mucoadhesivity of individual polymers for subsequent comparison with their incorporation into drug-containing tablet matrices. Flat-faced compacts containing each polymer only (30 mg) were prepared using a Carver press (Beckman, Scotland).

Preparation of Polymeric Mucoadhesive Matrix PHCl Tablets. Flat-faced tablets (300 mg) 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 to 90N (Pharma Tester PTB 311, Germany). These parameters ensured that a friability of < 1% was maintained (BP, 2002). Tablets from each batch formulated were composed of PHCl (80 mg) (26.67%), a polymer (10%), magnesium stearate (1%), and dicalcium orthophosphate (62.33%). Each batch contained a different polymeric component and these tablets were then subjected to routine quality control analysis tests for friability and assay determinations, prior to further characterization. A formulation composed of PHCl (80 mg) (26.67%), magnesium stearate (1%), and dicalcium orthophosphate (72.33%) was prepared. The lack of a polymeric component rendered the control formulation an ideal reference (negative control) for performing comparative analyses of mucoadhesion and drug release data.

Quality Control

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

Friability. A standard friability test as described in the British Pharmacopoeia (BP) (2002) was undertaken using an Erweka Friabilator (Germany). A friability of 1% was set as the upper limit of acceptability.

Characterization of the Various Matrix Tablet Formulations

Determination of In Vitro 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/compact was attached to one side of a double-sided metal disk using cyanoacrylate adhesive. The tablet surface was hydrated with 15 μL PBS pH 6.8 for 3.5 minutes. The double-sided disk containing the tablet was then attached to the Lutron force gauge via a nonelastic connector and brought into contact with the mucin. After 5 minutes the tablet surface was separated from the mucin (15 mm/min), using a crosshead pulley until a peak detachment force was obtained. The $M \pm SD$ of 10 individual replicates was expressed as the force required to separate the tablet from the mucin (maximum detachment force [MDF]). As a control for the tablets, the mucoadhesion experiments were conducted on tablet matrices containing PHCl, magnesium stearate, and dicalcium orthophosphate only (i.e., matrices containing no mucoadhesive polymers).

In Vitro Drug Release Studies. 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 ºC) (Erweka DT6R, Germany). At the end of predetermined time intervals (e.g., 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, and 8 hours), 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). A total of three replicate determinations for each batch were performed.

Modeling of Drug Release Data. Kinetic analysis of the drug release data was performed using WinNonlin Version 3.1 (Pharsight, California) and was based on nonlinear regression. In all least squares analyses, the Guass-Newton (Levenberg-Hartley) approach was adopted. The power law expression ($M_t/M_\omega = kt^n$) (Peppas & Sahlin, 1989), its variant incorporating a relaxational parameter ($M_t/M_\omega = k_1t^n + k_2t^n$), and the Hopfenberg's model ($M_t/M_\omega = 1- [1- kt]^n$) (Hopfenberg, 1976) were applied to the drug release data for model fitting purposes. The method employed the estimated variance-covariance matrix of the parameters and therefore it was chosen as a suitable method for the kinetic modeling of the in vitro release data obtained in this study. The release rates were further analyzed by the strong parametrical support from statistical descriptors such as the Akaike Information Criterion (AIC), Schwartz Bayesian Criteria (SBC), and the Condition Number (CN).

Textural Profile Analysis. The textural profile analysis studies were undertaken using a 25-kg load cell (Texture Analyser XT2í, 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, pretest and posttest speeds of 2 mm/sec, and a test speed of 1 mm/sec. 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 PBS pH 6.8 and maintained at a temperature of 37ºC for the duration of the study. Samples were removed in triplicate at predetermined time intervals and subjected to textural analysis. Tablets that disintegrated soon after contact with the medium, by virtue of their poor integrity, were considered unsuitable for textural profiling.

