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Original research paper

Development and *in vitro* evaluation of buccoadhesive carvedilol tablets

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Buccoadhesive tablets of carvedilol were prepared using HPMC K4M, HPMC K15M and Carbopol 934 as mucoadhesive polymers. Fifteen formulations were developed with varying concentrations of polymers. Formulations of the BC or BD series were composed of HPMC K4M or HPMC K15M in ratios of 1:1 to 1:5 whereas in the BE series Carbopol 934 was used (1:0.25 to 1:1.50). The formulations were tested for *in vitro* drug release, *in vitro* bioadhesion, moisture absorption and *in vitro* drug permeation through porcine buccal mucosa. Formulation BC3 showed maximum release of the drug (88.7 ± 0.4%) with the Higuchi model release profile and permeated 21.5 ± 2.9% of the drug (flux 8.35 ± 0.291 μg $h^{-1}cm^{-2}$) permeation coefficient 1.34 ± 0.05 cm h^{-1}) through porcine buccal membrane. BC3 formulation showed 1.62 ± 0.15 N of peak detachment force and 0.24 ± 0.11 mJ of work of adhesion. FTIR results showed no evidence of interaction between the drug and polymers. XRD study revealed that the drug is in crystalline form in the polymer matrix. The results indicate that suitable bioadhesive buccal tablets with desired permeability could be prepared.

Keywords: buccal tablets, carvedilol, formulation, bioadhesion, evaluation

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Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of administration. Problems such as high first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route (1–3). Moreover, buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally to prevent accidental swallowing. Therefore adhesive mucosal dosage forms were suggested for oral delivery, which included adhesive tablets (4–6), adhesive gels (7, 8) and adhesive patches (9, 10).

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Carvedilol is a non-selective β-adrenergic antagonist used in the treatment of hypertension and stable angina pectoris. It also possesses antioxidant and antiproliferative effects, which may enhance its ability to combat the deleterious effects of sympathetic nervous system activation in heart failure (11). Carvedilol was selected as a model drug for the investigation because its oral dose is low (6.25–25 mg) (12). A suitable buccal drug delivery system should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a predictable manner to elicit the required therapeutic response.

In our previous report (13), buccal patches of carvedilol released the drug for 5 h. To prolong the drug release and to reduce dosing frequency, a suitable formulation was required with a controlled rate to treat hypertension. In the present study, buccoadhesive tablets were developed using a hydrophilic polymer, hydroxypropyl methylcellulose (HPMC K4M and K15M) and Carbopol 934 to get controlled and zero order release.

EXPERIMENTAL

Materials

Carvedilol was donated by Sun-Pharmaceuticals, India, hydroxypropyl methylcellulose (Methocel K4M, Methocel K15M) by Colorcon Asia, India, Carbopol 934 (Noveon, Inc., USA.) and Perlitol SD 200 (Roquette, USA) by Zydus Cadila, India. All other chemicals and reagents used were of analytical grade and purchased from Merck Ltd., India.

Buccoadhesive tablets preparation

Carvedilol was mixed manually in glass bottles with different ratios of Methocel K4M and K15M, Carbopol 934 as mucoadhesive polymers and Pearlitol S.D 200 (mannitol) as diluent (Table I) for 10 min. The blend was lubricated with sodium stearyl fumarate (SSF) for 3–5 min and then compressed into tablets by the direct compression method using 8-mm flat-faced punches. The tablets were compressed using a Cadmach rotary tablet machine (Cadmach Machinery, India). The mass of the tablets were determined using a digital balance (Shimadzu Japan) and thickness with a digital screw gauge (Mitatyo, Japan).

Assay of carvedilol

Twenty tablets were taken and powdered; powder equivalent to one tablet was taken and was allowed to dissolve in 100 mL of 0.5% (m/V) of sodium lauryl sulphate solution on a rotary shaker overnight. The solution was centrifuged and the supernatant was collected. The absorbance was measured using a UV-Vis Spectrophotometer (Elico, India) at 244 nm.

