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RESEARCH PAPER

Preparation and In Vitro/In Vivo Evaluation of the Buccal Bioadhesive Properties of Slow-Release Tablets Containing Miconazole Nitrate

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ABSTRACT

Slow-release buccal bioadhesive tablets of miconazole nitrate were prepared by using polymer mixtures of buccoadhesive materials such as hydroxypropylmethylcellulose, sodium carboxymethylcellulose, carbopol 934p, and sodium alginate. The physicochemical properties, swelling index, microenvironment pH, in vitro drug release, in vivo buccoadhesion time, and miconazole salivary concentrations of the prepared tablets were shown to be dependent on the type and composition of the buccoadhesive materials used. The dissolution of miconazole from all the prepared tablets into phosphate buffer (pH 6.8) was controlled and followed non-Fickian release mechanisms. All the prepared tablets gave reasonable buccoadhesion time (2.45–3.65 hr). Infrared spectroscopy and differential scan calorimetry studies revealed the absence of significant interactions between miconazole nitrate and the selected buccoadhesive materials. Duration of the antifungal activity as measured by the inhibition zone of *Candida albicans* by extracted human saliva was significantly longer ($p < 0.05$), compared with commercial miconazole oral gel (Daktaren® oral gel). Based on the results obtained, the prepared slow-release buccoadhesive tablets of miconazole would markedly prolong the duration of the antifungal activity with more patient convenience.

Key Words: Miconazole nitrate; Slow-release; Buccal bioadhesive tablets; Physicochemical properties; Swelling index; Microenvironment pH; In vitro drug release; In vivo buccal bioadhesion time; Daktaren® oral gel; Duration of antifungal activity.

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INTRODUCTION

Recent years have seen an increasing interest in the development of novel mucoadhesive buccal dosage forms.[1–6] These are useful both for systemic delivery of drugs, as well as for local targeting of drugs to a particular region in the body. To determine the bioadhesive potential of different polymers, several techniques were reported,[7–9] mostly involving the measurement of the adhesive strength and using ex vivo tests. Some of these tests are used to classify polymers according to their adhesive properties. A technique based on a tensile testing apparatus was developed by Ponchel et al.,[10] determining the detachment force and the work of adhesion when tablets and tissue are pulled apart.

Miconazole nitrate is an established drug for the treatment of topical and systemic fungal infections, (e.g., oral candidiasis; buccal gels containing miconazole are currently used).[11] Because the drug does not persist in the oral cavity,[12] these gels have to be applied several times a day. Maximal salivary concentrations of miconazole nitrate are seen immediately after application, but the drug is rapidly cleared from the oral cavity.[12,13] To increase the buccal residence time of miconazole, a buccal miconazole-releasing device was developed in the form of a bioadhesive tablet which reversibly adheres to the oral mucosa and releases miconazole nitrate during adhesion time.

Several polymers—including polyethylene glycol,[14] cellulose derivatives [e.g., hydroxypropylmethylcellulose (HPMC)],[15] thermally modified starch, and polyacrylic acid (PAA)[10,16]—have been described for the formulation of bioadhesive systems. Some of these polymers adhere well for a few hours, although some are mildly irritating to the oral mucosa.[17–20]

Previous studies with miconazole nitrate as buccal bioadhesive tablets[11,21] were conducted using different grades of PAA (PAA 907, PAA 910, and PAA 934). However, PAA has been shown to induce severe irritation of the mucosa in volunteers.[19] There are no literature reports about the use of HPMC, sodium carboxymethylcellulose (NaCMC), and sodium alginate as polymers for miconazole nitrate buccal bioadhesive tablet formulations.

Therefore, the aim of the present study was to design and develop buccal bioadhesive tablet formulations containing miconazole nitrate using some selective bioadhesive polymers, such as HPMC, NaCMC, carbopol 934 (Cp), and sodium alginate. The prepared buccoadhesive tablet formulations were evaluated for their: physicochemical characteristics (weight, hardness, friability, diameter, and drug content); swelling index; microenvironment pH; in vitro drug release; in vivo buccal bioadhesion time; duration of antifungal activity; and in vivo miconazole saliva concentrations. Commercial gel (Daktaren® oral gel, containing 20 mg/g miconazole nitrate in a homogeneous base) was used as a reference for the in vivo study.

