Development and evaluation of controlled-release buccoadhesive verapamil hydrochloride tablets

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ABSTRACT

Background and purpose of the study: Verapamil hydrochloride is a calcium channel blocker which is used in the control of supraventricular arrhythmia, hypertension and myocardial infraction. There are considerable inter-individual variations in serum concencentration of verpamil due to variation in the extent of hepatic metabolism. In this study controlled-release buccoadhesive tablets of verapamil hydrochloride (VPH) were prepared in order to achieve constant plasma concentrations, to improve the bioavailability by the avoidance of hepatic first-pass metabolism, and to prevent frequent administration.

Materials and methods: Tablets containing fixed amount of VPH were prepared by direct compression method using polymers like carbomer (CP), hydroxypropylmethyl cellulose (HPMC) and sodium carboxymethyl cellulose (NaCMC) in various combination and ratios and evaluated for thickness, weight variation, hardness, drug content uniformity, swelling, mucoadhesive strength, drug release and possible interaction between ingredients.

Results: All tablets were acceptable with regard to thickness, weight variation, hardness, and drug content. The maximum bioadhesive strength was observed in tablets formulated with a combination of CP-NaCMC followed by CP-HPMC and NaCMC-HPMC. Decreasing the content of CP in CP-HPMC tablets or NaCMC in CP-NaCMC or NaCMC-HPMC systems resulted in decrease in detachment forces. Lower release rates were observed by lowering the content of CP in CP-HPMC containing formulations or NaCMC in tablets which contained CP-NaCMC or NaCMC-HPMC. The release behavior was non-Fickian controlled by a combination of diffusion and chain relaxation mechanisms and best fitted zero-order kinetics.

Conclusion: The buccoadhesive VPH tablets containing 53% CP and 13.3% HPMC showed suitable release kinetics (n = 0.78, K_0 zero order release = 4.11 mg/h, MDT = 5.66 h) and adhesive properties and did not show any interaction between polymers and drug based on DCS scanning. This buccoadhesive system may be useful for buccal administration of VPH.

Keywords: Verapamil hydrochloride, Controlled-release, Buccoadhesive tablets

INTRODUCTION

Verapamil hydrochloride (VPH) is a calcium-channel blocker and a class IV antiarrhythmic agent used in the control of supraventricular arrhythmias, and in the management of angina pectoris, hypertension and myocardial infarction (1,2). The VP serum concentration differs from 20 to 500 ng/ml depending on the administered dosage form and there is considerable inter-individual variation, which might be, in part; due to variation in the extent of hepatic metabolism (2-4). The oral absorption of the drug from oral dosage forms is about 90% but it is subjected to a very extensive first-pass metabolism in the liver (6) and its bioavailability is only about 20% (2, 5, 7). Since this drug has a short elimination half-life of 2 - 4 hours and is eliminated rapidly, repeated daily administration are required to maintain effective plasma levels (8). It has been suggested that drugs with biological half lives in the range of 2-8 hours are good candidates for sustained-release formulations (9). VPH slow release tablets in doses of 120 to 240 mg and controlled-onset extended release tablets in doses of 180 and 240 mg are available (10,11). Osmotic controlled-release oral delivery system (12), per-oral matrix,

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bioadhesive and novel chewable sustained-release tablets (13-16), microcapsules (17), coevaporate in polymer systems (18), coated pellets, floating tablet and capsules (19-21), matrix diffusion controlled transdermal patch (22), controlled-onset extended-release system (23), waxy microparticles prepared by spray congealing (24) are controlled-release forms of this drug which have been reported. The short half life and extensive first pass metabolism of VP makes it a suitable candidate for administration via a buccal delivery system that provides controlled drug delivery without pre-systemic metabolism. The buccal route offers many advantages including good accessibility, robustness of epithelium, non-keratinized mucosa, dense capillary vessel network, large drug absorption area, easy removal of the dosage form, low enzymatic activity, patient acceptance, lack of the hepatic first pass metabolism, reduced costs of the drug, better control of plasma levels, lower variation in bioavailability, better management of the patient, fewer side effects, and minimum fluctuations (25-28).

From a technological standpoint, an ideal buccal delivery system must possess three characteristics: a) remains in the oral cavity for a few hours to maximize the proximity of contact with mucosa; b) releases the drug in a controlled fashion under the conditions dominant in the mouth; and c) overcomes the low permeability of the oral mucosa (29). With regard to the first requirement, strong adhesion of the system to the buccal mucosa can be achieved by using appropriate combinations of mucoadhesive polymers. If these mucoadhesive polymers would be able to control drug release, the second requirement is also achieved. Therefore, the first step in the development of a buccal delivery system is selection of appropriate adhesives (25, 30). The third requirement may be fulfilled by preparation of a system having uniform adhesives.

While delivery of various therapeutic agents via the buccal route by conventional matrix tablets, films, bilayered and hydrogel systems have been reported (31-35), development of a buccoadhesive controlled-release formulation of VPH has not been documented. The aim of this study was, design, development and characterization of a buccoadhesive controlled-release tablet of VPH using some selective polymers like carbomer 934P (CP), hydroxypropylmethyl cellulose K4M (HPMC), and sodium carboxymethyl cellulose (NaCMC). Also the interaction between polymers and drug-polymers, bioadhesion and in vitro release characteristics of VPH from different buccoadhesive matrix tablets was evaluated to assess the suitability of such formulations.

