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Mucoadhesive Delivery Systems. II. Formulation and In-Vitro/In-Vivo Evaluation of Buccal Mucoadhesive Tablets Containing Water-Soluble Drugs

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ABSTRACT

From the previous work (Part I), mucoadhesive formulae containing 5% CP/65% HPMC/30% lactose and 2% PC/68% HPMC/30% mannitol as well as formulae based on sodium carboxymethyl cellulose (SCMC) were selected. Medicated tablets were prepared using diltiazem hydrochloride (DZ) and metclopramide hydrochloride (MP) in two different doses (30 and 60 mg). The effect of drug and dose on the mucoadhesive properties and in-vitro drug release was evaluated. All formulae produced extended drug release (over 8 to 12 h). Polyacrylic acid based matrices (PAA) showed Fickian's diffusion release pattern for both drugs. SCMC ensured zero-order release for DZ, which deviated to anomalous behavior in case of MP. Doubling the dose significantly reduced the bioadhesion strength ($p<0.05$) with a slight improvement in drug release rate. The formulation of bilayer tablets containing drug-free layer and medicated layer enhanced the drug release without affecting the bioadhesive performance. The bilayer tablet formulated with 2% PC/68% HPMC/30% mannitol (PC_2) was selected for studying the in-vivo metoclopramide release in four healthy volunteers. The tablet ensured controlled drug release for 12 h, in addition, good correlation ($r=0.9398$) was observed between in-vitro and in-vivo data. The effect of ageing on selected formulae containing DZ and MP, respectively, was studied. Storage at 40°C and 75% relative humidity for 6 months didn't influence the mucoadhesive performance, however, an enhanced released rate was observed.

Key Words: Buccal tablet; Mucoadhesion; Bioadhesive polymer; In-vitro/in-vivo; Sustained release; Ageing; Diltiazem; Metoclopramide.

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INTRODUCTION

Transmucosal routes of drug delivery offer distinct advantages over per oral administration for systematic drug delivery. These advantages include possible bypass of first-pass effect, avoidance of presystemic elimination within the GIT, and depending on the particular drug, a better enzymatic flora for drug absorption.[1] The buccal mucosa is relatively permeable with a rich blood supply. It is robust and shows short recovery time after stress or damage. In addition, the dosage form can be applied, localized, and removed easily. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery.[2]

Water-soluble drugs are considered difficult to deliver in the form of sustained or controlled release preparation due to their susceptibility to ''dose dumping phenomenon.'' Attempts have been made to regulate their release process by use of mucoadhesive polymers in order to achieve a once-a-day dose treatment.[3]

Diltiazem hydrochloride (DZ) is a calcium-channel blocker, which has been useful in the treatment of various cardiovascular disorders, particularly angina and systemic hypertension. DZ has been reported to be rapidly absorbed from GIT, and to be extensively metabolized in the liver, mainly by deacetylation. The bioavailability of oral DZ is approximately 40% in human. Because of its low biovailability and short half-life, attempts have been made to develop sustained release mucoadhesive formulations with extended clinical effect and reduced dosing frequency. Sublingual administration of mucoadhesive tablet containing chitosan and sodium alginate as bioadhesive matrix improved the bioavailability of DZ in rabbits to 69.6% compared to 30.4% by per oral administration.[4] Similarly Miyazaki et al.[5] concluded that the single and bilayer tablets of DZ, containing pectin and HPMC (1:1), ensured satisfactory bioadhesive strength, in-vitro sustained release over a 5 h period, as well as enhanced bioavailability. In another study, bioadhesive buccal multilayered tablets were developed using CP934 and polyvinyl pyrrolidone as the bioadhesive system. In-vitro release data indicated that 86% DZ were released after 4 h, which correlated well with the in-situ diffusion experiment.[6]

Metoclopramide hydrochloride (MP) is a powerful antiemetic and modifier of the gastric motility. However, more than 60% of the oral dose suffered from first-pass metabolism. Absorption via the buccal cavity through mucoadhesive devices is aimed to avoid metabolic drug loss and to ensure sustained release. Garcia-Gonzalez et al.[7] formulated bioadhesive metoclopramide buccal tablets using PAA/HPMC in different ratios. In-vitro release indicated that about 50% MP was released after 8 h. The same workers evaluated the effect of cross-linking of PAA hydrogels with sucrose[8] or beta cyclodextrin[9] on the release characteristics of metoclopramide. The results showed that both swelling and drug release are strongly reduced by increasing cross-linking agent concentration.