EXPERIMENTAL

Materials

Miconazole nitrate (Sigma Chemical Co., St. Louis, MO, USA), Cp (B. F. Goodrich, Cleveland, OH, USA), NaCMC (C. B. H. Laboratory Chemistry, Nottingham, UK), HPMC (K4M) (Methocel K100M, Ltd., Orpington, UK), mannitol (BDH, UK), and sodium alginate (Laba Chemie, India) were used. All other chemicals were of analytical grade.

Commercial Gel

Daktaren oral gel (Janssen Pharmaceuticals, Titusville, NJ, USA) contained 20 mg/g miconazole nitrate in a homogeneous starch base.

Methods

Preparation of the Buccal Buccoadhesive Miconazole Tablets by Direct Compression

Nine buccoadhesive miconazole tablets formulations were prepared by direct compression using a concave-faced, single punch (10 mm diameter) tableting machine (Erweka-AR 400 E, Germany) (Table 1). Each tablet contained a constant amount of miconazole nitrate (20 mg), mannitol (50 mg), talc (5 mg) and a varying composition of the buccal bioadhesive polymer mixture of either Cp/HPMC (Cp1, Cp2, and Cp3), sodium alginate/NaCMC (F1, F2, and F3), or Cp/NaCMC (N1, N2 and N3) (Table 1). All materials were passed through a 125-μm sieve and retained on 90-μm sieve. Miconazole nitrate was first mixed with the buccal bioadhesive polymer mixture for 10 min in a high-speed mixer (Erweka Turbula System S27, Germany). Mannitol and talc

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Table 1. Composition of the prepared buccal bioadhesive tablet formulations of miconazole nitrate.

	Cp/HPMC tablets			Sodium alginate/NaCMC tablets			Cp/NaCMC tablets		
Ingredients	Cp1	Cp2	Cp3	F1	F2	F3	N1	N2	N3
Miconazole	20	20	20	20	20	20	20	20	20
Cp	10	20	30	—	—	—	10	20	30
HPMC	200	190	180	—	—	—	—	—	—
Sodium alginate	—	—	—	150	200	250	—	—	—
NaCMC	—	—	—	150	100	50	200	190	180
Mannitol	40	40	40	50	50	50	40	40	40
Talc	5	5	5	5	5	5	5	5	5
Total weight (mg)	275	275	275	375	375	375	275	275	275

were then added, and mixing continued for another 10 min. The machine was adjusted to produce tablets of an approximate weight of 275 mg (Cp1, Cp2, and Cp3) or 375 mg (F1, F2, F3, N1, N2, and N3).

Evaluation of the Prepared Tablets

Physicochemical Properties

Weight Uniformity

Uniformity of weight was determined according to U.S. Pharmacopeia (USP)/NF 23 procedures. The weight of each of ten randomly selected tablets of each formulation was determined by using an electronic balance (Precisa 205 A Balances, Switzerland).

Diameter and Thickness Testing

The diameter and thickness testing of each of ten randomly selected tablets of each formulation were determined according to the USP using a micrometer (Mitutoyo, Japan).

Hardness and Friability Testing

Hardness and friability of each of ten randomly selected tablets of each formulation were determined using the Erweka hardness tester (TBH 30) and the Erweka friabilator (GmbH, Germany) respectively.

Drug Content Uniformity

Uniformity of drug content was determined according to USP/NF 23 procedures. Ten randomly selected tablets of each formulation were weighed accurately and powdered. Powder equivalent to 20 mg of miconazole nitrate was transferred into a 100-mL volumetric flask containing 50 mL of phosphate buffer (pH 6.8), sonicated for 30 min, and stirred continuously for 8 hr on a magnetic stirrer. The volume was made up to 100 mL with phosphate buffer (pH 6.8), and the absorbances were measured in a UV/Vis spectrophotometer at 220 nm (Shimadzu, UV/Vis Spectrophotometer, Tokyo, Japan). Concentrations of miconazole nitrate were calculated from a standard calibration curve of miconazole nitrate in phosphate buffer (pH 6.8) without interferences of excipients.