In vitro *release studies*

The drug release rate from buccal tablets was studied using the USP 28 (14) type II dissolution test apparatus (Lab India dissolution test apparatus Disso 2000) equipped

Table I. Composition of carvedilol buccal tablets

Formulation	Drug (mg)	Polymer (mg)			Filler Perlitol SD 200 (mg)	SSF (mg)
		HPMC K4M	HPMC K15M	Carbopol		
BC1 (1:1)	6.25	6.25	–	–	105.10	2.40
BC2 (1:2)	6.25	12.50	–	–	98.85	2.40
BC3 (1:3)	6.25	18.75	–	–	92.60	2.40
BC4 (1:4)	6.25	25.00	–	–	86.35	2.40
BC5 (1:5)	6.25	31.25	–	–	80.10	2.40
BD1 (1:1)	6.25	–	6.25	–	105.10	2.40
BD2 (1:2)	6.25	–	12.50	–	98.85	2.40
BD3 (1:3)	6.25	–	18.75	–	92.60	2.40
BD4 (1:4)	6.25	–	25.00	–	86.35	2.40
BD5 (1:5)	6.25	–	31.25	–	80.10	2.40
BE1 (1:0.25)	6.25	–	–	1.562	109.788	2.40
BE2 (1:0.50)	6.25	–	–	3.125	108.225	2.40
BE3 (1:0.75)	6.25	–	–	4.687	106.663	2.40
BE4 (1:1.00)	6.25	–	–	6.250	105.110	2.40
BE5 (1:1.50)	6.25	–	–	9.375	101.975	2.40

SSF – sodium stearyl fumarate

with an auto sampler and fraction collector for the collection and replenishment of the sample and dissolution medium, respectively. Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2x2 cm glass slide with a solution of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus. The dissolution medium was 500 mL of 0.5% (m/V) of sodium lauryl sulphate solution at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 mL were collected at different time intervals up to 8 h and analyzed spectrophotometrically.

Tissue isolation

Porcine buccal tissue from domestic pigs was obtained from a local slaughterhouse and used within 2 hours of slaughter. The tissue was stored in Krebs buffer pH 7.4 at 4 °C after collection. The epithelium was separated from the underlying connective tissue with a surgical technique and the delipidized membrane was allowed to equilibrate for approximately one hour in receptor buffer to regain lost elasticity.

In vitro *bioadhesion studies*

The bioadhesive strength of the tablets was measured using the Ultra test (Mecmesin, UK) equipped with a 5 kg load cell. The fresh porcine buccal mucosa obtained from the slaughterhouse and stored in simulated saliva solution (16.8 mmol L^{-1} of Na_2HPO_4, 1.4 mmol L^{-1} of KH_2PO_4 and 136.8 mmol L^{-1} of NaCl pH 6.75) was secured tightly to a circular stainless steel adaptor (diameter 2.2 cm) provided with the necessary equipment. A backup membrane was placed over the buccal tablet to be tested and fixed with the help of cyonoacrylate adhesive to the cylindrical stainless steel adaptor of similar diameter. The entire setup was mounted onto the platform of a motorized test stand. All measurements were conducted at room temperature. During measurement, 100 μL of 1% mucin solution (crude mucin procured from Sigma Chemical Co, USA) was used to moisten the porcine buccal membrane. The upper support was lowered at a speed of 0.5 mm s^{-1} until contact was made with the tissue at the predetermined force of 0.5 N for a contact time of 180 s. At the end of contact time, the upper support was withdrawn at a speed of 0.5 mm s^{-1} to detach the membrane from the tablet.

Data collection and calculations were performed using the data plot software package of the instrument. Two parameters, namely the work of adhesion and peak detachment force, were used to study the buccal adhesiveness of tablets (15).

Moisture absorption

Moisture absorption study was performed according to the modified procedure reported earlier (16). Agar (5%, *m*/*V*) was dissolved in hot water. It was transferred into Petri dishes and allowed to solidify. Six buccal tablets from each formulation were placed in a vacuum oven overnight prior to the study to remove moisture, if any, and laminated on one side with a water impermeable backing membrane. They were then placed on the surface of the agar and incubated at 37 °C for one hour. Then the tablets were removed and weighed and the percentage of moisture absorption was calculated.