EXPERIMENTAL

Materials

The following materials were used:

Verapamil hydrochloride (Sigma Chemical Co. St Louis, MO, USA), Carbomer 934P (Carbapol B. F. Goodrich, Belgium, MW 3×10^6, the viscosity of its neutralized 0.5% dispersion is 39400 cps), Hydroxypropylmethyl cellulose (Methocel K4M CR Premium USP/EP, Colorcon, England. Viscosity of its 2% solution is 4000 cps at 25°C), Sodium carboxymethyl cellulose (Netherland GO 2002, MW 7×10^5, the viscosity of its 1% solution is 1200 cps), Sodium alginate (BDH chemicals Ltd., Poole, UK), Potassium dihydrogen phosphate, Disodium hydrogen phosphate, Hydrochloric acid, Agar Agar (Merck, Germany)

Methods

Formulation of buccoadhesive tablets

Controlled-release buccoadhesive tablets were prepared by direct compression method using the formula shown in Table 1. Different ratios of CP, HPMC, NaCMC, fixed amount of VPH and 1% magnesium stearate were passed through a No. 85 sieve and mixed in mortar with a pestle to obtain uniform mixing. The blended powder were compressed into tablets weighing 150 mg on a single punch tablet machine (KS 43373-202 Kilian Co, GMBH, Koln-Niehl) using a flat-faced non-beveled punch and die set of 12-mm diameter.

Evaluation of physical properties of mucoadhesive tablets

The thickness, hardness, and weight uniformity were determined in a similar manner as stated for conventional oral tablets in the accredited pharmacopoeia (36).

Drug content uniformity

Drug content uniformity experiments were carried out by the procedure stated in the US pharmacopoeia (36).

Swelling studies

Each four tablets which was individually weighed (W_1) were placed on the surface of the agar gel (1% w/v) in a Petri dish (totally 7 Petri dishes) and incubated at 37º C. At time intervals of 0.5, 1, 2, 3, 4, 5, 6 hrs one Petri dish was removed from the incubator and swollen tablets were weighed out (W_2). Swelling index (SI) was calculated (37) using following formula.

$S1=(W_2-W_1)/W_1$

Bioadhesion experiments

A: Modified Fisher's tensiometer

A modified tensiometry method using Fisher's tensiometer (Fisher Scientific Co., Autotensiomat, Model 215 USA) (38) was used to assess the bioadhesiveness of tablets (Fig. 1). The buccoadhesive tablets were attached to a thin mica disk which was connected to the tensiometer ring and lowered until the tablet surface came in contact with 1% (w/w) sodium alginate solution and then was detached from the gel substrate by the speed of 0.2 inch per minute. The maximum force required for detachment of the tablet from the gel was measured in terms of dyn/cm^2. The test was performed six times on different tablets.

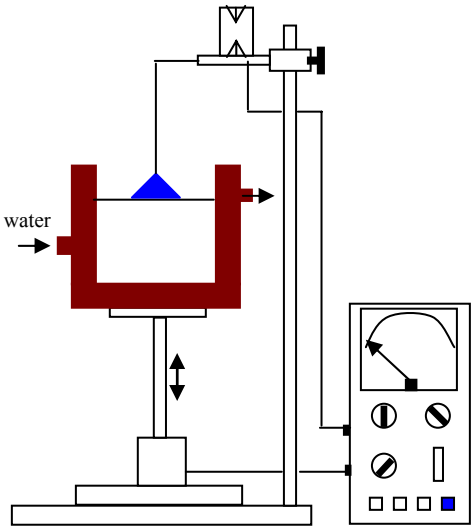

Figure 1. Schematic representation of the modified tensiometer used for bioadhession measurements in vitro.

B: Modified two-arm balance method

Two-arm balance method reported by Parodi (39) with minor modifications was also used to check and to validate the results of the aforementioned modified tensiometry method and the correlation between the results obtained from these two techniques was established. Briefly, buccal mucosa section (2-mm thick, 2×2 cm) was fixed on the bottom of smaller beaker attached to the bigger beaker (Fig. 2). Krebs solution was added to the beaker up to the upper surface of the buccal mucosa. A tablet was attached to the upper clamp and the platform was slowly raised until the tablet surface came in contact with mucosa. After a preload time of 5 minutes, water was added to the polypropylene bottle until the tablet was detached from the buccal mucosa. The water collected in the bottle was measured and expressed as weigh (g) required for the detachment (37, 40).

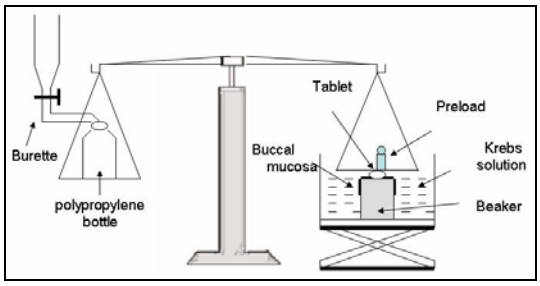

Figure 2. Modified apparatus for in vitro bioadhesion test

Dissolution studies

The dissolution of the buccoadhesive tablets was performed in 900 ml of phosphate buffer (PH = 6.8) using the USP 29 Apparatus II (Pharma Test, PTZWS3, Germany) dissolution tester under sink condition at 37 ± 0.2°C and 50 rpm. At appropriate time intervals, 3 ml of samples were withdrawn and an equal volume of medium was added to maintain the volume constant. Samples were filtered through a 0.45 um millipore filter and the amount of VPH which was released determined spectrophotometrically at 278 nm and the release data were evaluated kinetically. Six dissolution assays were performed for each formulation.