Optimization by ANN for Polymer Selection. A feedforward Multilayer Perceptron (MLP) neural network was employed to train the empirical data with static backpropagation. For the hidden and output layers, a genetic algorithm with the SigmoidAxon transfer function and ConjugateGradient learning rule was employed. A maximum of 1,000 epochs were run on NeuroSolutions Version 5.0 (NeuroDimension Inc., Gainsville, Florida) to ensure optimal training of data. Sensitivity analysis was used for extracting the cause and effect relationship between the inputs and outputs of the network. This provided feedback as to which input variable was the most significant by

TABLE 1
Artificial Neural Network Parameters
Employing Neural Builder

Parameter	Setting
Hidden layers	1
Exemplars	9
Transfers (hidden/output layers)	SigmoidAxon
Learning rule	ConjugateGradient
Maximum epochs	1,000
MSE threshold	0.01

testing the network with regard to its sensitivity about the mucoadhesivity and mean dissolution time (MDT) for each formulation and thus elucidating the polymer type that was most significant. The MDT is defined as the sum of different release fraction periods (release areas) during dissolution studies divided by the initial loading dose as calculated by the following equation (Kim & Fassihi, 1997):

$$MDT = \sum_{i=1}^{n} ti \frac{Mt}{M\infty}$$

Mt is the fraction of dose released in time *ti* = (ti + ti – 1)/2 and M_∞ is the total amount of drug released.

Input data was pruned by eliminating insignificant variables in order to reduce the size of the network and increased the accuracy of data modeling. Table 1 lists the parameters used for constructing the neural network simulation.

RESULTS AND DISCUSSION

Quality Control Tests on Matrix Tablets

All batches of tablets prepared were within the assay limits of 95% to 105% and friability limits of < 1%.

Characterization of the Various Polymeric Formulations

Mucoadhesivity Measurements

It was necessary to compare the mucoadhesive ability of the control formulation, polymer compacts, and the polymeric tablet dosage form in order to establish the effect of PHCl and the excipients on in vitro MDF measurements.

While it was not possible to manufacture compacts of GUAR, the MDF values for the various polymer compacts, arranged in descending rank order, were PVP, PAA, CMC, ALG, PECT, CHT, PEG, and EUD. While PVP, PAA, and CMC compacts produced considerably higher MDF values than those of the control formulation, polymer compacts of CHITO, EUD, PEG, ALG, and PECT appeared to have considerably lower MDF values than PVP, PAA, and CMC, and even the control formulation without a polymeric component. The lower mucoadhesive values associated with these polymer compacts could be related to the presence of water during contact between the mucin and polymer. In addition to exposure to water during prehydration, an additional amount of water may have been further present as water was extracted from the mucus gel on contact. The presence of excessive water would have resulted in a rapid hydration of the polymer and subsequent formation of a gel and, eventually, a "slippery mucilage" and hence low mucoadhesivity (Gurny, Meyer, & Peppa, 1984; Thirawong, Nunthanid, Puttipipatkhachorn, & Sriamornsak, 2007). The higher hydration capacity of Eudragit as compared with CMC and PAA matrices is indeed confirmed later in the textural profile analysis (TPA) studies.

The results for the various PHCl matrix tablet formulations showed that the MDF values were in the following order: PAA, CHITO, CMC, EUD, PEG, PVP, ALG, PECT, GUAR (Figure 1). Clearly, the rank order of adhesiveness between the polymer compacts and the tablet matrices differed. The MDF for EUD, CHITO, and PEG was found to be significantly greater in the presence of drug and excipients as opposed to the compacts alone. The lower mucoadhesive force associated with compacts for the above polymers may be related to an overhydration of the compacts at the surface, thereby producing small adhesive forces. With the matrix tablets, it was assumed that the incorporation of PHCl may have caused a competition for water uptake between drug and polymeric component (Pillay & Fassihi, 2000). This effect subsequently resulted in a restricted water uptake by polymer, thereby allowing optimal polymer disentanglement and subsequent entanglement between polymer and mucin, thus promoting stronger adhesive interactions. An increase in mucoadhesion with the incorporation of drug into a polymeric system has also been reported for the drug clotrimazole in another study (Kast, Valenta, Leopold, & Bernkop-Schnurch, 2002). Matrices containing PAA, CMC, and PVP showed a substantial decrease (22% to 88%) in adhesive force as compared with their compact forms (Figure 1). A reason for the lower mucoadhesivity of these specific polymeric tablet matrices when compared with the compacts may be due to the drug–polymer interactions, which could have reduced the number of interacting sites of the specific polymer with mucin.

