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European Journal of Pharmaceutics and Biopharmaceutics 54 (2002) 135–141

European Journal of Pharmaceutics and Biopharmaceutics

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Research paper

Development and characterization of buccoadhesive nifedipine tablets

J. Varshosaz*, Z. Dehghan

Department of Pharmaceutics, School of Pharmacy and Phamaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

Received 14 December 2001; accepted in revised form 31 May 2002

Abstract

The buccoadhesive controlled-release tablets for delivery of nifedipine were prepared by direct compression of carboxymethyl cellulose (CMC) with carbomer (CP), which showed superior bioadhesion properties compared to polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), hydroxypropylmethyl cellulose (HPMC), and acacia in a modified tensiometry method in vitro. The tablets containing 30 mg of nifedipine and various amounts of CMC and CP showed a zero-order drug release kinetic. The adhesion force was significantly affected by the mixing ratio of CP:CMC in the tablets. The weakest and highest adhesion force was observed at the mixing ratios of 1:0 and 8:2 of CP:CMC, respectively. The tablets containing 15% CMC and 35% CP adhered for over 8 h to the upper gums of six healthy human volunteers. These tablets released about 56% of the loaded drug after 8 h in vivo with a rate of 2.17 h^{-1} and were perfectly tolerated, while they released about 100% of their content after the same time with a rate of 3.49 h^{-1} in vitro. A good correlation ($r^2 = 0.989$) was observed between drug-released in vitro and in vivo. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Buccoadhesion; Nifedipine; Controlled release; Bioadhesive polymers

1. Introduction

Nifedipine, a systemic calcium channel blocker, is a practically water insoluble and light-sensitive drug used in angina pectorice and hypertension [1]. As its biological half-life is about 2 h and is eliminated rapidly, repeated daily administrations are needed to maintain effective plasma levels [2]. It shows a low and irregular bioavailability of about 50% after oral administration with a high first pass effect [3]. It has been suggested that drugs with biological half-lives in the range of 2–8 h are good candidates for sustained-release formulations [4].

Sustained-release formulations of nifedipine has become available [5]. Coated granules and matrix tablets [6], polyacrylate–polymethacrylate microspheres prepared by the solvent evaporation process [7], microcapsules and solid dispersions of nifedipine in polyvinylpyrrolidone (PVP)-microcrystalline cellulose [1] and sustained-release tablets containing hydroxypropylmethyl cellulose (HPMC) and cross-linked sodium carboxymethyl cellulose (CMC) [8] are controlled-release forms of this drug reported so far. The short half-life and severe first pass metabolism of nifedipine makes it suitable for administration via a buccal delivery system that provides controlled drug delivery, bypassing first pass effect. Successful buccal delivery requires at least three of the following: (a) a bioadhesive to retain the drug in the oral cavity and maximize the intimacy of contact with the mucosa; (b) a vehicle that releases the drugs at an appropriate rate under the conditions prevailing in the mouth; and (c) strategies for overcoming the low permeability of the oral mucosa [9]. Mucoadhesive drug delivery systems promote the residence time and act as sustained-release dosage forms [10]. Three steps of formation of bioadhesive bonds are: (a) wetting and swelling of polymer; (b) entanglement of polymer and mucin chains; and (c) formation of weak chemical bonds between entangled chains [9]. A mucoadhesive nasal formulation of nifedipine containing carbopol 941 gel with polyethylene glycol (PEG) 400 has been reported by Morimoto et al. [11]. Save and Venkitachalam [12] prepared a buccoadhesive erodible carrier consisting of sodium alginate, mannitol, and PEG 6000 for nifedipine.

The aim of this work was to develop and characterize a buccoadhesive controlled-release tablet of nifedipine. The buccal route was chosen because of its good accessibility, robustness of the epithelium, facile removal of the dosage form, relatively low enzymatic activity, natural clearance mechanisms for elimination of the drug from buccal area, satisfactory patient acceptance and avoiding the hepatic first pass metabolism [13]. Apart from the overall increased

* Corresponding author. Department of Pharmaceutics, School of Pharmacy and Phamaceutical Sciences, Isfahan University of Medical Sciences, P.O. Box 81745-359 Isfahan, Iran. Fax: +98-311-668-0011.