Swelling Studies of Buccoadhesive Miconazole Tablets

The swelling index (rate) of the prepared buccoadhesive miconazole tablets was determined by weighing five tablets and recording their weights before placing them separately in weighed beakers. The total weight was recorded (W1).[16] Four milliliters of distilled water was added to each beaker were placed in an incubator at 37°C. At time intervals of 0.5, 1, 2, 3, and 4 hr, excess water was carefully removed, and the swollen tablets were weighed (W2). The experiment was repeated six times, and the average W1 and W2 were reported. The swelling index was determined from the formula[16]:

$$\text{Swelling index} = (W2 - W1)/W1$$

Microenvironment pH

The microenvironment pH of the prepared buccoadhesive miconazole tablets was determined to

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evaluate the possible irritation effects on the mucosa. The tablets were left to swell in 4 mL of distilled water (pH 6.8) in small beakers, and the pH was measured at time intervals of 2, 4, and 6 hr by placing the electrode in contact with the microenvironment of the swollen tablets. The average pH of six determinations was reported.

In Vitro Drug Release Studies

Miconazole nitrate released from the prepared buccoadhesive miconazole tablets was determined by introducing single tablets in separate beakers containing 10 mL of phosphate buffer (pH 6.8). The beakers were shacked horizontally at 50 rpm in a water bath, which maintained at 37°C. Samples of 2 mL were withdrawn at predetermined time intervals over 7 hr and replaced with equal volumes of the dissolution medium equilibrated at the same temperature. Drug concentration of the withdrawn samples was analyzed after filtration (0.45 μm Millipore fitter) by UV spectroscopy (Shimadzu UV/Vis 1205, Tokyo, Japan) at 220 nm. The release studies were carried out on sets of six tablets from each formulation at the same time. Sink conditions were maintained throughout the study.[16,17]

Infrared (IR) Absorption Spectroscopy

To investigate any possible interactions between the drug and the utilized buccoadhesive materials, the IR spectra of pure miconazole nitrate and its physical mixtures (1:1) with Cp, HPMC, sodium alginate, and NaCMC were carried out using Shimadzu IR-470 spectrophotometer (Tokyo, Japan). The samples were prepared as KBr disks compressed under a pressure of 6 Ton/nm^2. The wavenumber selected ranged between 400 and 4,000 cm^{-1}.

Differential Scanning Calorimetry (DSC)

DSC thermograms of pure miconazole nitrate and its physical mixtures (1:1) with Cp, HPMC, sodium alginate, and NaCMC were carried out to investigate any possible interactions between the drug and the utilized buccoadhesive materials. The sample (10 mg) was sealed in an aluminium micropan and introduced into the analytical system (DSC-50; Shimadzu, Tokyo, Japan). Thermal scanning carried out at a rate of 10°C min^{-1} (from 0° to 300°C) and N2 perge 30 mL/min. The instrument was calibrated with indum for temperature and energy. Thermal analysis data were obtained using a TA 501 PC system with Shimadzu software programs.

In Vivo Evaluation of the Buccal Buccoadhesion Time and Salivary Concentration Behavior of the Prepared Tablets

Six healthy volunteers (3 males and 3 females, aged 22–40 years) participated in a crossover study. Informed consent was obtained from each volunteer before the study. Volunteers were instructed to finish their breakfast at least 1 hr before the study. Eating was restricted during the study, whereas drinking was allowed 60 min after a single administration of the buccoadhesive tablets (20 mg/tablet) or an equivalent amount (20 mg/g) of the commercial gel (Daktaren oral gel). However, no drinking was allowed 10 min before the collection of saliva.

Buccoadhesive tablets were applied manually by pressing them against the cheek for about 30 sec, without moistening before application.[21–23] Volunteers were instructed to record the time of tablet application, and the time and circumstances of the end of adhesion (erosion or detachment of the tablet). They were asked to record their experiences with tablets immediately after completion of the study.