The purpose of this study is to evaluate the effect of drug (DZ and MP) and dose on the mucoadhesive properties of the selected formulae. The in-vitro and the in-vivo drug release as well as the effect of ageing on the characteristics of the medicated buccal tablets are also considered.

EXPERIMENTAL

Materials

Diltiazem hydrochloride (DZ), Cynthelabo Canabe Chimie, supplied from Amriya Pharmaceutical Industries, Egypt. Metoclopramide hydrochloride (MP) supplied from Alexandria Pharmaceutical Co., Alexandria, Egypt. Carbopol 934 (CP934) of nominal molecular weight 3×10^6 (Goodrich Chemical Co, USA), Hydroxypropylmethyl cellulose 4000 cp (HPMC) and gum tragacanth (GT) were all kindly supplied from Alexandria Pharmaceutical Co, Egypt. Polycarbophil (PC) supplied from Pharco Pharmaceuticals, Egypt. Sodium carboxymethyl cellulose (SCMC) supplied from ADWIC, El-Nasr Pharmaceutical Chemicals Co, Egypt. Spray-dried lactose (Zeparox®), Borculo Whey Products, was supplied from Amriya Pharmaceutical Industries, Egypt. D(-)-mannitol, Riedel-De Haen AG Sleeze-Hannover.

Methods

Compression of Bioadhesive Medicated Tablets

Based on the previous work (Part I), the best formulations insuring satisfactory mucoadhesion were selected: carbopol-containing formula (5% CP/65% HPMC/30% lactose), polycarbophil formula (2% PC/68% HPMC/30% mannitol), SCMC and 75% SCMC/25% gum tragacanth formulae. In order to investigate the influence of the drug properties on the physical characteristics of the selected mucoadhesive systems, water soluble drugs diltazem HCL (DZ) and metoclopamide HCl (MP) were incorporated.

Table 1. Composition of prepared mucoadhesive tablet formulae.

	Formula code																			
Composition (mg)	CP	CP_1	CP_2		CP_3	CP_4		PC	PC_1	PC_2		PC_3	PC_4		C	C_1	C_2	C_3		C_4
			A	B		A	B			A	B		A	B				A	B	
Drug	–	30	30	–	60	60	–	–	30	30	–	60	60	–	–	30	30	30	–	60
CP	6.0	6.0	3	1.5	5	3	1.5	–	–	–	–	–	–	–	–	–	–	–	–	–
PC	–	–	–	–	–	–	–	2.4	2.4	1.2	0.6	2	1.2	0.8	–	–	–	–	–	–
HPMC	78	78	39	19.5	65	39	19.5	81.6	81.6	40.8	20.4	68	40.8	27.2	–	–	–	–	–	–
Lactose	36	6	18	9	30	18	9	–	–	–	–	–	–	–	–	–	–	–	–	–
Mannitol	–	–	–		–	–	–	36	6	18	9	30	18	12	–	–	–	–	–	–
SCMC	–	–	–		–	–	–	–	–	–	–	–	–	–	120	67.5	90	60	30	90
GT	–	–	–		–	–	–	–	–	–	–	–	–	–	–	22.5	–	–	–	–
P/D	–	2.8	1.4		1.17	0.7		–	2.8	1.4		1.17	0.7		–	3	3	2		1.5

P/D indicates polymer to drug ratio.
(A) and (B) indicate the medicated and the plane layers in the bilayer tablets, respectively.

Medicated tablets (120–160 mg) containing 30, 60 mg drug (DZ or MP) were compressed using flat-faced punch, 9 mm in diameter (Erweka single punch tablet machine, GmbH, Frankfurt, Germany). Tablet compositions are listed in Table 1. Before direct compression, the powders were screened through a 125 μm sieve and then thoroughly blended. To prepare bilayer tablets, the non-medicated layer was first compressed then the medicated layer was filled into the die cavity and both are compressed together. The mean weight, thickness and hardness of the compressed tablets (n=20) were determined.