E-mail address: j_varshosaz@hotmail.com (J. Varshosaz).

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PII: S0939-6411(02)00078-4

bioavailability, because of bypassing the first pass effect and sufficient time to produce therapeutic effect [14], an important advantage of buccal delivery for nifedipine is also potentially better control of plasma levels, typically lower variation in bioavailability, reduced costs of the drug because of application of much lower doses than necessary for oral products.

2. Materials and methods

2.1. Materials

Nifedipine (mean particle size 90 μm as a gift of Tolidarou Laboratories, Iran), sodium CMC low viscosity (Merck, Germany, viscosity of its 2% solution was 150 mPa s), carbomer 934P (CP) (Carbopol, B.F. Goodrich, Belgium, Mw 3000000, the viscosity of a neutralized 0.5% dispersion was 39400 cps), polyvinyl alcohol (PVA) (BDH Chemicals Ltd., Poole, UK, Mw 23300, viscosity of its 4% solution was 4 mPa s), PVP K-30 (Merck, Germany, Mw 49000, viscosity of its 10% solution was 7 mPa s), HPMC (Methocel K4M, Colorcon, England, viscosity of its 2% solution was 6 cps at 25 °C), sodium alginate (BDH Chemicals Ltd., Poole, UK) , acacia (Brome and Schimmer Ltd., Romsey, Hants), PEG 6000 (Merck, Germany), lactose USP (Merck, Germany), magnesium stearate (Merck, Germany), Mucin type II from porcine stomach with 1% bound sialic acid (Sigma Chemical Company, USA) and other chemicals were all from analytical grade and from Merck, Germany. The experiments were carried out under conditions of protection from light since nifedipine is photosensitive in nature.

2.2. In vitro mucoadhesion measurements

To choose the best type of bioadhesive polymers in preparation of tablets, at first an aqueous solution of each polymer was studied for its bioadhesive properties and then different mixing ratios of the polymers which showed the highest bioadhesion were compared from this point of view. A modiefied tensiometry method based on Fisher's tensiometer (Fisher Scientific Co., Autotensiomat®, model 215, USA) was developed to evaluate the bioadhesive properties of the polymers and tablets (Fig. 1). The limitation of the measurable surface tension or adhesive forces by this instrument was set at 0–100 dyn/cm^2. The strength of the apparatus was such that it would not allow the rupture of the mica glass plate at the interface. According to the catalogue of the device, at this limit the device can tolerate a weight as heavy as 1 g, so the weight of the mica disk with the tablet attached to it caused no problem or disruption of the mica disk.

Different polymers consisting CMC, CP, PVP, PVA, HPMC, and acacia were studied for their bioadhesive properties by the developed method. After calibration the tensiometer with a standard weight, the following procedure was

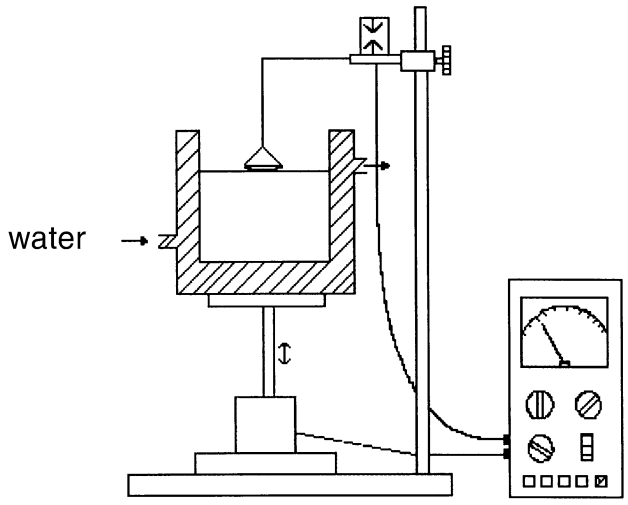

Fig. 1. Schematic representation of the modified tensiometer used for bioadhesion measurements in vitro.