The drug release kinetics were analyzed by plotting the fraction released versus time and the data fitted to the following simple exponential model $M_t/M_\infty = kt^n$, where M_t corresponds to the amount of drug released in time t, M_∞ is the total amount of drug released after infinite time, K is a constant related to the properties of the drug delivery system incorporating structural and geometrical characteristics of the device, and n is the diffusional exponent indicating the type of drug release mechanism during the dissolution process. When n is less than 0.45 the drug diffuses through and is released from the polymeric matrix with a quasi-Fickian diffusion mechanism. For $0.0.45<n<0.89$ an anomalous (non-Fickian) drug diffusion occurs. For zero order release n =0.89, and when n is >0.89, a non-Fickian super Case II release kinetics could be observed (40, 41). The values of n were estimated by linear regression of log (M_t/M_∞) vs log (t). Mean dissolution time was used to compare the dissolution behaviors of fabricated buccoadhesive tablets.

To study the release kinetics of VPH from the tablets, different kinetic equations including Zero-order release rate equation, $dQ/dt=k_0$, and its integrated form, $Q=Q_i+k_0t$; first order release rate equation, $dQ/dt=k_1Q$, and its integrated form $ln(Q_0-Q)=lnQ_0-k_1t$; Higuchi model, $Q=k_H\ t^{1/2}$; and Hixon-Crowell model, $(Q_0-Q)^{1/3} = Q^{1/3} - k_5t$, where Q_0 is the initial amount of drug in the

pharmaceutical dosage form, Q is the amount of drug released at time t, Q_i is the initial amount of drug in the solution (Y intercept), and k are dissolution constants which were applied to interpret the release rate from the matrices.

Differential scanning calorimetry

About 3-4 mg of the individual components or drug-excipient combinations were weighed in aluminum DSC pans and hermetically sealed capsules were prepared with aluminum lids. A Dupont Differential Scanning Calorimeter (Model 910) with a thermal and a data acquisition unit (Series 9900) was used. The instrument was calibrated using Indium and all experiments were run at a heating rate of 10 ºC/min and a sensitivity setting of 1X. An initial ramp was used to jump the temperature to 25ºC and then a constant heating rate of 10 ºC/min was used up to 300 ºC under nitrogen atmosphere

Statistical analysis

Statistical comparisons of differences between bioadhesive force of tablets with different polymer mixing ratios, different polymers, swelling indices, correlation coefficients of different release kinetic studies, and dissolution rate constants were performed by analysis of variance (ANOVA) based on Fisher's PLSD test. In all cases, $P < 0.05$ was accepted as significant.

RESULTS AND DISCUSSIONS

Physical characteristics of tablets

Bioadhesive polymers such as CP, HPMC and NaCMC are suitable for use in buccoadhesive preparations because by uptake of water, can stick to the oral mucosa, and control the drug release while they resist salivation, tongue movement and swallowing for a significant period of time. The results of physical characteristics of prepared buccoadhesive tablets of VPH are shown in Table 2. The buccoadhesive tablets showed uniform thickness throughout, in the range of 2.10-2.22 mm. No significant difference in the weight of individual formulations from the average value was observed and variations were within the limits. The drug contents in the buccoadhesive tablets were also within the limit of 89.4 -112.6%. Hardness of buccoadhesive tablets varied with various ratios and type of polymers and was less for formulations containing NaCMC alone. NaCMC is a hygroscopic material which under high humidity conditions can absorb a large quantity (>50%) of water. In tablets, this phenomenon is associated with a decrease in tablet hardness and an increase in disintegration time (47). The hardness of tablets containing only NaCMC was lower and increased by increase in the amount of CP or HPMC in the formulation. Tablets containing CP exhibited greater hardness which decreased by increase in the amount of HPMC. The differences in the tablet hardness did not affect the release of the drug from hydrophilic matrices which is released by diffusion through the gel layer and/or erosion of this layer and is therefore independent of the dry state of the tablet (42).

Bioadhesion properties

Figure 3 shows the adhesion force of CP-HPMC, CP-NaCMC and NaCMC-HPMC tablets to the bovine mucosa at various mixing ratios of the polymers (Fig. 3A and 3B). The bioadhesion characteristics were affected by the type and ratio of the bioadhesive polymers. The polymers showed significant differences in their bioadhesion in the order of NaCMC>CP>HPMC ($P<0.05$). The highest detachment force was observed with the formulation N10V5 followed by C10V5, C2N8V5 and C8H2V5 ($P< 0.05$). However, the bioadhesion differences between C2N8V5 and C8H2V5 did not reach a significant level ($p > 0.05$). The detachment forces of CP-NaCMC were greater than those of CP-HPMC and NaCMC-HPMC at similar mixing ratios. Decreases in the amount of CP in tablets containing CP-HPMC or NaCMC and in systems containing CP-NaCMC or NaCMC-HPMC resulted in decrease in the detachment forces ($P< 0.05$) which is in compliance with the literature (37, 42-43, 46, 48). The adhesion force in the formulation C5H5V5 at a weight ratio of 1:1 of CP-HPMC was improportionally less than those with other mixing ratios in this group. This could be attributed to a possible interpolymer complex formation between CP and HPMC which in turn inhibited, at least in part, the adhesion force of the tablet. This type of interaction results from hydrogen binding between the OH groups of HPMC and the carbonyl groups of CP in the acidic medium (43, 44). Although an interpolymer complexation for CP-NaCMC at weight ratio of 1:4 (44) has been reported, in tablet C8N2V5 which contained CP and NaCMC at mixing ratio of 4:1, the bioadhesion did not decrease dramatically which indicates that bioadhesion is not affected by complexation to a large extent and still adequate OH groups are available for adhesion. The detachment forces of tablets of CP-NaCMC and Na CMC-HPMC decreased by decrease in the amount of NaCMC.