In vitro *drug permeation through porcine buccal membrane*

In vitro permeation of carvedilol from matrix tablets through the porcine buccal membrane was studied. The membrane was mounted over a Franz diffusion cell of i.d. 2.1 cm and the selected matrix tablet (BC3) containing 6.25 mg of carvedilol was placed on the membrane. A dialysis membrane (HiMedia, India) with molecular mass cut off 5000 was placed over it to prevent the tablet from getting dislodged. The receiver compartment of the diffusion cell was filled with 12.0 mL of alcohol : propylene glycol : phosphate buffer saline pH 7.4 mixture (40:15:45).

The entire setup was placed over a magnetic stirrer and the temperature was maintained at 37 °C by placing the diffusion cell in a water bath. One mL samples were collected at predetermined time intervals from the receptor compartment and replaced with an equal volume of the above mixture. The amount of carvedilol in the diffusion samples was estimated by the HPLC method.

HPLC analysis

Analysis of samples was performed using a Shimadzu HPLC system equipped with an LC-10AT pump (Shimadzu), RF10AXL spectrofluorimetric detector and a RP C18 Phenomenex column (250 x 4.6 mm i.d., particle size 5 μm) at ambient temperature. The mobile phase was a mixture of acetonitrile, methanol, water and triethylamine (25:20:54.9:0.1, *V/V*). The pH was adjusted to 2.5 with orthophosphoric acid. The flow rate was 1 mL per minute. The detection was carried on at 285 and 380 nm as excitation and emission wavelengths respectively.

A calibration curve was plotted for carvedilol in the range of 50–500 ng mL^{-1}. A good linear relationship was observed between the concentration of carvedilol and its peak area (R^2 = 0.999). Precision and accuracy of the HPLC method were estimated (13).

Spectroscopic and diffraction characterization

The buccoadhesive tablets (BC3) were compressed and powdered. The pelletized powder, along with KBr, was used for FTIR studies. The IR spectra were recorded using an IR-spectrophotometer (Perkin Elmer FT-IR, Perkin Elmer, USA). A powder X-ray diffractometer (Siemen's D-5000, Germany) was used for diffraction studies. PXRD studies were performed on the samples by exposing them to CuKa radiation (40 kV, 30 mA) and scanned from 2 to 70°, at a step size of 0.045 2θ and step time of 0.5 s.

RESULTS AND DISCUSSION

Our previous report showed that 75.3% of carvedilol penetrated through the porcine buccal epithelium in 3 h and 60.2% of the drug was absorbed from buccal patches in 16 min through the buccal cavity in healthy human volunteers (13).

Mass, thickness and drug uniformity

The mass and the thickness of the tablets (Table II) were within the limits of uniformity. The mass ranged from 119.2 to 122.3 mg with RSD values 0.7–1.2%. Thickness ranged between 1.74 and 2.00 mm with RSDs of 0.5 to 1.2%. The drug content ranged from 96.7 ± 0.4% in formulation BC1 to 101.4 ± 0.3% in formulation BC5, 97.0 ± 0.8% in formulation BD1 to 103.2 ± 3.0 in formulation BD5 and 98.5 ± 0.9% in formulation BE1 to 102.4 ± 1.7% in formulation BE4.

In vitro *drug release studies*

The release of carvedilol from buccoadhesive tablets (Figs. 1a–c) varied according to the type and ratio of matrix forming polymers. The drug release was governed by the amount of matrix forming polymer. Burst release was observed in formulations BC1 and