carried out: the thin glass plates (1 cm^2 surface area) were attached to the ring of the tensiometer by cyanoacrylate adhesive and coated on their both sides by dipping into a 1% aqueous solution of the test polymer, and drying at 37 °C to constant weight. Coating the plate was done for three times. The coated plate with the bioadhesive polymer was then penetrated into a 1% mucus sample or sodium alginate gel that was placed into the 37 °C water-jacketed glass vial of the instrument to touch the base of the container (almost 2 cm deep). The plate was left in contact with the gel for 1 min, and then it was detached from the gel by a 0.2 inch/min speed. The maximum force required to detach the plate from the gel was measured in terms of dyn/cm^2. The test was carried out at least for six times. The adhesion force between the uncoated glass plates and the solution of the substrate was used as the blank and considered in all subsequent tests with the polymer samples. After each experiment the glass plate was removed and as recommended by the catalogue of the instrument, the palladium–platin ring of the tensiometer was washed with methanol, then with aceton and to ensure the removal of the remaining contaminants, it was heated to redden in the flame.

To validate and evaluate the method of bioadhesion measurements within- and between-day variations were studied: six samples obtained from a polymer solution (CMC) were subjected to the bioadhesion test during a single day and the same procedure was repeated in six different experimental run days, respectively and the surface tension and coefficient of variation (CV%) were determined.

The in vitro bioadhesion measurement method reported by He et al. [15] was used to check the results of the aforementioned modified tensiometry method. Briefly, stock solutions (2 mg/ml) of the test polymers and mucin were prepared with pH 4.5 acetate buffer. They were then filtered with Whatman no. 1 filter paper. The samples were prepared by mixing 1:1 ratio of mucin stock solution with the stock

solution of one of the test polymers (CMC, HPMC, CP, PVP, PVA or acacia). The absorbance of these samples were recorded at 500 nm with a UV-550SE Perkin–Elmer spectrophotometer after 30 min of mixing and were used to give the theoretical values for a non-interacting system [15]. The absorbance of the individual polymers and mucin in acetate buffer were measured as controls. The theoretical absorbance (A_{theor}) for the mixture of polymer/mucin system was calculated from the individual absorbance:

$$A_{theor} = \frac{x(A_{mucin}) + y(A_{polymer})}{x + y} \quad (1)$$

where x and y are the ratios of mucin and polymer in the mixture, respectively. A_{mucin} and $A_{polymer}$ are the absorbances of the mucin and individual polymers measured at 500 nm, respectively. The absorbance difference (ΔA) between the measured and theoretical values for the mixture of mucin/polymer system was also calculated. If $\Delta A = 0$, no interaction took place, while $\Delta A \gg 0$ suggests a strong interaction (probably secondary interactions due to the macromolecular interpenetration) between the polymer and mucin [15]. Considering that the rank order of bioadhesion of the test polymers was attributed to ΔA, no conversion of the absorbance to the concentration was needed and the absorbance was used directly.

2.3. Complexation studies between bioadhesive polymers via turbidity measurements

To study the presence of any interpolymer complexation between the mixture of CP and CMC, which showed the greatest bioadhesive properties, turbidity measurements were carried out [16]. A 0.02% solution of the mixture of CP:CMC with different ratios 10:0, 8:2, 7:3, 6:4, 5:5, 4:6, 2:8 and 0:10, were prepared in distilled water and stirred for 12 h at room temperature. The turbidity of each sample solution was determined at 600 nm spectrophotometrically, which showed the presence of complexation between the studied polymers [16].