As it is illustrated in Figure 3C, a very good correlation ($r = 0.86$, $p < 0.001$) between bioadhesive forces obtained by modified

Table 1. Formulation of buccoadhesive VPH tablets and their formulation codes

Ingredients (mg)[1]	Formulation codes											
	C10 V5	H10 V5	N10 V5	C8 H2	C5 H5	C2 H8	C2 N8	C5 N5	C8 N2	N8 H2	N5 H5	N2 H8
Verapamil	50	50	50	50	50	50	50	50	50	50	50	50
HPMC[2]	*	100	*	20	50	80	*	*	*	20	50	80
CP[3]	100	*	*	80	50	20	20	50	80	*	*	*
NaCMC[4]	*	*	100	*	*	*	80	50	20	80	50	20

[1]All formulation contained 1% magnesium stearate; [2]HPMC hydroxypropylmethyl cellulose ; [3]Cp indicates carbomer 934p
[4]NaCMC sodium carboxymethyl cellulose

Table 2. Physical characteristics of buccoadhesive tablets of VPH

Formulations	Thickness (mm)	Content Uniformity (mg)	Weight Uniformity (mg)
C10V5	2.11 ± 0.05	47.9 ± 0.72	143.6 ± 15.5
H10V5	2.15 ± 0.12	48.5 ± 0.52	153.6 ± 6.74
N10V5	2.10 ± 0.21	47.2 ± 0.41	157.8 ± 8.92
C8H2V5	2.13 ± 0.07	47.5 ± 0.95	152.5 ± 10.2
C5H5V5	2.22 ± 0.12	48.2 ± 0.52	148.9 ± 12.8
C2H8V5	2.14 ± 0.16	49.3 ± 0.85	153.5 ± 9.96
C2N8V5	2.12 ± 0.14	55.1 ± 0.75	152.0 ± 17.4
C5N5V5	2.15 ± 0.17	55.5 ± 0.59	169.3 ± 15.3
C8N2V5	2.15 ± 0.11	44.7 ± 0.83	154.6 ± 17.8
N8H2V5	2.11 ± 0.13	55.8 ± 0.62	158.0 ± 11.4
N5H5V5	2.13 ± 0.15	53.3 ± 0.97	151.3 ± 13.5
N2H8V5	2.20 ± 0.15	56.3 ± 0.86	164.0 ± 8.20

Table 3. Correlation coefficient (r^2) of different models, drug release exponents (n), zero-order release rate constants (k_0), and MDT of different formulations of buccoadhesive VPH tablets in phosphate buffer solution (pH = 6.8) (n=6).

Formulations	n	r^2	MDT (hr)	K_0 (mg/h)	r^2 Zero-order	r^2 First-order	r^2 Higuchi	r^2 Hixon-Crowel
C10V5	0.82	0.9898	4.72	4.61	0.9907	0.9493	0.9433	0.9774
H10V5	0.91	0.9842	5.06	4.12	0.9905	0.9699	0.9411	0.9840
N10V5	0.97	0.9829	4.43	5.73	0.9892	0.8745	0.9105	0.7886
C8H2V5	0.78	0.9738	5.66	4.11	0.9802	0.9518	0.9569	0.9574
C5H5V5	0.76	0.9936	5.99	2.99	0.9718	0.9701	0.9138	0.9619
C2H8V5	0.74	0.9894	6.74	2.74	0.9856	0.9823	0.9657	0.9779
C2N8V5	1.60	0.9867	7.37	3.91	0.9840	0.9457	0.8531	0.9622
C5N5V5	1.59	0.9958	11.4	3.32	0.9667	0.9391	0.8157	0.9494
C8N2V5	1.57	0.9672	17.8	1.18	0.9811	0.9726	0.8578	0.9757
N8H2V5	1.16	0.9923	4.48	4.89	0.9933	0.9781	0.9226	0.9903
N5H5V5	1.18	0.9963	9.23	3.20	0.9940	0.9771	0.8896	0.9844
N2H8V5	1.01	0.9966	11.9	2.18	0.9955	0.9945	0.9269	0.9934

tensiometer method and bioadhesive strength resulting from modified balance method was observed. This may indicates that the modified tensiometry method based on Fisher's tensiometer could be confidently substituted with balance method and used conveniently to study muccoadhesion of tablet formulations. Furthermore, we have previously reported a remarkable degree of accuracy, precision, and reproducibility for this method (38).