As expected, considerable differences in mucoadhesivity among the various tablet formulations themselves were also evident (Figure 1). MDF values for ALG, GUAR, PECT, and PVP matrix formulations were actually lower than that for the control formulation. For example, the magnitude of the MDF for Alginate (ALG), which was 211.25 ± 67.06 mN, may result in poor mucoadhesivity for a PHCl formulation. This observation, however, was contrary to the findings reported for omeprazole tablets where ALG was found to bind strongly with the oligosaccharide chains and was found to possess the best mucoadhesive force (Choi & Kim, 2000). Similarly, PECT (208.75 ± 59.86 mN) also demonstrated poor mucoadhesive properties, which was inconsistent with the findings of

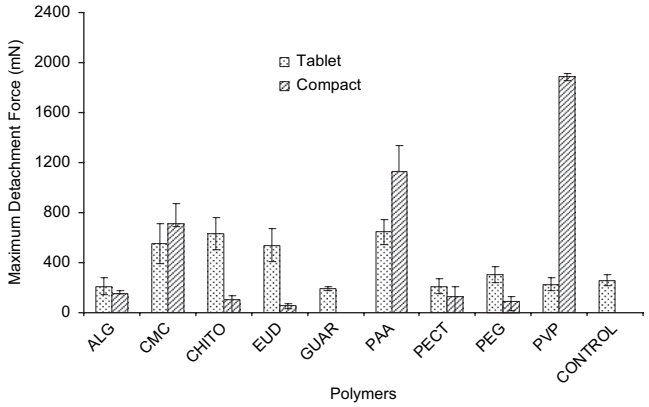

FIGURE 1. A comparison of the mucoadhesivity of compacts and PHCl matrix tablets containing various polymers (n = 10).

Miyazaki and coworkers (Miyazaki et al., 2000), who evaluated diltiazem HCl tablets. The results of the present study for ALG and PECT containing matrices of PHCl differed from those reported in the literature, possibly due to the incorporation of different active ingredients and drug.

Of the nine polymers investigated in this study, it was found that PAA-containing matrices displayed the highest mucoadhesivity overall. The results showed differences in mucoadhesivity between the compacts and tablet matrices, as well as differences from findings reported in the literature. This emphasizes the need for selective identification of mucoadhesive polymers for a specific drug and delivery system.

In Vitro Drug Release Studies

Natural Polymer Matrices. Tablets incorporating the specific natural polymers studied (ALG, CHITO, PECT, and GUAR) disintegrated instantaneously (within 10 minutes) upon introduction into the dissolution vessel (Figure 2). Due to the poor integrity of the dosage forms, these specific natural polymers on their own were therefore considered unsuitable as homopolymeric systems for use in formulation optimization of a buccal, controlled-release, mucoadhesive delivery system. Although CHITO has provided controlled release of other drugs (Perugini et al., 2003; Ritthidej, Chomto, Pummangura, & Menaosveta, 1994), it failed to promote controlled release of PHCl in this study. Nigalaye, Adusumilli, & Bolton (1990) reported that concentrations less than 33% led to a fast-releasing matrix and at concentrations less than 10%, CHITO acted as a disintegrant. The observations in this study, together with those reported in the literature, suggest that CHITO cannot be used at low concentrations such as 10% for controlled release of PHCl in a dissolution medium of pH 6.8.

Although GUAR- and ALG-based matrices disintegrated almost immediately upon placement in the dissolution medium, the drug release was slower than expected. This may be due to a possible weak cross-linking between drug and GUAR that may account for the observed retarded drug release. Also, with the ALG formulation, a visible gel layer over the drug and polymer mass was observed, even after disintegration. The gel formation could have contributed to retardation of the drug release despite the disintegration of the dosage form.