2.4. Preparation of buccoadhesive tablets

The mixture of CP and CMC that showed the greatest bioadhesion, were used in tablet matrix. Flat, 160 mg tablets were prepared by a direct compression method using a single-punch tableting machine (GMBH—KS Kilian, Germany). All tablets contained 1% magnesium stearate (as lubricant), 20.25% spray dried lactose (as filler), 10% PEG 6000 (as solubilizer), 18.75% nifedipine and 50% of total bioadhesive polymers with different mixing ratios of CP and CMC (Table 1). Compression parameters as an average of 20 tablets contained: diameter, 5 mm; thickness, 2 mm; hardness, 100 N; and friability, less than 1%.

2.5. Bioadhesion measurements of the tablets

A thin mica disk was attached to the tensiometer ring with a cyanoacrylate adhesive. The buccoadhesive tablets were wetted by dropping phosphate buffer solution (pH 6.6) on their surface and attached to the mica disk. A preload of 20 g was placed over the disk for 5 min to establish the adhesion bonding. After removal of the preload weight, the ring with the tablet attached to it was transferred to the tensiometer. The tablet came in contact with the 1% (w/w) solution of sodium alginate for 5 min. This hydration time (5 min) was kept constant in all other experiments and then the tablet was detached from the gel substrate by a 0.2 inch/min stress speed, the detachment force was measured in terms of dyn/cm^2. The test was performed at least for six times on six different tablets.

Table 1
Intraday and interday variations of surface tension measurements (dyn/cm^2) in bioadhesion test of polymers using CMC 1% solution on the sodium alginate substrate ($n = 6$)

	Intraday	Interday
Mean	54.25	50.07
SD	2.22	1.84
CV%	4.09	3.67

2.6. In vitro release studies

The drug content of the tablets of each formulation was analyzed before the dissolution test in six tablets. Six dissolution assays were performed for each formulation using the USP XXIII apparatus 1 at 100 rev/min (PTSW 3, Pharma Test, Germany). The dissolution medium consisted of 900 ml phosphate buffer (pH 6.6) and 0.5% w/v Tween 80 [8] at 37 ± 0.5 °C. At appropriate time intervals, samples were taken, filtered through a 0.45 μm millipore filter and the absorbance of each sample was measured spectrophotometrically at 340 nm. Each time the withdrawn samples were replaced by fresh 37 °C medium solution.

2.7. In vivo release studies in human volunteers

The tablets of formulation CM-3 were applied to the upper gums above the canine tooth of healthy volunteers, four females and two males for 1, 3, 5, 7 and 8 h. The age of the subjects ranged between 15 and 26 years. Fresh tablets were applied at each time point and a minimum 24 h was allowed between replicate applications to the same subject. The percentage of nifedipine released was calculated from the amount remaining in the dosage form. After removal from the site of application, each tablet was dissolved in 50 ml of methanol and centrifuged for 10 min. One milliliter of the supernatant was diluted to 10 ml by methanol and assayed spectrophotometrically at 350 nm.

2.8. Statistical analysis

The independent sample t-test was used to evaluate the difference between substrates of mucin and sodium alginate

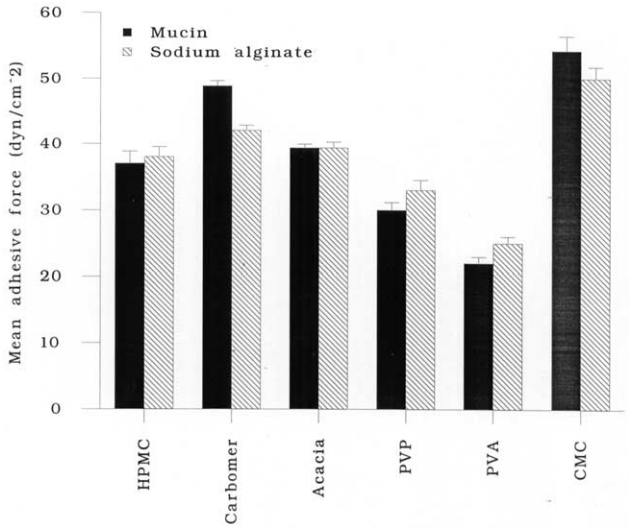

Fig. 2. Comparison of the bioadhesion force of different polymers by a modified tensiometry method on a 1% w/v sodium alginate solution or mucin substrate ($n = 6$).