Swelling index and In vitro release studies

The swelling behavior of a buccal adhesive system is an important property for uniform and prolonged release of drug and bioadhesiveness. The agar plate model used in this study simulates the secreting fluid around the buccal mucosa which is required for adhesion, swelling and release of the drug from tablets. The swelling as well as the release of VPH from buccoadhesive tablets varied according to the type and ratio of

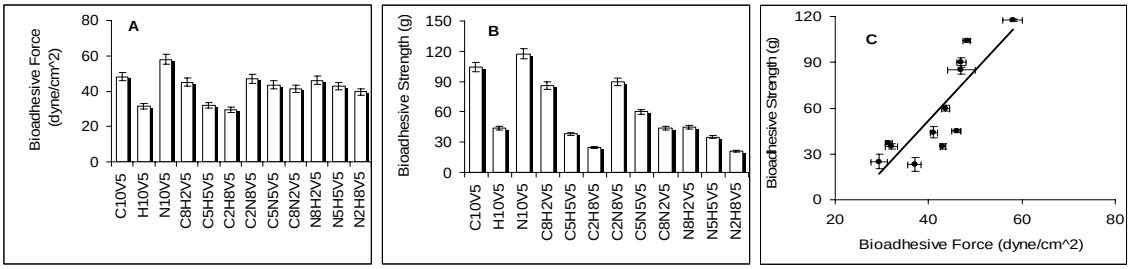

Figure 3. In vitro bioadhesion study of prepared buccoadhesive tablets, using modified tensiometer (A), and modified balance method (B), and relationship between two methods (C).

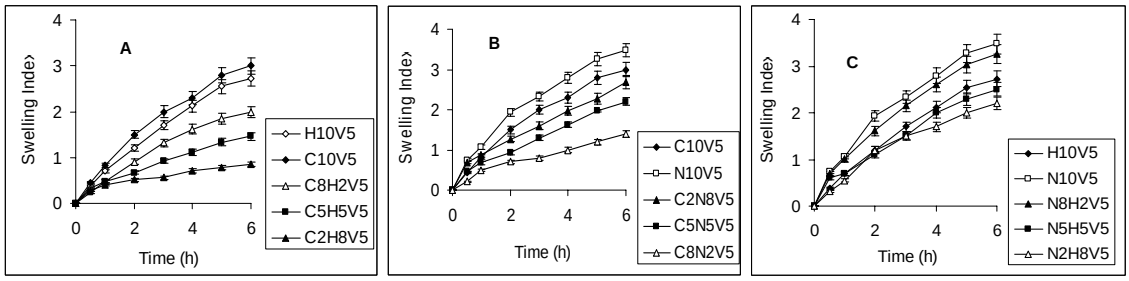

Figure 4. Swelling index of buccoadhesive tablets containing CP-HPMC (A), CP-Na-CMC (B), and NaCMC-HPMC (C) of different weight ratios.

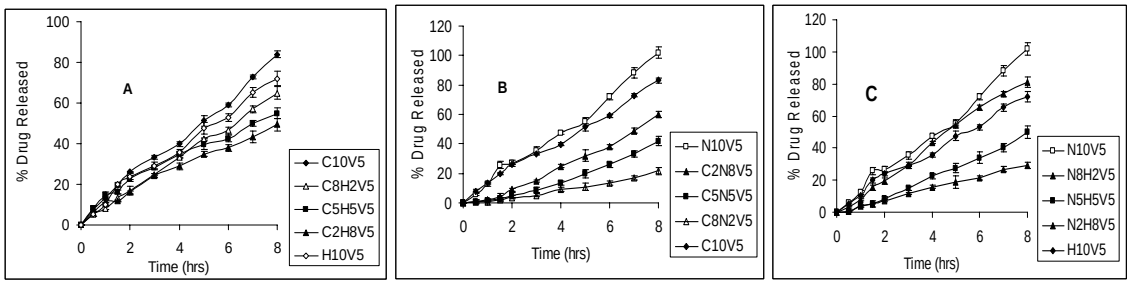

Figure 5. In vitro cumulative release profiles of VPH from sustained release buccal adhesive tablets containing CP-HPMC (A), CP-Na-CMC (B), and NaCMC- HPMC (C) at different weight ratios.

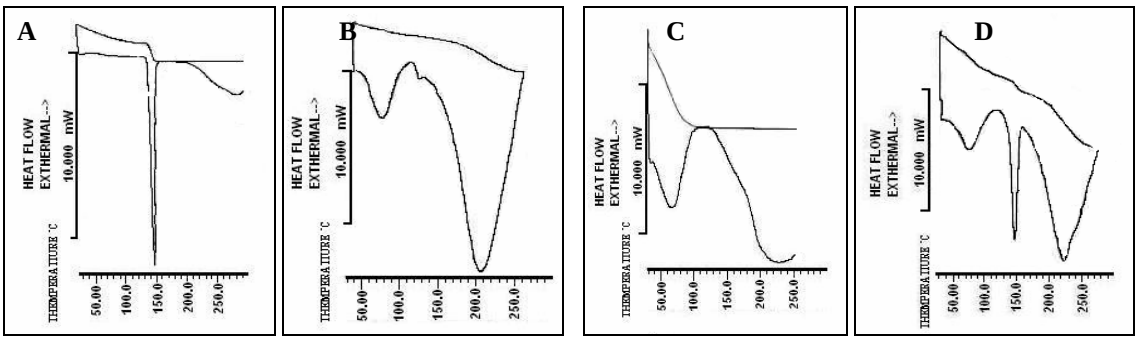

Figure 6. DSC heating curves of (A) VPH, (B) Carbomer 934P, (C) hydroxypropylmethyl cellulose, and (D) tablet formulation of C8H2V5.

the matrix forming polymers. Swelling index of buccoadhesive tablets as a function of time is shown in Figure 4. The polymers showed significant differences in their swelling indices in the order of NaCMC > CP > HPMC ($P<0.05$) (Fig. 4 A, B, and C). The same order, as indicated by their MDT (Table 3), was also observed for drug release from matrices containing only NaCMC (N10V5), CP (C10V5), and HPMC (H10V5) (Figure 5A). These formulations showed highest percentage of VPH release within 8 hrs. Matrices containing CP-HPMC (Fig. 4A) demonstrated increase in swelling values ($P<0.05$) in VPH release, indicated by smaller Mean Dissolution Time (MDT) values (Table 3), as the content of CP was increased (Fig. 5A and Table 3). This observation could be due to higher and faster swelling of CP which might leads to higher drug diffusion coefficients.