Determination of the Bioadhesion Force

The bioadhesion force was determined by measuring the tensile strength required for complete breakdown of the bioadhesive bond between the tablet and the mucosal surface. The apparatus and the procedure used were previously described.[10] In case of bilayer tablets, the medicated layer was glued to the platinum lamina while the plain layer was the one exposed to the mucosal surface. The mean of five replicate determinations was calculated.

Determination of the In-Vitro Residence Time

The time necessary for complete erosion or detachment of the bioadhesive tablet from the mucosal membrane was determined using the locally-modified USP disintegration apparatus described in Part I. The experiment was carried out in triplicate.

Average Drug Content

Five medicated tablets were finely ground in a mortar. An accurately weighed amount was shaken with 1 liter isotonic phosphate buffer, IPB pH 6.75. Aliquots were filtered and assayed spectrophotometrically at 232 nm and 272 nm for diltiazem hydrochloride and metoclopramide hydrochloride, respectively.

In-Vitro Release Test

The drug release study was carried out using the USP24 dissolution apparatus type 1 with automatic sampler. The baskets were removed and the tablets were attached to the central axis through cyanoacrylate adhesive, so that only one surface of the tablet was exposed to the dissolution medium. In case of diltiazem hydrochloride, 900 ml distilled water were used as the dissolution medium, while 900 ml IPB pH 6.75 were used for the release of metoclopramide hydrochloride. The release study was done at 37± 0.5°C with a rotation speed 50 rpm. The concentration of drug dissolved at different time intervals was analyzed spectrophotometrically at 232 nm and 272 nm for DZ and MP, respectively. The data presented were the mean of three determinations.

In-Vivo Release Test

Four human healthy volunteers (25–50 years old) were enrolled in the study of metoclopramide release from the optimized bioadhesive formulation (Informed consents from the volunteers were obtained). Half an hour after breakfast, the subjects were asked to place the tablet on the buccal mucosa between the cheek and gingiva in the region of the upper canine. The tablet was slightly pressed with the tip of the finger for 30 s. Eating and drinking were not allowed in the first hour of the study, after which drinking of water was permitted. After 4 h, a standard meal was given to the volunteers. At fixed intervals; 2, 4, 6, 8, 10, and 12 h, the tablet was carefully removed and soaked into 500 ml IPB pH 6.75, with occasional shaking. One tablet was used for the determination of drug released at each interval. After complete disintegration of the soaked tablet, a sample was filtered using Millipore filter and analyzed spectrophotometrically at 272 nm for the concentration of metoclopramide remaining in the tablet. The concentration of drug released is then calculated. A minimum period of 48 h was required between replicate applications of the tablets for the same subject. During the experiment, volunteers were requested to comment on the acceptability, ease of speaking and eating and also to monitor any signs of irritation, ulceration or dislodgment of the tablet from the site of application.

Effect of Ageing

For both drugs, optimized medicated tablets were stored in glass vials maintained at 40°C, 75% RH, for 6 months. The effect of storage was monthly investigated; the change in the physical properties, bioadhesive characteristics and the release behavior of the bioadhesive tablets was determined.

RESULTS AND DISCUSSION

Medicated tablets were formulated as single layer as well as bilayer tablets containing either 30 or 60 mg

drug. The average thikness of all prepared tablets ranged from 1.5–2.1 mm and the hardness ranged from 7–14 kg. Table 2 shows the effect of the addition of the two drugs DZ and MP in two different doses 30 and 60 mg on the bioadhesion force of mucoadhesive tablet formulae. It is observed that the addition of 30 mg of either drug to formulae based on CP/HPMC (CP_1) reduced the bioadhesion by almost 25%. However, no or slight reduction in adhesive performance was observed when both drugs are added to formulae based on SCMC (C_1 and C_2) and PC/HPMC (PC_1). When 60 mg of either drug was added, a marked reduction in bioadhesion force from 35–53% was observed in all cases (CP_3, PC_3 and C_4). Two-way ANOVA applied to the result of bioadhesion force indicated that the effect of DZ and MP on bioadhesion force of plain formulae was not significantly different at 1% level ($F_{1,2}=1.58$). While, the effect of dose of either DZ or MP on the bioadhesion force of plain formulae was found to be statistically significant at the 1% level ($F_{2,4}=83.18$ and 22.499 for DZ and MP respectively). The change in polymer/drug ratio (P/D) from 2.8 to 1.17 (Table 1), when doubling the dose may be responsible for the reduced mucoadhesion. Higher polymer density at the mucosal interface enabled better interpenetration and entanglement and consequently stronger mucoadhesion. Comparative observation was obtained by Bouckaert and Remon;[11] 30% miconazole nitrate didn't influence the bioadhesive characteristics of tablets containing thermally modified starch and CP907, whereas a significant decrease in bioadhesion was seen at a concentration of 50% miconazole nitrate. Regarding the bilayer formulae (CP_2, CP_4, PC_2,PC_4 and C_3) no effect on bioadhesion was observed due to the presence of the drug in the outer release layer and the plain layer is in contact with the mucus (Table 2).