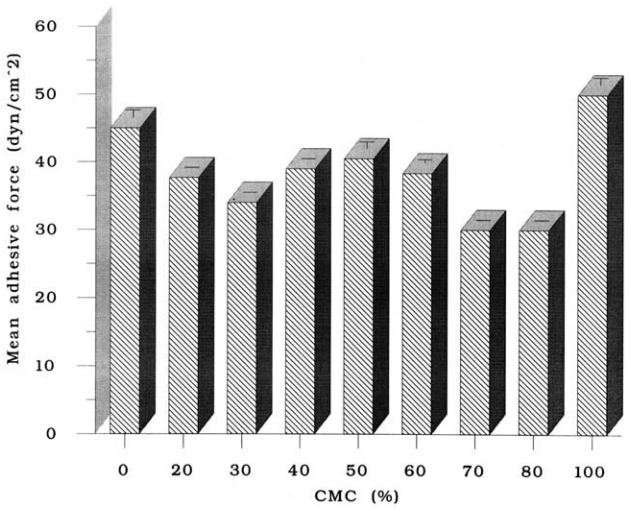

Fig. 3. Comparison of the bioadhesion force of different mixing ratios of carbopol/sodium CMC by a modified tensiometry method on a 1% w/v sodium alginate solution or mucin substrate ($n = 6$).

in bioadhesion test of polymers. Statistical comparisons of bioadhesive force of tablets with different polymer mixing ratios, different polymers and correlation coefficients of different release kinetic studies were performed by one-way analysis of variance (ANOVA) based on Fisher's PLSD test. In all cases, $P < 0.05$ was accepted to denote significance.

3. Results and discussion

Fig. 2 shows the adhesion forces according to tensile strength (dyn/cm^2) of different polymers on substrates of 1% w/v of mucin or sodium alginate solution. The results showed no significant difference between the two substrates ($P < 0.05$) so in all other bioadhesion tests; sodium alginate was used instead of mucin. The polymers showed significant differences in their bioadhesive properties ($P < 0.05$) (Fig. 2). Parodi et al. [17] also used this substrate for bioadhesion tests. The same rank order for the bioadhesion property of the polymers was reported using a Wilhelmy plate method by Smart [18]. Table 1 shows that the bioadhesion test process for polymers has a considerable degree of intraday and interday reproducibility and accuracy. The results of the mixed mucin/polymer absorbances are summarized in Table 2. As this table indicates, the same rank order is seen in the bioadhesion properties of the studied polymers that confirm the results of the developed tensiometry method as a valid procedure for measuring in vitro bioadhesion. Considering CMC and CP showed the highest bioadhesion among the studied polymers, they were chosen for preparation of tablets. Different mixing ratios of these polymers are compared for their bioadhesion properties in Fig. 3. As this figure shows the lowest bioadhesion is seen in the aqueous mixtures of 70–80% of CMC and 20–30% of CP ($P < 0.05$). The turbidimetric method also showed the highest absorbance at concentrations of 70–80% of CMC (Fig. 4). This may suggest that at this ratio there is a high inter-polymer chain entanglement and complexation, that has reduced the availability of the free functional groups of the polymers to the OH groups of the sodium alginate substrate and so in Fig. 3 a low bioadhesion force is seen in this ratio. Pochel et al. [19] investigated the effect of the Carbopol 934 percentage in the polymer mixture on the bioadhesive properties of controlled-release systems. They concluded that due to the strong penetrating characteristics of the uncross-linked polyacrylic acid chains in the mucus, excessive amounts of CP were not necessary to achieve the