It has been shown that swelling of the CP is greatest at pH 6-7 as compared to acidic or alkaline pH (45). CP with the pK_a of 4.75 is almost completely ionized at pH 6.8 which gives rise to negative charges along the CP backbone whose repulsion induces CP molecule to uncoil into an elongated structure. Diffusion of counter-ion inside the gel generates an osmotic pressure difference across the gel that leads to higher water uptake which results in the substantial swelling of the polymer. The continued swelling of the polymer matrix causes the drug to diffuse from the formulation at a faster rate (40). Since HPMC is a nonionic polymer, swelling behavior of this compound is not affected by pH. Therefore, the swelling rate of HPMC is less than that of CP (43). CP is more hydrophilic than HPMC and if it is added in high ratios causes high release rates (42). Higher swelling and faster release of drug from matrices containing different ratios of CP and HPMC has also been reported for matrices containing greater amount of CP (43), for morphine sulfate (43), and propranolol hydrochloride (37). In this series, formulations containing 13.3% (C2 H8V5) or 33.3% (C5H5V5) CP showed incomplete drug release which was less than 60% within 8 hrs.

The swelling values and the release rate of VPH, as indicated by greater MDT (Table 3, Figs. 5B and 5C), from the matrices with CP-NaCMC (Fig. 4B) or NaCMC-HPMC (Fig. 4C) increased by an increase in NaCMC content ($P<0.05$). Swelling and eroding of NaCMC explains the relatively high release rates of VPH from formulations containing this compound (42). As it is illustrated in Figures 4B and 4C, although matrices containing CP-NaCMC exhibited maximum swelling values, they showed lower release rates which could be attributed to higher hydrophilicity and water uptake of CP and NaCMC compared to HPMC, which produces a water-swollen gel-like state that may substantially reduce the penetration of dissolution medium into the tablets and as a result the drug release rate. In these groups, as expected, the drug was released much more slowly from matrices containing 13.3% (C8N2V5 and N2H8V5) or 33.3% (C5N5V5 and N5H5V5) NaCMC with respect to other groups. Formulation N8H2V5 released its contents fairly faster (K_0 = 4.9 mg/h, Table 3) than it was expected and showed low bioadhesion (45 g, Fig. 4C). Formulation C2N8V5 released its content fairly slower (K_0 = 3.92 mg/h, Table 3) than it was expected and showed interaction in DSC thermogram (Figure not shown) but had a good bioadhesion (89 g, Fig 4B). The buccoadhesive VPH tablet containing 53% CP and 13.3% HPMC as in C8H2V5, showed suitable release kinetics (n =0.78, K_0 zero order release = 4.11 mg/h, MDT = 5.66 h, Table 3). This matrix tablet formulation released its entire content within 12 hours and seems appropriate for twice daily buccal administration of VPH. This formulation also showed adhesive properties to the buccal mucous membrane (Fig. 3). In addition, this selected percentage of CP-HPMC seems free of complexation between two polymers and therefore both polymers could act independently. Furthermore, the DSC did not reveal any interaction between CP and HPMC at this ratio in the formulation. The DSC analyses were used to characterize the complexation of VPH with CP and HPMC at the solid state (Fig. 6).

The DSC scan of pure VPH showed a sharp endothermic transition which corresponds to the melting point of drug at 146.3 °C. HPMC and CP did not show any characteristic transitions at this region. The DSC of pure HPMC and CP exhibited some major and minor endothermic transition at 68.5 °C, 235 °C and 82.5 °C, 238 °C, respectively which were not in the region where VPH transition occurred. The mixture of these two polymers at weight ratio of 4:1 with VPH as in C8H2V5 formulation showed the characteristic VPH, HPMC and CP peaks without any major additional or new peaks. Hence no interactions were observed which indicates that the drug is in crystalline form without undergoing any degradation and that HPMC and CP could be considered compatible with VPH.

The release exponent (Table 3) in all formulation is significantly greater than 0.5, which indicates anomalous (non-Fickian) drug release. When liquid diffusion rate and polymer relaxation rate are of the same order of magnitude, anomalous or non-Fickian diffusion is considered (46). The

value of n was greater than 1 for tablets containing CP-NaCMC or NaCMC-HPMC than the group containing CP-HPMC. This observation could be attributed to the high swelling nature of these polymers which is in accordance with the higher swelling indices observed for these formulations.