The duration required for complete tablet erosion was recorded in Table 2, indicating that the addition of 30 mg of either drugs had a marginal influence on the in-vitro residence time of the tablets, while the addition of 60 mg of each drug resulted in a delay of one hour and 2–3 h. in residence time for MP and DZ formulae respectively.

The release profiles of DZ and MP from different mucoadhesive formulations based on CP, PC and SCMC are illustrated in Figs. 1 and 2 respectively. The in-vitro release study showed satisfactory sustained release of DZ and MP from all medicated formulae. CP, PC and HPMC are hydrophilic swellable polymer matrices; they are able to form a viscous gel layer; which controls the drug release via diffusion through the gel and erosion of the gel barrier.[12] At salivary pH, 6.8, DZ ($pk_a=7.7$) will be 88.8% ionized and MP ($pk_a=9$) 99.9% ionized according to Henderson–Hasselebach equation. Therefore, interaction between the cationic drugs and the anionic polymer (pK_a of PAA range from 4.5–7) is obvious at this pH. A complex formation between CP934 and the cationic drug propranolol hydrochloride in alkaline medium was

Table 2. Bioadhesion force and in-vitro residence time for different mucoadhesive tablet formulae.

Formulae code	Bioadhesion force ($\times 10^3$dyne.cm^{-2})			In–vitro residence time (h)		
	Plain formulae	DZ formulae	MP formulae	Plain formulae	DZ formulae	MP formulae
CP	37.62			11.5		
CP_1		28.05*	28.3		12.5**	12.0
CP_2		42.16	39.68		14.0	10.75
CP_3		21.42	24.52		14.0	11.5
CP_4		38.51	40.11		15.0	12.5
PC	37.99			11.25		
PC_1		31.02	35.36		12.0	11.0
PC_2		38.27	38.09		13.5	11.75
PC_3		17.53	22.7		13.0	12.0
PC_4		38.35	37.51		14.0	13.0
C	46.48			8.0		
C_1		46.9	–		8.0	–
C_2		43.46	43.9		7.67	7.75
C_3		47.05	47.01		8.15	8.0
C_4		27.8	30.6		11.0	8.75

*Standard deviation ranges from 1.84 to 4.91, n = 5.