A blank salivary sample was taken before application of the formulations. Salivary samples (2 mL) were collected directly into borosilicate centrifuge tubes before drug administration, and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, and 8 hr after administration. No drinking was allowed 10 min before the collection of saliva. Miconazole concentration in saliva was determined by measuring the growth inhibition zone surrounding each agar well inoculated with *Candida albicans*, agar diffusion method.[22,23]

Agar Diffusion Assay of Miconazole Nitrate

Concentrations of miconazole nitrate in the collected saliva samples were determined by measuring the diameter (mm) of the growth inhibition zone of *C. albicans* as follows.[24] The saliva samples were centrifuged at 2,000 rpm for 5 min, and 1 mL of the supernatant was diluted to 5 mL with phosphate buffer (pH 6.8). Aliquots 100 μL of each sample were carefully pipetted into uniformly spaced 7 mm

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diameter wells of the agar plates. These plates were allowed to prediffuse for 2 hr at room temperature and then incubated at 24 hr. The diameter (mm) of the growth inhibition zone surrounding each agar well inoculated with *C. albicans* was measured, and the concentrations of miconazole nitrate was determined from the standard calibration curve constructed under identical conditions.[24] The mean of two determinations of each saliva sample was determined.

Preparation of the Agar Plates

The agar plates used in this study were prepared by dissolving 28 g nutrient agar in 1 L of distilled water and sterilized by autoclaving (at 15 lb pressure and 121°C) for 15 min. After cooling, 80 mg of gentamycin and 500 mg of ampicillin each in 2 mL sterile solutions were then added to the agar solution and mixed before pouring into sterile petri dishes. The agar plates are then allowed to cool and solidify at room temperature; then they were inoculated (cultured) with *C. albicans* by using a sterile swab and a five-dimension method.[22] In the proposed method, antibiotics were added to eliminate any possible interference with the assay from nonpathogenic bacteria normally found in the saliva.

Data Analysis

Results are given as the means ± SD. Maximum salivary concentration (C_{max}) and the time to reach the maximal salivary concentration (T_{max}) were determined from the concentration-time curves. The area under the curve (AUC_{0-8}) was calculated using the trapezoidal rule.[21,22,25,26]

Statistical Analysis

The results obtained were subjected to statistical analysis using a computer program PC-Stat for one-way analysis of variance, ($p < 0.05$).[27]

RESULTS AND DISCUSSION

Table 1 shows the composition of the prepared buccoadhesive miconazole tablets. Three formulations (Cp1, Cp2, and Cp3) were prepared with HPMC containing 10, 20, and 30 mg of Cp, respectively. It was reported that the use of carbopol alone caused severe irritation to the buccal mucosa; therefore, HPMC was used with different concentrations (10, 20, and 30 mg) of carbopol to enhance the buccoadhesive properties of HPMC. Three other formulations F1, F2, and F3 were prepared using different proportions of NaCMC and sodium alginate (Table 1). The last three formulations, (N1, N2 and N3) were prepared using different proportions of NaCMC and Cp.

Physicochemical Properties

Table 2 shows the physicochemical properties of the prepared buccoadhesive miconazole tablets. It could be observed that all the prepared tablets fulfill the USP requirements for uniformity of weight, diameter, thickness, and drug content. These tablets showed acceptable hardness and friability values (Table 2).

Swelling Index

For HPMC/carbopol formulations (Cp1, Cp2, and Cp3), the swelling index increased by increasing the concentration of carbopol in the formulation from Cp1 to Cp3 (Table 1). After 2 hr, the mean swelling index values were 0.74, 0.88, and 1.00 for Cp1, Cp2, and Cp3, respectively (Table 3). For NaCMC/sodium alginate formulations (F1, F2, and F3) after 2 hr, the mean swelling index values were 2.53, 2.19, and 1.70 for F1, F2, and F3, respectively (Table 3). This decrease in the swelling index could be attributed to the decreased concentration of NaCMC relative to sodium alginate (Table 1). For NaCMC/carbopol formulations (N1, N2, and N3) after 2 hr, the mean swelling index values were 1.41, 0.91, and 0.85 for N1, N2, and N3, respectively (Table 3). Therefore, decreasing concentration of NaCMC resulted in decreasing the swelling index.