Table II. Mass, thickness and drug content

Formulation	Mass (mg)[a]	Thickness (mm)[a]	Assay (%)[b]
BC1	121.5 ± 1.2	1.74 ± 0.02	96.7 ± 0.4
BC2	120.5 ± 1.8	1.86 ± 0.03	97.2 ± 0.5
BC3	120.0 ± 1.2	1.83 ± 0.02	99.8 ± 0.4
BC4	122.3 ± 1.5	1.82 ± 0.01	101.0 ± 2.3
BC5	120.0 ± 1.2	1.92 ± 0.01	101.4 ± 0.3
BD1	119.7 ± 1.2	1.82 ± 0.03	97.0 ± 0.8
BD2	120.0 ± 1.3	1.96 ± 0.01	97.3 ± 1.0
BD3	121.8 ± 1.9	1.98 ± 0.01	100.4 ± 0.5
BD4	119.8 ± 1.6	1.99 ± 0.01	101.2 ± 1.0
BD5	121.3 ± 1.1	2.00 ± 0.01	103.2 ± 3.0
BE1	120.0 ± 0.9	1.86 ± 0.01	98.5 ± 0.9
BE2	121.3 ± 0.6	1.82 ± 0.01	100.4 ± 1.0
BE3	119.2 ± 0.8	1.76 ± 0.02	101.3 ± 1.5
BE4	121.5 ± 0.5	1.84 ± 0.02	102.4 ± 1.7
BE5	121.7 ± 1.4	1.83 ± 0.01	99.6 ± 1.2

Mean ± SD; [a] $n = 10$, [b] $n = 20$.

BD1. The concentration of HPMC K4M and HPMC K15M was the lowest in BC1 and BD1 among all within the series. The most important factor affecting the rate of release from the buccal tablets is the drug : polymer ratio. An increase in polymer concentration causes an increase in the viscosity of the gel as well as formation of a gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore a reduction in the drug release rate. In the present study, the results followed this predictable behaviour (Fig. 1a–c). Buccal tablets that contained lower concentrations of either HPMC K4M, HPMC K15M or Carbopol 934 in BC, BD and BE series, respectively, tended to release the drug in shorter time periods, while the release slowed down as the concentration of the gelling polymer increased, thus confirming the dominant role of the swellable hydrophilic polymer in the release of carvedilol from buccal tablets.

Data of the *in vitro* release was fit into different equations and kinetic models to explain the release kinetics of carvedilol from buccal tablets. The kinetic models (17, 18) used were zero-order equation, first-order equation, Higuchi and Korsemeyer-Peppas models. Formulations with HPMC K4M (BC1, BC2, BC3) (correlation coefficient between 0.800 and 0.980) and HPMC K15M (BD1, BD2, BD3) (correlation coefficient between 0.844 and 0.985) followed the Higuchi model whereas formulations BC4, BC5 (correlation coefficient 0.985 and 1.000), BD4 and BD5 (correlation coefficient 0.998 and 0.999) followed zero-order release. In the case of Carbopol 934, BE series BE1, BE2 and BE5 (correlation coefficient between 0.961 and 0.981) followed the Higuchi model; BE3 and