**Standard deviation ranges from 0.37 to 2.09, n = 3.

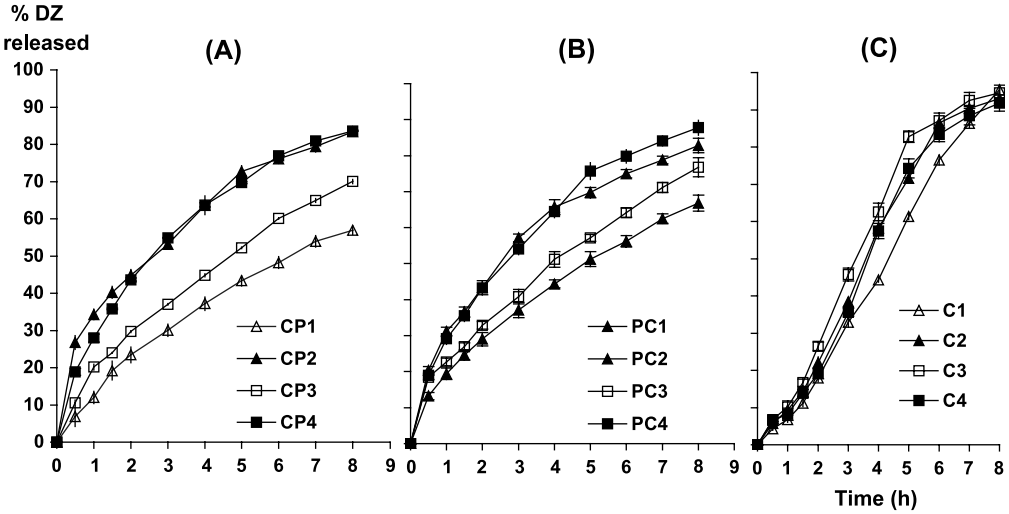

Figure 1. Release profiles of diltiazem hydrochloride from mucoadhesive tablets based on (A) CP/HPMC/lactose, (B) PC/HPMC/mannitol, and (C) SCMC formulae.

reported.[13,14] Doubling the dose of the drugs enhance the release rate as shown in Figs. 1 and 2. The bilayer tablets promote the release rate at all intervals compared to the single layer loaded with the same dose. The P/D in single layer formulae is double that in bilayer formulae (Table 1). Reducing the amount of the polymer to the half ensures faster release. This can be attributed to the reduction of the strength of the gel layer, which enhances drug diffusion and water uptake through the matrix.[15] Doubling the dose didn't show increase in drug release in the bilayer formulae as in single layer formulae (Figs. 1 and 2); this finding may be due to the higher interaction between CP and PC and the drug at this ratio (P/D=0.7).

Figures 1–C and 2–C illustrate the drug release form tablets based on SCMC. The addition of gum tragacanth (C_1) showed no obvious influence on the release compared to C_2. Gum tragacanth is known to process a sustaining effect. No remarkable change in the release rate was observed when the dose was

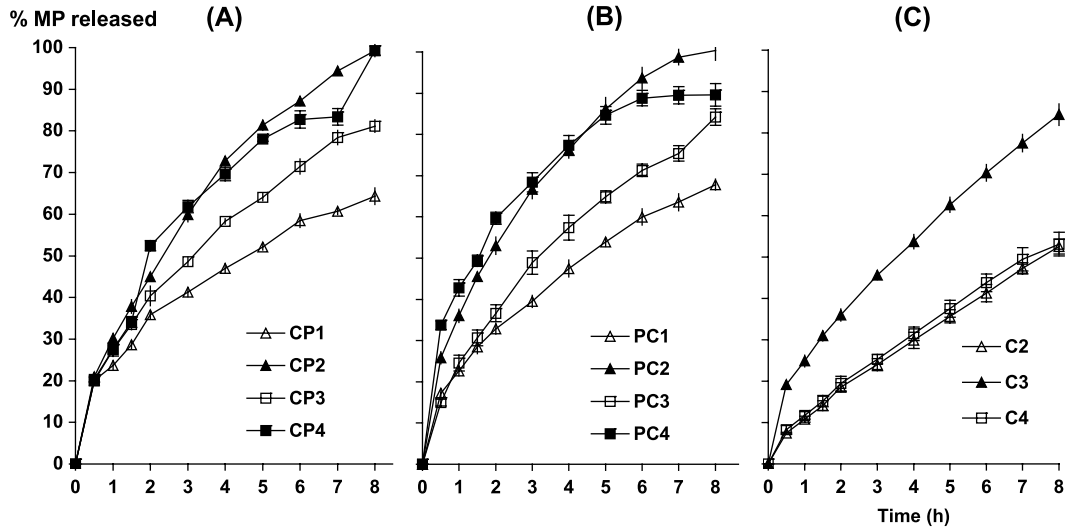

Figure 2. Release profiles of metoclopramide hydrochloride from mucoadhesive tablets based on (A) CP/HPMC/lactose, (B) PC/HPMC/mannitol, and (C) SCMC formulae.

Table 3. Release kinetic parameters of diltiazem hydrochloride and metoclopramide hydrochloride from different mucoadhesive tablet formulae.