Statistical analysis showed significant differences ($p < 0.05$) in the swelling index between all the tested formulations, except Cp2 and N3 (Table 4). The values of the swelling index were decreased in the following order: F1 > F2 > F3 > N1 > Cp3 > (N2, Cp2, and N3) > Cp1 (Table 4).

Microenvironment pH Characteristics

The mean microenvironment pH values after 2 hr were 4.50, 4.45, and 3.94 for Cp1, Cp2, and Cp3,

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Table 2. Physicochemical properties (mean ± CV%) of the prepared buccal bioadhesive tablet formulations of miconazole nitrate.

Physical parameters	Cp/HPMC tablets			Sodium alginate/NaCMC tablets			Cp/NaCMC tablets		
	Cp1	Cp2	Cp3	F1	F2	F3	N1	N2	N3
Weight (mg)	275 ± 1.52	274.3 ± 0.8	275.2 ± 0.9	375.5 ± 1.11	374.3 ± 1.1	376.1 ± 1.1	276.2 ± 0.76	275.5 ± 0.75	275.3 ± 0.76
Hardness (N)	97.0 ± 3.60	99.5 ± 7.13	98.6 ± 7.40	63.3 ± 3.31	64.3 ± 6.80	47.1 ± 3.18	66.9 ± 3.43	67.9 ± 3.73	68.5 ± 3.21
Friability (%)	0.35 ± 2.85	0.38 ± 2.10	0.54 ± 5.55	0.64 ± 4.60	0.55 ± 4.90	0.78 ± 6.41	0.36 ± 2.80	0.55 ± 3.63	0.61 ± 3.27
Diameter (mm)	9.9 ± 0.30	9.93 ± 0.10	9.96 ± 0.31	9.99 ± 0.10	10.01 ± 0.10	10.0 ± 0.02	9.80 ± 0.02	9.9 ± 02	9.8 ± 0.03
Thickness (mm)	4.0 ± 1.50	3.9 ± 2.01	4.1 ± 0.50	3.9 ± 0.50	4.0 ± 0.30	3.8 ± 0.31	4.1 ± 0.01	3.9 ± 0.21	4.0 ± 0.11
Drug content (%)	99.5 ± 0.9	98.6 ± 1.21	98.9 ± 0.8	99.5 ± 0.50	98.8 ± 0.73	99.7 ± 1.2	99.9 ± 1.2	98.5 ± 1.52	99.9 ± 1.86

Each value represents the mean of ten determinations.

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Table 3. Index of swelling in water and microenvironment pH characteristics of the prepared buccal bioadhesive tablet formulations of miconazole nitrate.

Formulation code	Swelling index			Microenvironment pH		
	0.5 hr	2 hr	4 hr	2 hr	4 hr	6 hr
Cp1	0.51 ± 0.05	0.74 ± 0.08	0.89 ± 0.06	4.50 ± 0.08	4.62 ± 0.06	4.32 ± 0.11
Cp2	0.55 ± 0.06	0.88 ± 0.09	1.04 ± 0.09	4.45 ± 0.09	4.47 ± 0.18	4.31 ± 0.12
Cp3	0.56 ± 0.06	1.00 ± 0.09	1.14 ± 0.09	3.94 ± 0.15	4.29 ± 0.15	4.29 ± 0.13
F1	1.50 ± 0.09	2.53 ± 0.12	3.02 ± 0.10	7.50 ± 0.11	7.40 ± 0.11	7.50 ± 0.30
F2	1.25 ± 0.10	2.19 ± 0.11	2.19 ± 0.11	7.90 ± 0.17	7.90 ± 0.17	7.50 ± 0.19
F3	1.10 ± 0.09	1.70 ± 0.13	1.70 ± 0.13	8.28 ± 0.21	8.28 ± 0.40	8.50 ± 0.40
N1	1.10 ± 0.05	1.41 ± 0.11	1.81 ± 0.13	6.31 ± 0.09	6.52 ± 0.15	6.60 ± 0.14
N2	0.86 ± 0.06	0.91 ± 0.06	1.02 ± 0.05	6.50 ± 0.09	6.42 ± 0.15	6.45 ± 0.13
N3	0.75 ± 0.04	0.85 ± 0.05	0.97 ± 0.08	6.85 ± 0.11	6.71 ± 0.08	6.63 ± 0.05

Each value represents the mean of six determinations.