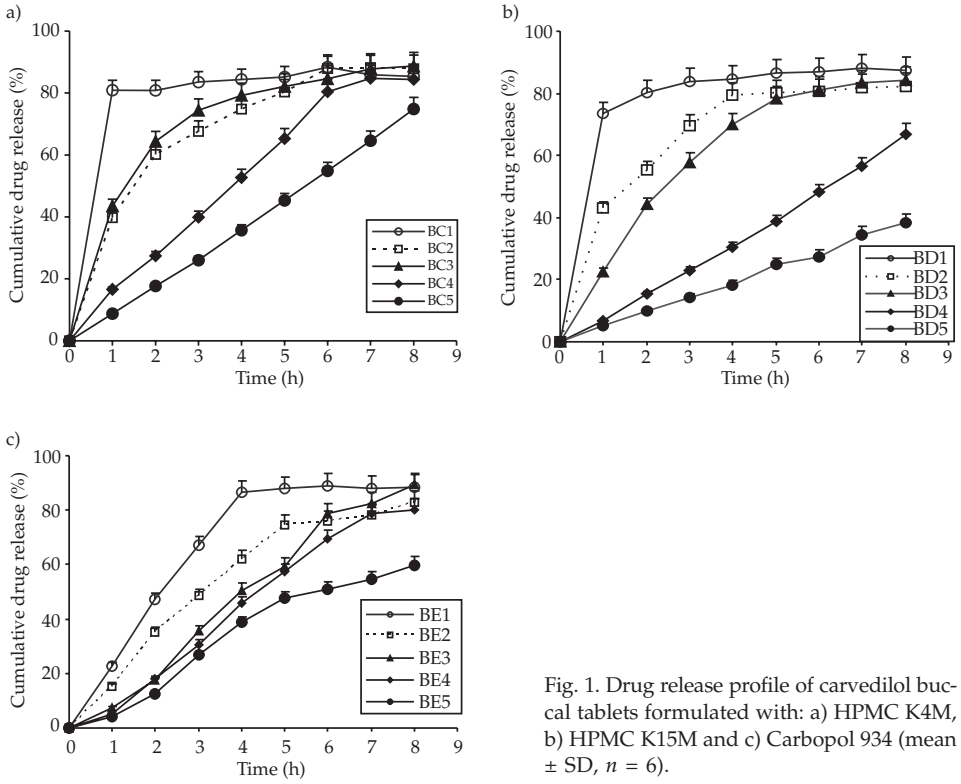

Fig. 1. Drug release profile of carvedilol buccal tablets formulated with: a) HPMC K4M, b) HPMC K15M and c) Carbopol 934 (mean ± SD, n = 6).

BE4 (correlation coefficient 0.985 and 0.997), followed zero-order model. The results indicate that as the concentration of each polymer increases in the respective series, Higuchi diffusion mechanism turns to zero-order release profile.

Formulation BC3 (88.7 ± 0.4%) composed of 1:3 drug : HPMC K4M ratio; BD3 (84.2 ± 0.3%) 1:3 drug : HPMC K15M ratio and BE3 (89.2 ± 0.3%) 1:0.75 drug : Carbopol 934 ratio showed maximum release among their respective series. Increasing the concentration of the polymer in the formulations showed a sustained effect on carvedilol release. The rapidly hydrating polymer dominated in controlling the release of carvedilol from the buccal tablets, as seen from the dissolution profiles and moisture absorption data. Release rates slowed down when the concentration of HPMC K4M or HPMC K15M or Carbopol 934 increased from 1:1 to 1:5 ratios and 1:0.25 to 1:1.50 in BC, BD and BE series, respectively. This is because as the proportion of these polymers in the matrix increased, there was an increase in the amount of water uptake and proportionally greater swelling leading to a thicker gel layer. Zero-order release from swellable hydrophilic matrices occurs as a result of constant diffusional pathlengths. When the thickness of the gelled layer and thus the diffusional pathlengths remain constant, zero-order release can be expected, as seen for formulations BC4, BC5, BD4, BD5, BE3 and BE4.

Table III. Peak detachment force, bioadhesion and moisture absorption studies

Formulation	Peak detachment force (N)[a]	Work of adhesion (mJ)[a]	Moisture absorbed (%)[b]
BC1	0.81± 0.01	0.09 ± 0.01	31.2 ± 1.0
BC2	1.29 ± 0.09	0.12 ± 0.03	31.3 ± 3.1
BC3	1.62 ± 0.15	0.24 ± 0.11	31.7 ± 1.4
BC4	2.08 ± 0.18	0.33 ± 0.05	33.1 ± 1.2
BC5	2.50 ± 0.20	0.43 ± 0.12	45.5 ± 2.9
BD1	0.92 ± 0.10	0.23 ± 0.11	31.5 ± 0.9
BD2	1.64 ± 0.21	0.35 ± 0.09	32.7 ± 2.6
BD3	2.03 ± 0.30	0.47 ± 0.05	36.8 ± 1.6
BD4	3.00 ± 0.42	0.98 ± 0.10	44.3 ± 3.9
BD5	3.85 ± 0.17	1.02 ± 0.13	48.4 ± 2.8
BE1	2.00 ± 0.11	1.00 ± 0.13	36.2 ± 1.5
BE2	2.50 ± 0.35	1.85 ± 0.35	53.3 ± 5.0
BE3	3.00 ± 0.41	2.25 ± 0.43	68.2 ± 1.3
BE4	4.25 ± 0.40	3.50 ± 0.51	68.6 ± 3.2
BE5	6.00 ± 0.47	4.25 ± 0.40	70.7 ± 3.3

Mean ± SD; [a]n = 3, [b]n = 6.