Table 2
Spectrophotometric measurement of the bioadhesion between mucin and polymer (1:1) as the absorbance (A) at 500 nm ($n = 6$)

	CMC	HPMC	CP	PVP	PVA	Acacia	Mucin
Mucin/polymer mixture							0.681
A_{500}	0.368	0.355	0.488	0.350	0.343	0.359	
A_{theor}	0.346	0.344	0.470	0.341	0.343	0.344	
$\Delta A = A_{500} - A_{theor}$	0.021	0.011	0.018	0.009	0.000	0.015	
Indiviodual polymer							
A_{500}	0.012	0.007	0.259	0.001	0.006	0.007	

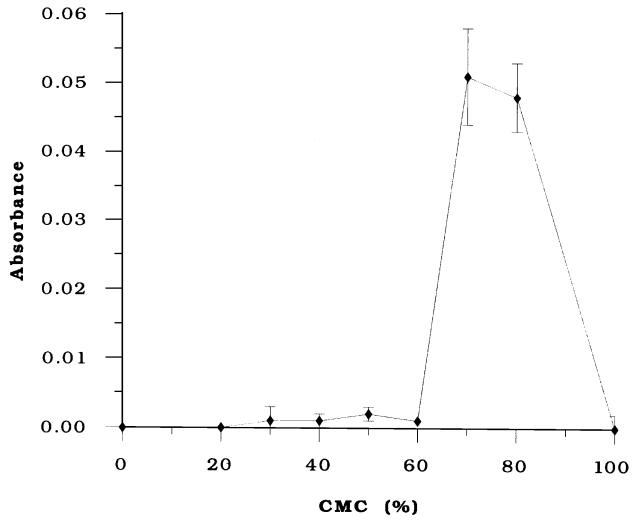

Fig. 4. Spectrophotometric turbidity measurement of mixtures of carbopol/sodium CMC in water media at 600 nm ($n = 6$).

maximum bioadhesive strength and that only about 30 wt% CP was sufficient. However, Table 3 indicates that the tablets CM-8 with the same polymer ratio have the highest bioadhesion. The discrepancy between the results of bioadhesion of the tablets and the polymer mixtures, may be related to the presence of lactose and other ingredients of the tablets, which prevent the entanglement of the polymer chains by producing a physical barrier between the chains and so the functional groups of these two polymers are free for adhesion to the OH group of the sodium alginate substrate and the presence of drug and other tablet ingredients has a great effect on the bioadhesive strength formed.

Fig. 5 shows the release profiles of tablets with different ratios of CP:CMC. To study the release kinetic of nifedipine from the tablets, the goodness-of-fit method was used. In all formulations, a zero-order equation showed a significantly better fit than first-order, Higuchi's square-root of time, or cube-root (Hixon–Crowel) equation (Table 4). The highest release rate constant (K) according to zero-order kinetic was seen in tablet CM-10 (Table 4) that was related to the high erosion rate of this tablet during dissolution test. However, the tablets of CM-7 and CM-8 showed the slowest release rate (the least K) compared to others ($P < 0.05$). According to Mortazavi and Smart [20], mucoadhesive materials adhere much better to solid surfaces and the opportunity for macromolecular interpenetration and secondary interactions is clearly minimal. Thus, in coincidence with the in vitro bioadhesion measurements of the tablets (Table 3), it may be concluded that the high attachment forces of these tablets in the dissolution test, results in the reduction of penetration of the dissolution medium within the tablets and the drug release rate. Besides, polymers swell in the dissolution medium because of an imbalance between the chemical potential of solvent within the polymer and that in the surrounding medium [21]. The osmotic pressure produced by the polymers causes the solvent movement until achievement of equilibrium between the internal and external chemical potentials [22]. Increasing the percentage of CMC in the tablets, produces a water-swollen gel-like state that substantially can reduce the penetration of dissolution medium into the tablets and so the drug release rate.