	Diltiazem hydrochloride				Metoclopramide hydrochloride			
Formula code	$t_{50\%}$(h)	n	k (h^{-n})	r	$t_{50\%}$(h)	n	k (h^{-n})	r
CP_1	6.8	0.74	12.97	0.997	4.8	0.446	25.42	0.995
CP_2	2.7	0.428	34.61	0.997	2.2	0.582	30.83	0.998
CP_3	5.0	0.726	13.5	0.999	3.2	0.515	27.93	0.999
CP_4	2.7	0.553	28.72	0.994	2.0	0.539	28.83	0.998
PC_1	5.0	0.478	33.42	0.996	4.5	0.509	23.41	0.998
PC_2	2.2	0.498	30.8	0.997	2.8	0.513	36.89	0.999
PC_3	4.0	0.547	23.7	0.992	3.1	0.613	23.88	0.999
PC_4	2.5	0.564	28.6	0.998	1.6	0.478	44.07	0.993
C_1	4.3	1.1	10.53	0.994	–	–	–	–
C_2	3.5	0.959	13.001	0.996	7.2	0.722	11.23	0.998
C_3	3.2	0.939	14.31	0.997	3.5	0.651	25.76	0.999
C_4	3.5	1.2	8.118	0.994	7.8	0.698	12.24	0.998

$t_{50\%}$ indicates the time for 50% release of the drug.

doubled, although the polymer content was reduced from 3 to 1.5 weight ratio (Figs. 1 and 2, Table 1). At salivary pH, both drugs and the polymer matrix are highly ionized (pK_a of SCMC is 4.3). The concentration of SCMC in the buccal tablet range from 56.25 to 75% compared to 5% for CP and 2% for PC tablets, leading to pronounced ionic drug-polymer interaction in SCMC formulae. This may explain the improvement in release rate with dose doubling in CP and PC formulae but not with SCMC one (Figs. 1 and 2).

Refering to Figs. 1 and 2 and the data of $t_{50\%}$ listed in Table 3, it is observed that MP exhibit a faster release profile compared to DZ with the two studied doses. Almost 10% increase in the amount released was noticed with MP relative to DZ in case of tablets based on CP formulae. Tablets based on CP_1 formula release 50% of MP and DZ after 4.8 h. and 6.8 h. respectively. This effect is less obvious in case of mucoadhesive tableta based on PC formulae. On the contrary, a significant increase in the rate and extent of DZ released from SCMC based tablets is observed compared to MP when 30 and 60 mg drug were applied (Figs. 1 and 2). The $t_{50\%}$ of the C_2 formula was found to be about 3.5 h. and 7.2 h. for DZ and MP respectively (Table 3).

To examine the kinetic behavior, the release data were analyzed using Peppas equation:

$$M_t/M_\infty = Kt^n$$

where, M_t/M_8 is the fractional release of the drug, t denotes the release time, K is a constant incorporating structural and geometric characteristics of the controlled release device and n is the release exponent, indicative of the mechanism of drug release. The release keinetic parameters were calculated for each formulae and listed in Table 3. The majority of the mucoadhesive systems based on CP/HPMC and PC/HPMC showed Higuchi diffusion-controlled kinetics ($n \sim 0.5$, Table 3). Changing drug content and/or polymer content in the tablets didn't reflect changes in the release kinetics; except for single layer formulae CP_1 and CP_3 containing 30 and 60 mg DZ, respectively where non-Fickian release behavior is observed ($1 > n > 0.5$, Table 3). In case of the mucoadhesive formula based on SCMC, the release keinetics indicate a zero order release for DZ ($n \sim 1$) and anomalous release for MP ($1 > n > 0.5$, Table 3). The mechanism of drug release for swellable and errodible hydrocolloid systems is a complex phenomenon. The rates of swelling, erosion and drug diffusion determine the mechanisms and the release kinetics. Higuchi controlled diffusion ($n \sim 5$) indicated that the erosion of the swollen gel layer is very slow,[16,17] while non-Fickian release prevailed when the difference between the penetration of the diffusion front and the erosion front is not too high. Ponchel et al.[18] suggested that non-Fickian release behavior could be controlled by a combination of diffusion and chain relaxation mechanism. Previous studies indicates that the zero order effect is due to either electrostatic interaction between SCMC backbone and the drug cations[19] or due to the equivelance of the rates of swelling and erosion.[20]

Formula PC_2 prepared as a bilayer tablet containing 30 mg MP was selected for in-vivo testing. This formula was characterized by complete MP release