Synthetic Polymer Matrices. With respect to the synthetic polymer–containing matrices (Figure 3), the release of PHCl demonstrated the following trend, in order of increasing drug release rate: PAA, PEG 4000, CMC, PVP, EUD. From the results obtained, it was observed that for EUD-containing matrices the release rate was most rapid, with almost 95% of the drug being released within 4 hours. The incorporation of sodium CMC (Figure 4) demonstrated not only mildly retarded

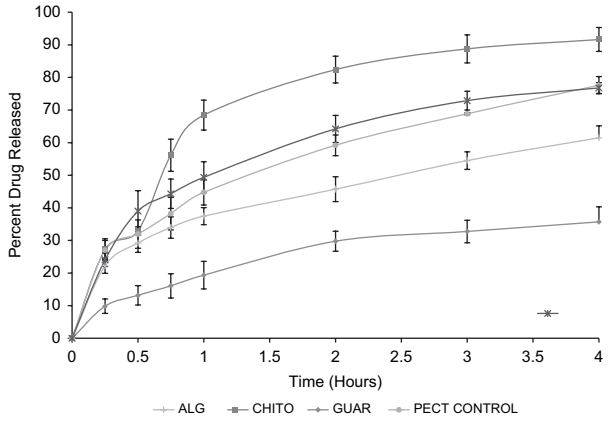

FIGURE 2. Drug release profiles of PHCl buccal tablets containing natural polymers (n = 3).

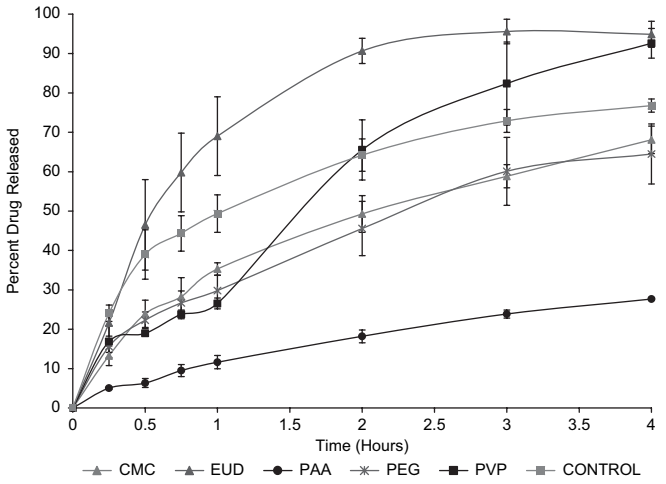

FIGURE 3. Drug release profiles of PHCl buccal tablets containing synthetic polymers (n = 3).

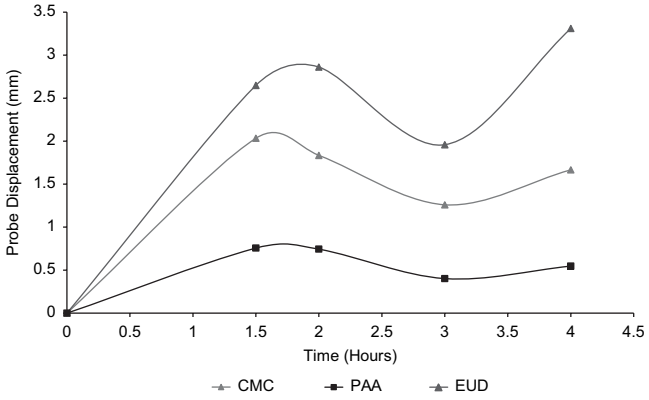

FIGURE 4. Effect of polymers on the hydration dynamics of PHCl buccal tablets.

release (68.08% ± 3.48%) of PHCl, but also maintenance of the integrity of the dosage form. This may be attributed to ionic interactions between the amine group of the drug molecules and the carboxyl groups of the cellulose. This postulation can be supported by experimental findings reported in the literature by others (Freely & Davis, 1988; Ranga-Rao, Padmalatha, & Buri, 1990).

PAA, compared with other polymer systems (Figure 3), displayed a drug release of 11.63% ± 1.68% at the end of the first hour, which was clearly the most retarded effect on the in vitro dissolution of PHCl. This distinctly slow release rate corresponded to the induction time required by PAA before starting to dissolve (Narasimhan, 2001). The decreasing drug release rate with time may possibly be due to the slow erosion of the outer gel layer of PAA-containing matrices, which subsequently increased the diffusional path length for the drug with time, thereby decreasing the drug release rate.