To study the release kinetics of VPH from the tablets, the goodness-of-fit method was applied and different kinetic equations were applied to interpret the release rate from the matrices. In the present study, the linear nature of the curves obtained for zero-order, first order, Higuchi model and Hixon-Crowel model as demonstrated by very close and higher r squared values (Table 3) suggests that the release from the formulations may follow any one of these models. When the higher correlation coefficient values are considered, the release data seem to fit better with the zero order kinetics (Table 3). Therefore, the release rate $dQ/dt=k_0$ is independent of its concentration or amount of drug incorporated in the formulation which could be considered as an advantage for fabricated systems. There is almost a good coincidence with the results obtained from the equation of Korsmeyer-Peppas in which n value is nearly 1 and the best fitted equation for drug release, according to the zero-order and/or first-order release kinetics**.**

According to Higuchi model, the drug release from insoluble matrix is directly proportional to square root of time and is based on Fickian diffusion. Lower linearity observed in this model is coincident with n values close to unity in Korsmyer-Peppas and indicates that Fickian diffusion mechanism could be ruled out. Smaller correlation coefficient observed for Hixon-Crowell cube roots model (Table 3) indicates that the possibility of a change in surface area or the diameter of the tablets with time are less likely in the release mechanism.

CONCLUSIONS

In conclusion, a new buccoadhesive system for the controlled release of VPH was developed by using CP and HPMC in appropriate ratios. The developed tensiometry method seems a valid, simple, and rapid technique for in vitro bioadhesion measurements and could be substituted for balance technique. The release rate of VPH from tablets was significantly affected by the type and changes in the polymer mixing ratios. Lower release rates were observed by lowering the content of CP in CP-HPMC containing formulations or NaCMC in tablets which contained CP-NaCMC or NaCMC-HPMC. The presence of CP or NaCMC seems essential for promotion of bioadhesion in buccoadhesive tablets of VPH. The buccoadhesive VPH tablets containing 53% CP and 13.3% HPMC (C8H2V5) showed suitable release kinetics, and properties for adhesion to the buccal mucous membrane and was free of any interaction between polymers and drug. This buccoadhesive system may be useful for buccal delivery of VPH.

REFERENCES

1. Kirsten R, Nelson K, Kirsten D, Heintz B. Clinical pharmacokinetics of vasodilators. Clin Pharmacokinet 1998; 34:457-482.
2. Reynolds JEF. Martindale, The Extra Pharmacopoeia, Vol. 33, The Royal Pharmaceutical Society, Great Britain, London 2002; 989-991.
3. Buzinkaiova T, Skacani I, Netriova J. Quantitative assay of verapamil in drugs and serum by capillary isotachophoresis. Pharmazie, 1995; 50:799–800.
4. Clarke EG. Isolation and identification of drugs, London, The pharmaceutical press. 2004; 1695-1697.
5. Jankowski A, Marzec A, Lamparczyk H. Comparative bioavailability of verapamil from rapidly absorbed and slow release preparations. J Pharm Biomed Anal 1991; 10:1101–1103.
6. Harder S, Thurmann P, Siewert M, Blume H, Huber TH, Rietbrock N. Pharmacodynamic profile of verapamil in relation to absolute bioavailability: investigations with a conventional and controlled release formulation. J Cardiovasc Pharmacol 1991; 17:207–212.
7. Elkheshen SA. Bioadhesive matrix as controlled release dosage form for verapamil hydrochloride. Pharm Ind 1998; 60:555–559.
8. Ahmed JH, Merdith PA, Ellott HL. The influence of age on the pharmacokinetics of verapamil. Pharmacol Res 1991; 24 (3):227-233.
9. Longer MA, Ch'ng HS, Robinson JR. Bioadhesive polymers as platform for oral controlled drug delivery. J Pharm Sci 1985; 74:406-411.
10. Smith DHG. Pharmacology of cardiovascular chronotherapeutic agents. Am J Hypertens 2001; 14:2965-3015.
11. Pfizer Canada Inc. Submission Control No: 106194. Product monograph.