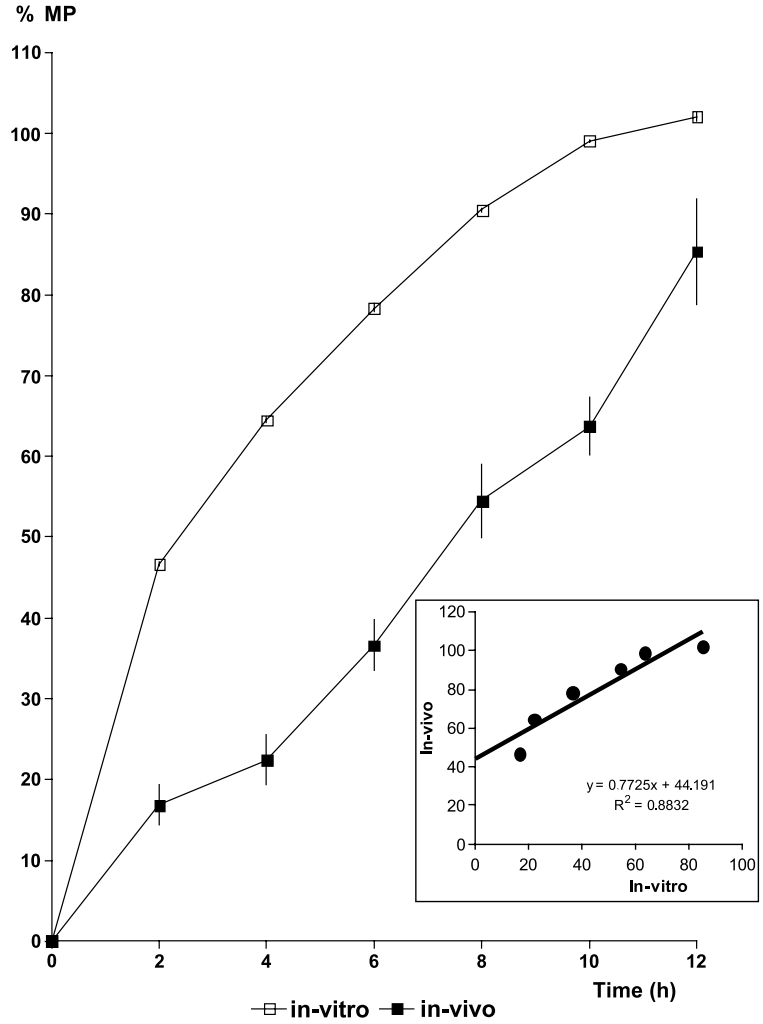

Figure 3. In-vitro and in-vivo release profiles of metoclopramide hydrochloride from mucoadhesive formula PC_2. The inser represents the correlation between the in-vivo and the in-vitro release.

after 8 h, (Fig. 2B). In all volunteers, the bioadhesive tablet remained in place for >12 h without detachment. The formulation was well accepted by the subjects; no complaints due to discomfort, irritation, or ulceration were recorded. The bioadhesive tablets allowed the gradual MP release over a 12 h period (Fig. 3). After 2 h, about 16.84% MP was released, while 54.47% drug release was achieved after 8 h. Maximum MP release was recorded after 12 h (85.36%). The low inter subject variation denoted at the beginning of the study ($S.D_{2\ h}$=2.489), may be attributed to the limited tablet swelling owing to the limited volume of salivary secretion. By time, a comparatively higher variance ($S.D_{12\ h}$=6.582) in release was noted among volunteers (Fig. 3). This may be explained by the subject's habits like talking, jaw and tongue movement, which all affect tablet erosion and consequently drug release. Comparable variation was obtained from the in-vivo release properties of various buccal controlled release devices.[21,22] Estimation of the amount of drug released through the determination of the amount of drug remaining in the recovered tablets was previously conducted by, Mumtaz and Ch'ng[22] for the buccal delivery of triamcinolone acetonide.

Comparing in-vitro and in-vivo drug release profiles (Fig. 3), it is observed that at the same intervals, higher amount of MP was released in-vitro compared to in-vivo release. After 2 h, 46.61% MP were released in the dissolution apparatus compared to 16.84% released in human volunteers. Complete in-vivo drug release was achieved within 12 h, while only 85.36% MP was released at the same duration in-vivo.