The results obtained (Figures 2 and 3) demonstrated that the natural polymeric additives investigated in this study, for example ALG, CHITO, GUAR, and PECT, all disintegrated rapidly, while the synthetic polymers (PAA, PEG 4000, CMC, PVP, EUD) maintained the dosage form integrity for longer periods in the dissolution medium (PBS, pH 6.8). Furthermore, various polymers at an equivalent concentration of 10% had varying effects on modifying drug release. Due to their ability to maintain the dosage form intact throughout the period of study, which would be essential for prolonged mucoadhesivity and controlled drug release, it was suggested that the specific synthetic polymers used in this study could be best suited to modify drug release for a PHCl buccal tablet formulation.

Mechanistic Analyses of Drug Release Kinetics

Table 2 summarizes the important model fitting and statistical parameters for release kinetics from CMC, EUD, PAA, PEG, and PVP polymeric tablet matrices. Polymeric systems containing ALG, CHITO, PECT, and GUAR were excluded from the kinetic analyses since these models should not be used for such systems that disintegrate but show controlled drug release. Studies on binding interactions could be studied to elucidate their mechanism.

The kinetic constant k ranged between 0.114 and 0.619, which indicated the existence of considerable variability in drug release among the different formulations. This observable difference amongst the matrices was expected, as the selected polymers differed in terms of their physicochemical characteristics.

From the model fitting, it was observed that the simple exponential expression ($M_t/M_\omega = kt^n$) provided release exponents (n values) ranging from 0.380 to 0.756. This indicated that drug release from most polymers was not regulated primarily through the process of diffusion, but rather through both the mechanisms of diffusion and polymer relaxation.

Tablet matrices comprising CMC and PEG produced release exponents of 0.521 and 0.536 respectively, which indicated a Fickian-type release mechanism. The mechanism of drug release from PEG-containing matrices correlated with the data presented by Mandal (2000). That study also indicated that the release exponent pointed towards the predominance of a Fickian diffusion mechanism of release from hydrogels prepared with PEG using miconazole nitrate formulations for controlled delivery.

However, on the basis of the application of the geometry-independent bi-exponential expression ($M_t/M_\omega = k_1t^n + k_2t^n$), it became apparent that through separation of the release constant into Fickian and relaxational components, the magnitudes of the Fickian diffusion constant (k_1) ranged between $3*10^{-6}$ and 0.007, and case II relaxation constant ranged between 0.114 and 0.611. This data revealed that the mechanism of drug release was predominantly polymer relaxation/erosion, with a relatively minor contribution of diffusion as well. In view of the k_2/k_1 ratios (Table 2), the magnitude of the data obtained strongly supported the dominance of polymer relaxation controlling the drug release mechanism. However, a lower ratio for PEG-containing matrices compared with CMC, PVP, and EUD matrices was obtained.

Using a release exponent of 2 in the Hopfenberg model ($M_t/M_\omega = 1- (1- kt)^n$ as a user defined parameter, k_1 values obtained ranged from 0.042 to 0.355. The following trend of surface erosion was apparent. In descending order: EUD, PVP, CMC, PEG, PAA. As k_1 incorporates the erosion constant k_0, it was evident that all polymers tested displayed matrix erosion to different extents.

The release mechanisms from the three equations were further analyzed by the strong parametrical support from pertinent statistical descriptors such as the AIC, SBC, and CN. The CN value refers to the matrix of partial derivatives. Very large CN values may be indicative of instability in the model fitting process. The AIC and SBC values are a measure of goodness of fit based on maximum likelihood. When comparing several models for a given set of data, the model associated with the