12. Conley R, Gupta SK, Sathyan G. Clinical spectrum of the osmotic-controlled-release osmotic delivery system (OROS), an advanced oral delivery form. Current Medical Research and Opinion, 2006; 22 (10):1879-1892.
13. Elkheshen S, Yassin AE, Alkhaled, F. Per-oral extended release bioadhesive tablet formulation of verapamil HCL. Bolletino Chimico Farmaceutico 2003; 142 (5):226-231.
14. Siahi MR, Barzegar-Jalali M, Monnajemzadeh F, Ghaffari F, Azarmi S. Design and evaluation of 1- and 3 layer matrices of verapamil HCL for sustaining its release. AAPS PharmSciTech, 2005; 6(4):626-632.
15. El-Gazayerly ON, Rakkanka V, Ayres JW. Novel chewable sustained-release tablet containing verapamil hydrochloride. Pharm Dev Tech 2004; 9(2):181-8.
16. Gohel MC, Patel TP, Bariya SH. Studies in preparation and evaluation of pH-independent sustained-release matrix tablets of verapamil HCl using directly compressible Eudragits Pharm Dev Tech 2003, 8(4):323-33.
17. Mukherjee B, Mahanti B, Panda P, Mahanpatra S. Preparation and evaluation of verapamil hydrochloride microcapsules. Am J of Ther 2005; 12(5):417-424.
18. Govindarajan R, Nagarsenker MS. Basic drug-enterosoluble polymer co-evaporates: development of oral controlled release systems. Drug Dev Ind Pharm 2004; 30(8):847-857.
19. Chen GL, Hao WH. In vitro performance of floating sustained-release capsule of verapamil. Drug Dev Ind Pharm 1998; 24(11):1067-1072.
20. Sawicki W, Glod J. Preparation of floating pellets with verapamil hydrochloride. Acta Poloniae Pharmaceutica 2004; 61(3):185-90, 2004.
21. Dashevsky A, Kolter K, Bodmeier R. pH-independent release of a basic drug from pellets coated with the extended release polymer dispersion Kollicoat SR 30 D and the enteric polymer dispersion Kollicoat MAE 30 DP. Eur J Pharm Biopharm 2004; 58(1):45-9.
22. Kusum Devi V, Saisivam S, Maria GR, Deepti PU. Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. Drug Dev Ind Pharm 2003, 29(5):495-503.
23. Neutel JM, Alderman M, Anders RJ, Weber MA. Novel delivery system for verapamil designed to achieve maximal blood pressure control during the early morning. Am Heart J 1996; 132(6):1202-6.
24. Passerini N, Perissutti B, Albertini B, Voinovich D, Moneghini M, Rodriguez L. Controlled release of verapamil hydrochloride from waxy microparticles prepared by spray congealing. J Control Release 2003; 88(2):263-75.
25. Salamat-Miller N, Chittchang M, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Deliver Rev 2005; 57:1666-1691.
26. Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhesive drug delivery- A promising option for orally less efficient drugs. J Control Release 2006; 114:15-40.
27. Shojaeei AH. Buccal mucosa as a route for systemic drug delivery: A review. J Pharm Pharmaceut Sci 1998; 1(1):15-30.
28. Burgalassi S, Panichi L, Saettone MF, Jacobsen J, Rassing MR. Development and in vitro/ in vivo testing of mucoadhesive buccal patches releasing benzylamine and lidocaine. Int J Pharm 1996; 133:1-7
29. Remunan-lopez C, Portero A, Vila-jato JL, Alonso MJ. Design and evaluation of chitosan/ethylcellulose mucoadhesive bilayered device for buccal drug delivery. J Control release 1998; 55:143-152.
30. Ahuja A, Khar RK, Ali J. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm 1997; 23:489-515.
31. Giunchedi P, Juliano C, Gavini E, Cossu M, Sorrenti M. Formulation and in vivo evaluation of chlorhexidine buccal tablets prepared using drug-loaded chitosan microspheres. Eur J Pharm Biopharm 2002; 53:233-239.
32. Martin L, Wilson CG, Koosha F, Uchegbu IF. Sustained buccal delivery of the hydrophobic drug denbufylline using physically cross-linked palmitoyl glycol chitosan hydrogels. Eur J Pharm Biopharm 2003; 55:35-45.
33. Park CR, Munday DL. Development and evaluation of a biphasic buccal adhesive tablet for nicotine replacement therapy. Int J Pharm 2002; 237:215-226.
34. Minghetti P, Colombo A, Montanari L, Gaeta GM., Gombos F. Buccoadhesive slow-release tablets of acitretin: Design and 'in vivo' evaluation. Int J Pharm 1998; 169(2):195-202.
35. Llabot JM, Manzo RH, Allemandi DA. Double layered mucoadhesive tablets containing nystatin. AAPS PharmSciTech. 2002; 3(3):E22.

36. The United States Pharmacopeia, 29 th Ed. and The National Formulary 24 th Ed. The United States Pharmacopeial Convention Rockville, MD, prepared by the council of experts and published by the Board of Trustee printed in Canada by Webcom Limited. Toronto, 2005; 2246-2249.
37. Desai KGH, Kumar TMP. Preparation and evaluation of a novel buccal adhesive system. AAPS PharmSciTech 2004; 5 (3): Article 35.
38. Varshosaz J, Dehghan, Z. Development and characterization of buccoadhesive nifedipine tablets. Eur J Pharm Biopharm 2002; 54:135-141.
39. Parodi B, Russo E, Caviglioli G, Cafaggi S, Bigbardi G. Development and characterization of a buccoadhesive dosage form of oxycodane hydrochloride. Drug Dev Ind Pharm 1996; 22 (5):445-450.
40. Agarwal V, Mishra B. Design, development, and biopharmaceutical properties of buccoadhesive compacts of pentazocine. Drug Dev Ind Pharm 1999; 25 (6):701-709.
41. Peppas NA. Analysis of Fickian and Non-Fickian drug release from polymers. Pharm Actahelv 1985; 60(4):110-112.
42. Dortung B, Ozer L, Uyanik N. Development and In Vitro evaluation of a buccoadhesive pindalol tablet formulation. Drug Dev Ind Pharm 1998; 24 (3):281-288.
43. Anlar S, Capan Y, Guven O, Gogus A, Dalkara T, Hincal A. Formulation and In vitro-In vivo evaluation of buccoadhesive morphine sulfate tablets. Pharm Res 1994; 11(2):231-236.
44. Gupta A, Garg S, Khar RK. Interpolymer complexation and its effect on bioadhesive strength and dissolution characteristics of buccal drug delivery systems. Drug Dev Ind Pharm 1994; 20 (3):315-325.
45. Anlar S, Capan Y, Hincal AA. Physico-chemical and bioadhesive properties of polyacrylic acid polymers. Pharmazie, 1993; 48:285-289.
46. Perioli L, Ambrogi V, Rubini D, Giovagnoli S, Ricci M, Blasi P, Rossi C. Novel mucoadhesive buccal formulation containing metronidazole for the treatment of periodontal disease. J Control Release 2004; 95:521-533.
47. Rowe RC, Shesky PJ, Weller PJ. Handboock of pharmaceutical excipients, Pharmaceutical Press. UK. 4th Ed. 2003; P 98.
48. Mortazavi SA, Aboofazeli R. Preparation and in vitro assessment of various mucosa-adhesive films for buccal delivery. Daru 2000; 8(1):9-17.