Table 4. Short-term stability data of mucoadhesive tablets containing diltiazem hydrochloride (formula C_2) and metoclopramide hydrochloride (formula PC_2) stored at 40°C/75% RH for 6 months.

	Duration of storage (months)							
	Diltiazem hydrochloride (formula C_2)				Metoclopramide hydrochloride (formula PC_2)			
Characteristics	0	2	4	6	0	2	4	6
Tablet hardness (kg)	8	7.5	7.5	7	8	7.5	7.5	7
In-vitro residence time (hr)	8 (0.515)*	8 (0.855)	7.5 (0.842)	7.25 (0.799)	10 (0.848)	11 0.937	11.25 (0.757)	11.75 (0.823)
Bioadhesion force ($\times 10^3$dyne.cm^{-2})	43.46 (1.58)**	40.51 (1.62)	37.55 (2.88)	36.27 (1.66)	38.84 (2.08)	36.82 (1.331)	39.48 (1.68)	31.3 (1.877)
% released								
(2 h)	16.5	25.3	29.6	33.6	36.9	44.1	46.6	51.9
(6 h)	80.4	91.9	97.3	100.0	64.9	74.7	76.5	83.3
$t_{50\%}$ (h)	3.8	3.3	2.9	2.54	3.0	2.75	2.4	1.9
Release kinetics								
n	1.1	1.01	1.17	1.2	0.49	0.49	0.49	0.49
k (h^{-n})	9.863	12.24	14.45	15.28	28.08	31.05	32.81	37.07
r	0.996	0.994	0.993	0.991	0.999	0.993	0.995	0.997

*Values between brackets indicate the standard deviation (n=3).
**n=5.

This may be due to the different conditions of the in-vitro study such as high stirring rate and the relatively large volume of the dissolution medium compared to the salivary volume, which allowed faster swelling and dissolution of the drug in the medium. Significant in-vitro and in-vivo correlation (r=0.9398) is obtained (Fig. 3-insert). The higher in-vitro release is again reflected by the positive intercept on the y-axis. Therefore, the in-vitro release of metoclopramide from the bioadhesive tablet seems to provide good information on the release pattern of MP in the oral cavity. In a similar release approach, the in-vitro and in-vivo fluoride release from biadhesive slow release buccal tablets ensured sustained fluoride levels in saliva compared to conventional fluoride tablets with the same fluoride content.[21]

The effect of ageing was studied for formulae C_2 and PC_2 containing 30 mg DZ and MP, respectively. The storage conditions were maintained at 40±0.5°C and 75±5% RH for 6 months. The data shown in Table 4 reveal no marked change in hardness or residence time. A slight reduction in the bioadhesion strength was noticed for DZ but no obvious alteration in bioadhesion of MP formula was observed. Improvement of release rate was observed for both C_2 and PC_2. At the end of the study, t_{50} (time necessary for 50% drug release) was found to be about 2.54 h and 1.9 h for DZ and MP respectively compared to 3.8 h and 3.0 h for fresh samples. The gradual increase in the release rate constant, k, with storage is an additional proof of the release improvement with ageing (Table 4). The nearly constant n values (close to unity for DZ and to 0.5 for MP) reveal that the release behavior of both drugs from mucoadhesive tablets is not affected by the storage conditions.

CONCLUSIONS

Mucoadhesive buccal tablets containing 30 mg diltiazem hydrochloride (DZ) or metoclopamide hydrocloride (MP) provided sustained release for 8 to 12 h.Doubling the dose of either drug (60 mg) significantly reduced the mucoadhesive performance and relatively enhanced the release rate. Large doses could be better formulated as bilayer tablets. The difference in the release behavior from one formula to the other may be attributed to the drug properties, its relative affinity to the polymer system, which determines the extent of drug-polymer interactions. In-vivo study of MP release from the bilayer tablets prepared with PC/HPMC/mannitol ensured extended drug release for 12 h. In-vitro/in-vivo correlation was successfully demonstrated. Study of the effect of ageing on mucoadhesive tablets based on SCMC containing DZ and PC/HPMC/manitol containing MP revealed stable bioadhesive performance despite some enhancement in release rate.

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