Table 3
Bioadhesion force of different formulations of buccoadhesive nifedipine tablets on a 1% w/v sodium alginate solution substrate ($n = 6$)

Formulation	CMC%	CP%	Mean bioadhesion force (dyn/cm^2) ± SD
CM-0	0	50	30.7 ± 0.4
CM-2	10	40	34.2 ± 0.5
CM-3	15	35	39.1 ± 0.5
CM-4	20	30	37.8 ± 0.4
CM-5	25	25	38.1 ± 0.3
CM-6	30	20	39.3 ± 0.3
CM-7	35	15	38.8 ± 0.7
CM-8	40	10	41.7 ± 0.4
CM-10	50	0	37.6 ± 0.7

From the pharmaceutical standpoint, the ability of the model to simulate the release rate of the drug on the basis of knowledge of the various diffusibilities can be of main predictive interest at the formulation stage, but for analysis of experimental release data conventional t plots are to be preferred. However, the semi-empirical equation $M_t/M_\infty = Kt^n$ was used to determine the drug release mechanism [23]. In all cases the exponent n was greater than 1 and ranged almost between 1.25 and 1.60 (Table 4). These high values may be because of the high swelling nature of these formulations. This means that swelling and diffusion normally do not follow Fickian kinetics due to the existence of a slow macromolecular relaxation process in the swollen region [24]. Low water-soluble drugs like nifedipine must go through the polymer matrix. These drugs are more soluble in the organic interior domain of the polymer than in water. This also tends to shift the release profile towards swelling

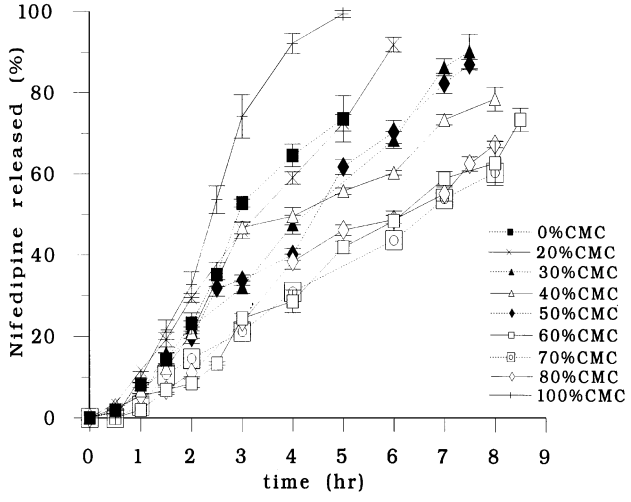

Fig. 5. Release profiles of nifedipine from different formulations of buccoadhesive tablets containing 50% of the mixtures of CP/CMC ($n = 6$).

Table 4
Correlation coefficient (r) of different models, drug release mechanism (n), ($M_t/M_\infty = Kt^n$) and zero-order release rate constant (K), (h^{-1}) of different formulations of buccoadhesive nifedipine tablets in phosphate buffer solution (pH 6.6) ($n = 6$)

Formulation	r				n	K (h^{-1}) ±SD
	Zero-order	First-order	Higuchi	Hixone–Crowel		
CM-0	0.994	0.980	0.890	0.780	1.267	3.88 ± 0.136
CM-2	0.996	0.878	0.898	0.810	1.260	3.437 ± 0.091
CM-3	0.994	0.911	0.884	0.796	1.254	3.491 ± 0.067
CM-4	0.974	0.956	0.923	0.792	1.476	3.015 ± 0.029
CM-5	0.990	0.934	0.900	0.797	1.265	3.506 ± 0.087
CM-6	0.987	0.951	0.681	0.859	1.563	2.607 ± 0.08
CM-7	0.987	0.976	0.882	0.777	1.325	2.202 ± 0.081
CM-8	0.976	0.970	0.873	0.930	1.267	2.561 ± 0.036
CM-10	0.990	0.865	0.830	0.790	1.599	5.870 ± 0.330