In vitro *bioadhesion studies*

The results of the peak detachment force and bioadhesion strength of carvedilol buccal tablets are given in Table III. The peak detachment force and work of adhesion for formulation BC3 were 1.62 ± 0.15 N and 0.24 ± 0.11 mJ. In all the formulations, as the polymer concentration increased, both the peak detachment force and work of adhesion increased. The order of bioadhesion was HPMC K4M < HPMC K15M < Carbopol. Buccal tablets formulated with Carbopol 934 and HPMC K15M showed stronger mucoadhesion than HPMC K4M formulations. Very strong bioadhesion could damage the epithelial lining of the buccal mucosa.

Moisture absorption

The moisture absorption studies give an indication of the relative moisture absorption capacities of polymers and whether the formulations maintain their integrity after moisture absorption. The order of increasing moisture absorption was HPMC K4M < HPMC K15M < Carbopol 934 (Table III). This may be due to the more hydrophilic nature of the polymer Carbopol.

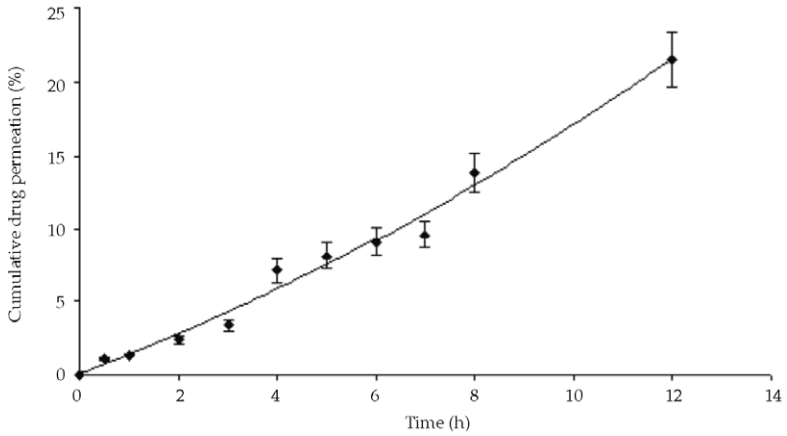

Fig. 2. *In vitro* permeation of carvedilol from buccal tablets through porcine buccal mucosa (mean ± SD, n = 3).

In vitro *drug permeation*

Based on the *in vitro* drug release and bioadhesion strengths of all formulations, the BC3 formulation was selected for *in vitro* permeation studies. The oral mucosa of pigs resembles that of humans more closely than any other animal in terms of structure and composition (19, 20) and therefore porcine buccal mucosa was selected for drug permeation studies. The results of drug permeation from buccal tablets through the porcine buccal mucosa reveal that carvedilol was released from the formulation and permeated through the porcine buccal membrane and could possibly permeate through the human buccal membrane. The drug permeation was slow and steady (Fig. 2) and 21.5 ± 2.9% of carvedilol could permeate through the buccal membrane in 12 hours with a flux of 8.35 ± 0.29 μg $h^{-1}cm^{-2}$ (permeation coefficient 1.34 ± 0.05 cm h^{-1}).

Spectroscopic characterization

Figs 3a–c show IR spectra of the carvedilol, HPMC K4M and buccal tablets (BC3). Carvedilol alone showed principal peaks of 2923.68, 1449.96, 1340.13, and 1097.31 cm^{-1}. The main peaks of the physical mixture and buccal tablets with HPMC K4M were 2924.95, 1451.18, 1339.71 cm^{-1}, and 1097.31 and 2933.10, 1459.17, 1334.32 and 1059.89 cm^{-1}, resp. However, some additional peaks were observed with the physical mixture, which could be due to the presence of the polymer. These results suggest that no interaction took place between the drug and the polymer.

The X-ray powder diffraction pattern having major peaks at about 2θ 4.17, 4.48, 4.74, 5.51 and 6.51 in both the drug and carvedilol buccal tablet (BC3) suggests that the drug in the buccal tablet is not undergoing any polymorphic transitions (see Figs. 4a–c).