TABLE 2
Drug Release Kinetic Data Derived from Various Mathematical Models

Polymer and Equation	Kinetic Parameters						
	k_1	k_2	k_2/k_1	n	AIC	SC	CN
CMC							
kt^n	0.340	–		0.521	–47.771	–49.691	4.773
$k_1t^n + k_2t^n$	$3*10^{-6}$	0.334	111353.67	0.260	–45.771	–48.652	123.500
$1 – (1 – k_1t)^n$	0.132	–		2	–21.982	–22.942	1.120
EUD							
kt^n	0.619	–		0.380	–20.008	–21.929	2.567
$k_1t^n + k_2t^n$	0.006	0.611	888.983	0.191	–17.992	–20.873	227
$1 – (1 – k_1t)^n$	0.355	–		2	–19.342	–20.302	1.790
PAA							
kt^n	0.114	–		0.648	–65.901	–67.821	14.740
$k_1t^n + k_2t^n$	0	0.114	-	0.324	–63.901	–66.782	109.60
$1 – (1 – k_1t)^n$	0.042	–		2	–40.389	–41.349	1.380
PEG							
kt^n	0.315	–		0.536	–46.707	–48.627	5.086
$k_1t^n + k_2t^n$	0.007	0.308	42.037	0.271	–44.709	–47.590	119.200
$1 – (1 – k_1t)^n$	0.124	–		2	–23.255	–24.215	1.560
PVP							
kt^n	0.340	–		0.756	–27.366	–29.287	6.122
$k_1t^n + k_2t^n$	$2.4*10^{-5}$	0.340	14202.667	0.378	–25.366	–28.247	81.090
$1 – (1 – k_1t)^n$	0.188	–		2	–31.804	–32.764	1.240

smallest value of AIC or SBC is regarded as giving the best fit. Table 3 provides an indication of the model(s) that best describes each system.

It was apparent that most systems followed Fickian release, if not a combination of Fickian and erosion type release, as was expected based on the complexity of the dissolution process.

TABLE 3
Summary of Model Fitting

Polymer	Power Law(kt^n)	Hopfenberg's Model $(1 – (1 – k_1t)^n$
ALG	*	
CMC	*	
CHITO	*	*
EUD	*	*
GUAR	*	
PAA	*	
PECT	*	
PEG	*	
PVP	*	*

*Selected model[s] based on n values.

Textural Profile Analysis (TPA)

TPA was undertaken to determine the hydration dynamics of the compacts. Polymer-containing matrices that disintegrated within the 4 hours of dissolution testing in this study were not subjected to textural analysis. The following order in terms of increasing matrix plasticity was apparent for the following polymer matrices: EUD, CMC, PAA (Figure 4). The greater probe displacement (PD) of the EUD matrices was indicative of their greater hydration capacity, as supported by the drug release profile (Figure 2). Interestingly, the PD did not increase for all polymer systems throughout the test period, as was expected. This may be due to a "heterogenous hydration rate," that is, after a peak PD at the matrix core (1.5 to 2 hours) and a subsequent decrease due to a lower extent of hydration (2 to 3 hours), hydration of the previous core layers (constituting the new peripheral layers) was facilitated, and the PD therefore increased from 3 hours onwards. Interestingly, the MDF values for these three polymers were in the order of EUD, CMC, PAA, which was in the reverse order of its hydration capacity, EUD, CMC, PAA. This suggested that mucoadhesion was controlled by some extent by its water uptake and swelling capacity. For example, with EUD-containing matrices the extent of hydration was the greatest while the mucoadhesivity was the lowest. On the other hand, for PAA matrices the

hydration capacity was the lowest and the MDF was the highest. It was therefore postulated that excess hydration decreased the MDF and that a lower hydration capacity instead was positively related to MDF. This indicated that the chemical forces of interaction may be more dominant than hydration-induced gelation and chain disentanglement in the promotion of mucoadhesion by these polymers.

Identification of Polymers for Future Incorporation Into a Mucoadhesive Controlled-Release PHCl Matrix Tablet