controlled, case II (zero-order) type release mechanism [25]. Considering the best fitted equation for drug release, according to the zero-order kinetic, $dQ/dt = k$ and in its integrated form, $100 - Q = Q_0 - Kt$ [26], or the presence of a linear relationship between the amount of drug remained to be released with the first power of time, there is almost a good coincidence with the results obtained from the equation of $M_t/M_\infty = Kt^n$ in which n value is nearly 1. Swelling of the tablet due to the diffusion of water into the polymer matrix, results in lowering the transition temperature of the polymers. The presence of water causes stresses within the glassy matrix due to the relaxation of the polymer chains. These stresses are compensated by an increase in the radius of gyration and end-to-end distance of the polymer molecules that is manifested as the swelling of the polymer matrix [27]. On the other hand, it seems that the rate of advancement of the swelling front into the glassy polymer and attrition of the rubbery state polymer might be nearly equal. To confirm this hypothesis, the rate of advancement of the swelling front into the glassy matrix and also erosion studies should be measured to see the effect of different percentages of CMC or CP on diffusional path length for the drug. Studies in this direction are in progress in our laboratory.

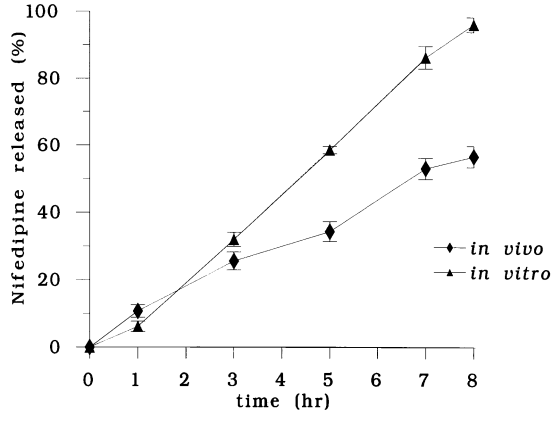

Fig. 6. Nifedipine released (%) in vitro and in vivo from CM-3 buccoadhesive tablets consisting of nifedipine (18.75%), CMC (15%), CP (35%), lactose (20.25%), PEG 6000 (10%) and magnesium stearate (1%).

The tablet CM-3 was chosen for in vivo release studies in human volunteers, because of the complete release of the loaded drug in the dissolution test (about 100% after 8 h), its superior bioadhesive properties after CM-8, and lack of interpolymer complexation. Fig. 6 shows the relationship between the percentage of nifedipine released in vitro and in vivo by taking the corresponding percentages released in vivo and in vitro at the same time intervals up to 8 h. There was a high in vitro–in vivo correlation ($P < 0.05$) between the drug-released from the bioadhesive-formulated tablets with a determination coefficient of 0.989. Considering the complete differences in the test conditions of in vitro and in vivo release tests, the high correlation and coincidence of the in vitro and in vivo release profiles demonstrates the validity of the release tests.

4. Conclusion

The developed tensiometry method seems a valid, simple and rapid method for in vitro bioadhesion measurements. The results indicate a remarkable degree of accuracy, precision, and reproducibility for this method. Increasing the CMC percentage in the buccoadhesive tablets of nifedipine slows down the drug release rate. However, the presence of CP is necessary for increased bioadhesion. The tablets containing just CP are too eroding and show the least bioadhesion with a fast release rate of drug while, the tablets with just CMC are less bioadhesive than those with a mixture of CP and have the fastest release rate. The tablets containing 15% CMC and 35% CP, seems to be optimum from drug release rate and bioadhesion, showing sustained drug release after application to the upper gums of the healthy volunteers. The release profile in vivo fitted well in the in vitro profiles. A linear relationship between the mean in vitro release pattern and that in vivo was observed. As this tablet formulation showed a zero-order release kinetic, the rate of drug release was almost constant and provided

that the entire amount released is topically absorbed in the tissue, it seems the rate-limiting step in the drug absorption.

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