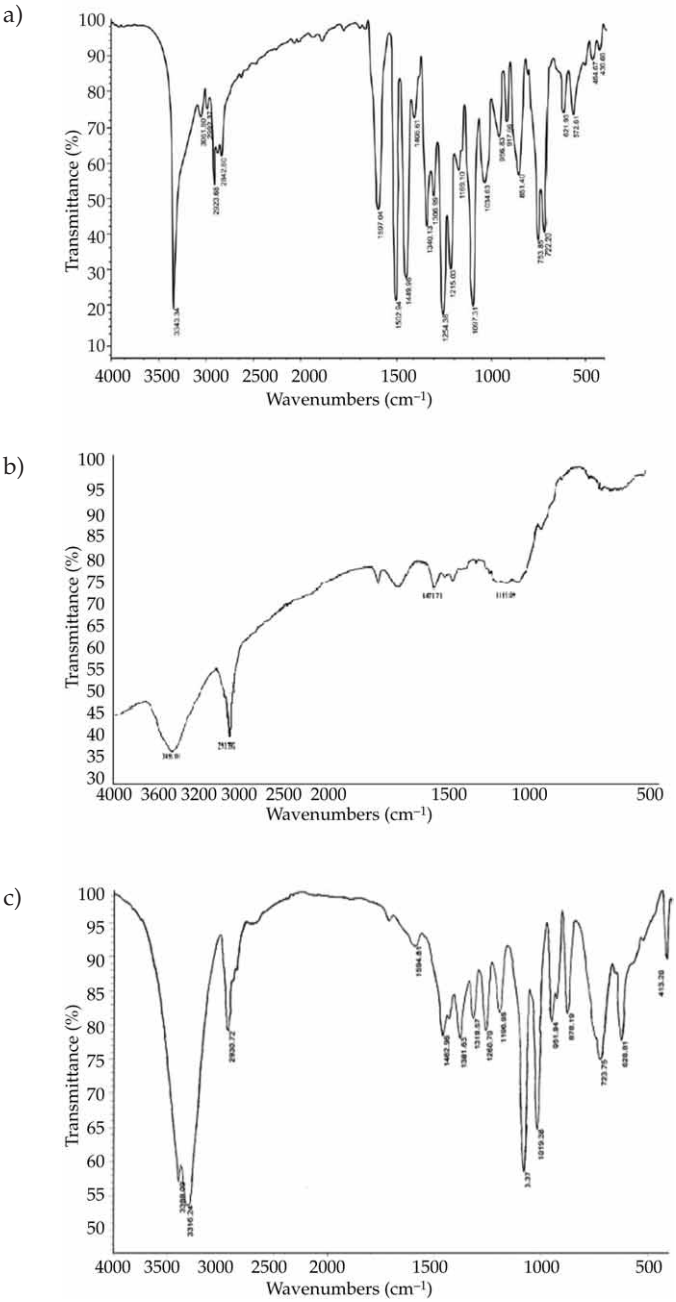

Fig. 3. FTIR spectra of: a) carvedilol, b) HPMC K4M and c) carvedilol buccal tablet (BC3).