A system with both maximum mucoadhesivity and an appropriate controlled release profile would be essential for a mucoadhesive controlled release buccal PHCl tablet. Although PAA displayed the highest mucoadhesivity when compared with the other polymers, further maximization of mucoadhesivity using increasing PAA concentrations could not be achieved (data not shown). An increase in polymer concentration increased the mucoadhesivity up to a certain level (10%), but then it decreased at higher concentrations of 20% and 30%. Similar decreases in mucoadhesivity with high concentrations of a specific polymer have been reported elsewhere (Gurny et al., 1984). Increasing concentrations also retarded the drug release to a much greater extent than required. Too slow drug release is undesirable from a cost perspective as greater amounts of drug would be required in the unit dosage form, thereby increasing the cost of the product. While PAA showed potential, it was however not suitable for simultaneously providing maximum mucoadhesivity and a desired controlled release profile over 8 hours. Therefore, a homopolymeric system of a PHCl buccal tablet matrix could not be considered feasible for providing both maximal mucoadhesivity and a desired controlled release profile over 8 hours. Based on the mucoadhesivity and drug release data obtained for the various polymers, the use of PAA in combination with other polymers would have to be considered. The selection of three suitable polymers for formulation into a mucoadhesive controlled-release PHCl tablet was therefore considered and based on those that would provide a combination of good dosage form integrity (in terms of remaining intact for a desired time period), high in vitro mucoadhesivity, and appropriate drug release characteristics. For instance, the natural polymer-containing matrices of the specified molecular weights and quantities used in this study (ALG, CHITO, GUAR, and PECT), which displayed adequate mucoadhesivity but disintegrated soon after contact with the dissolution medium, were not selected for further analysis on the basis of poor dosage form integrity and too rapid drug release, which is unsuited for controlled drug delivery over an 8-hour period. The synthetic polymers, however, displayed improved characteristics with regard to drug release and mucoadhesivity to varying extents, for example PAA-containing matrices (645 ± 99.85 mN). This polymer was selected, by virtue of its high mucoadhesivity, for incorporation into a polymeric blend. The second polymer chosen was CMC, due to its good in vitro mucoadhesivity with an MDF of 551.25 ± 158.50 mN, and improved drug release properties with up to 68.08% ± 3.48% PHCl being released at the end of 4 hours. Lastly, PEG was chosen since this polymer demonstrated the next highest highest mucoadhesivity (303.75 ± 64.12 mN) and controlled-drug release profile. EUD was not chosen despite its slightly higher mucoadhesivity due to its too rapid drug release. These three polymers, PAA, CMC, and PEG, may be incorporated into a multipolymeric mucoadhesive controlled-release PHCl tablet for formulation optimization.

Selection of Polymer Combinations as per ANN Optimization

Results indicated that for non-disintegrant polymers in the study, the MLP network was able to accurately confirm that PAA, CMC, and PEG were the most significant input variables in terms of both mucoadhesivity and drug release of the buccal tablet formulation based on empirical data. The approach reported in this work required prior assumption for the selection of a mathematical model before applying the ANN models, to confirm sensitivity coefficients of the various polymer types as input variables that significantly contributed to characterizing the mucoadhesivity and drug release dynamics. The gradual levelling of the mean square error (MSE) with *SD* boundaries for the training runs indicated the sequential improvement of data modelling and is illustrated in Figure 5. Table 4 reflects the average MSE values for all training runs, the best network run out of 1,000 epochs, and the overall efficiency and performance of the neural network during data training. Overall, it is evident that the training model employed

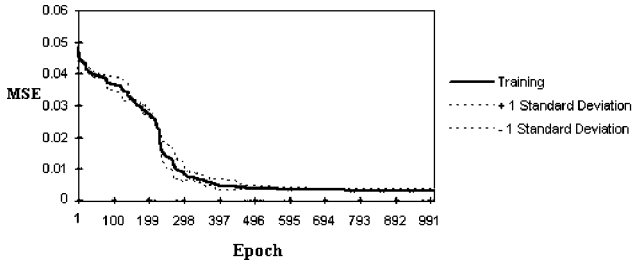

FIGURE 5. Average MSE with standard deviations for 1,000 epochs.

TABLE 4
Neural Network Indicators Characterizing the Efficiency and Performance of Data Training

Best Network	Training	Performance	MDT
Epoch #	1,000	MSE	0.030
Minimum MSE	0.002	NMSE	0.051
Final MSE	0.002	MAE	0.105
R^2	–	–	0.974

TABLE 5
Statistical Performance Indicators of the Modeling Process as per ANN

Criterion	Mean Dissolution Time	Mucoadhesivity
MSE	0.14	4320.59
NMSE	0.23	0.13
Min Abs Error	0.01	7.59
Max Abs Error	0.74	124.00
R^2	0.98	0.97