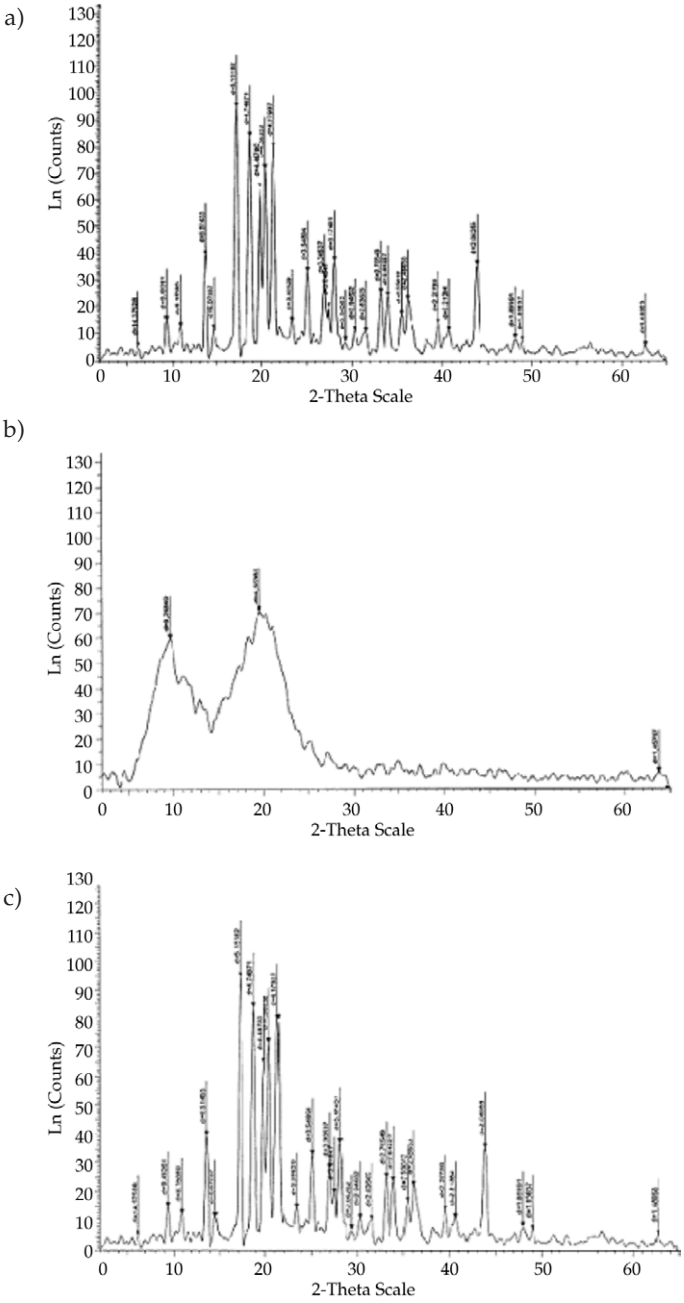

Fig. 4. XRD of: a) carvedilol, b) HPMC K4M and c) carvedilol buccal tablets (BC3).

CONCLUSIONS

HPMC K4M shows satisfactory buccoadhesive properties. Formulation BC3 using this polymer in a drug : polymer (1:3) ratio showed significant bioadhesive properties with an optimum release profile and could be useful for buccal administration of carvedilol. Further work is recommended to support its efficacy claims by long term pharmacokinetic and pharmacodynamic studies in human beings.

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S A Ž E T A K

Priprava i *in vitro* vrednovanje bukoadhezivnih tableta karvedilola

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Varirajući koncentracije bukoadhezivnih polimera HPMC K4M, HPMC K15M i Carbopol 934 pripravljeno je 15 tableta karvedilola. Pripravci iz serije BC ili BD izrađeni su iz karvedilola i HPMC K4 M ili HPMC K15M u omjerima 1:1, 1:2, 1:3, 1:4 i 1:5, a pripravci iz BE serije iz karvedilola i Carbopol 934 u omjerima 1:0.25, 1:0.50, 1:0.75, 1:1.00 i 1:1.50. *In vitro* je ispitivana brzina oslobađanja ljekovite tvari, bioadhezija, apsorpcija vlage i permeacija kroz bukalnu membranu svinje. Iz pripravka BC3 postignuto je maksimalno oslobađanje (88,7 ± 0,4%) koje je slijedilo Higuchijev model i maksimalna permeacija 21,5 ± 2,9% (fluks 8,35 ± 0,291 μg h^{-1} cm^{-2}; permeacijski koeficijent 1,34 ± 0,05 cm h^{-1}). Sila odvajanja za taj pripravak bila je 1,62 ± 0,15 N, a adhezija 0,24 ± 0,11 mJ. FTIR ispitivanja su pokazala da nije bilo interakcija između ljekovite tvari i polimera, a XRD ispitivanja da je ljekovita tvar u kristaliničnoj formi u polimernom matriksu. Pripravljene bukalne tablete su dovoljno bioadhezivne, a permeacija iz njih je zadovoljavajuća.

Ključne riječi: bukalne tablete, karvedilol, bioadhezija, vrednovanje

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