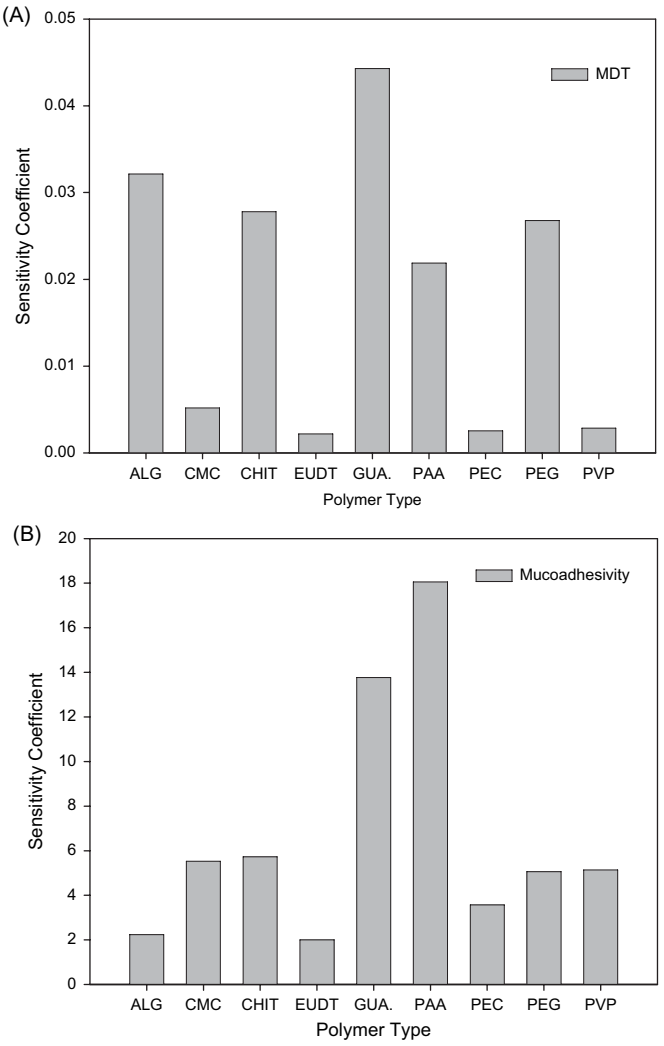

FIGURE 6. Typical bar graphs depicting the sensitivity coefficients of each polymer type on the (A) mean dissolution time and (B) mucoadhesivity.

was highly efficient (MSE = 0.002). The parameters depicted in Table 4 are standard statistical indicators used by scientists involved in neuro-computing to quantitate the accuracy of a model. Results revealed a highly satisfactory fit for the input variables (R^2 = 0.98 and R^2 = 0.97 for MDT and mucoadhesivity, respectively). Table 5 lists the performance criterion employed to assess the closeness and correlation between the actual and desired network output for the MDT and mucoadhesivity values obtained from each formulation. The sensitivity coefficients of each polymer type (input variables) on the MDT and mucoadhesivity are depicted in Figures 6a and 6b. While the three most significant input variables that affected the drug release dynamics were GUAR, ALG, and CHT (Figure 6a), these matrices disintegrated during the dissolution test and cannot be considered suitable for prolonged retention on the mucosa. Hence, the following three polymers with the most significant input variables were PAA, PEG, and CMC. The sensitivity coefficient data of each polymer on the mucoadhesivity (Figure 6b) showed that PAA and GUAR were the most significant variables and that again PEG and CMC followed closely. Since GUAR was considered unsuitable due to its disintegrant properties, the three common polymers identified for optimal mucoadhesivity and controlled drug release were PAA, PEG, and CMC. In this regard it may be envisaged that an appropriate combination/permutation of PAA, PEG, and CMC may produce a polymeric matrix that displays both superior mucoadhesivity and rate-controlled drug release.

CONCLUSIONS

A comprehensive comparative analysis of several polymers for a PHCl buccal tablet matrix was undertaken in terms of their mucoadhesivity, controlled-release profiles, drug release kinetics, and hydration dynamics. The results of this study have contributed to a mechanistic understanding of mucoadhesive-controlled drug-release polymeric matrix tablets. It has also simultaneously highlighted polymeric effects on both the mucoadhesivity and drug release properties of a PHCl buccal tablet; and variability between reports in the literature highlighted their dependence on the specific drug delivery system under investigation. Together with ANNs modeling, the study identified three polymers,. PAA, CMC, and PEG, that could be used for formulation optimization of a multipolymeric propranolol HCl tablet for buccal delivery.

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