Table 4. PC-Stat one-way analysis of variance of the index of swelling in water and microenvironment pH characteristics of the prepared buccal bioadhesive tablet formulations of miconazole nitrate.

Swelling index (after 2 hr)			Microenvironment pH (after 2 hr)		
Code	Mean	Grouping	Code	Mean	Grouping
F1	2.53	A	F3	8.28	A
F2	2.19	B	F2	7.90	B
F3	1.70	C	F1	7.50	C
N1	1.40	D	N3	6.85	D
Cp3	1.00	E	N2	6.50	E
N2	0.91	F	N1	6.31	F
Cp2	0.88	F	CP1	4.50	G
N3	0.85	F	CP2	4.45	G
Cp1	0.74	G	CP3	3.94	H

Means with the same letter are not significantly different ($p < 0.05$).

respectively (Table 3). Therefore, increasing carbopol concentration increased the swelling index and decreased the microenvironment pH (Table 3). This decrease in the microenvironment pH could be the cause of increased irritation of the buccal mucosa, with formulations containing high concentrations of Cp. These results are in agreement with previous findings.[11] For F1, F2, and F3, the mean microenvironment pH values after 4 hr were 7.40, 7.90, and 8.28, respectively (Table 3). This increase in the microenvironment pH could be attributed to increased concentration of sodium alginate (an antacid commonly used in the treatment of esophageal reflux). For N1, N2, and N3, the mean microenvironment pH values after 4 hr were 6.52, 6.42, and 6.71, respectively (Table 3). Therefore, tablets prepared with NaCMC/Cp, produced microenvironment pH values within satisfactory limits (range from 6.31 to 6.85); hence, these formulations should not cause irritation to the buccal cavity (Table 3). Statistical analysis showed significant differences between all the tested formulations, except Cp1 and Cp2 (Table 4). The values of microenvironment pH were decreased in the following order: F3 > F2 > F1 > N3 > N2 > N1 > (Cp1 and Cp2) > Cp3 (Table 4). Only Cp1 and Cp2 were not significantly different ($p < 0.05$) (Table 4). Statistical analysis showed significant differences between all the tested formulations, except Cp1 and Cp2 (Table 4).

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Drug Release Characteristics

The drug release profiles from the prepared buccal buccoadhesive miconazole tablets are shown in Figs. 1 to 3. The drug was gradually released from all formulations over a period of 7 hr. Therefore, all the prepared tablets could be adequately sustained (Figs. 1 to 3). Miconazole nitrate was more rapidly released from Cp1, compared with Cp2 and Cp3 (Fig. 1). However, increasing concentration of sodium alginate from F1 to F3 increased the release of miconazole (Fig. 2). This could be attributed to rapid erosion of the resultant gel layer upon increasing sodium alginate concentration. Also, for carbopol/NaCMC, increasing carbopol concentration from N1 to N3 resulted in decreasing the drug release (Fig. 3). Miconazole nitrate was more rapidly released from N1, compared with N2 and N3 (Fig. 3). These results indicated that increasing concentration of carbopol (Cp1, Cp2, Cp3, N1, N2, and N3) resulted in decreasing the drug release and linearization of the drug release curve (Figs. 1 and 2). Therefore, the release of miconazole nitrate could be prolonged and controlled by Cp (Cp1, Cp2, Cp3, N1, N2, and N3) and NaCMC (N1, N2, and N3) in a concentration-dependent manner. These results are in agreement with Khan and Jiabi,[28] who found a reduction in the release rate with increasing Cp concentration in the formulation.

Drug Release Kinetics

To examine the release mechanism of miconazole nitrate from the prepared buccoadhesive tablets, the results were analyzed according to the following equation:[29–34]

$$\frac{M_t}{M_\infty} = K_t^n$$

where M_∞/M_t is the fractional drug released at time t, k is a kinetic constant incorporating structural and geometrical characteristics of the drug/polymer system (device), and n is the diffusional exponent that characterizes the mechanism of drug release. For non-Fickian release, the n value falls between 0.5 and 1.0 ($0.5 < n < 1.0$), whereas in the case of

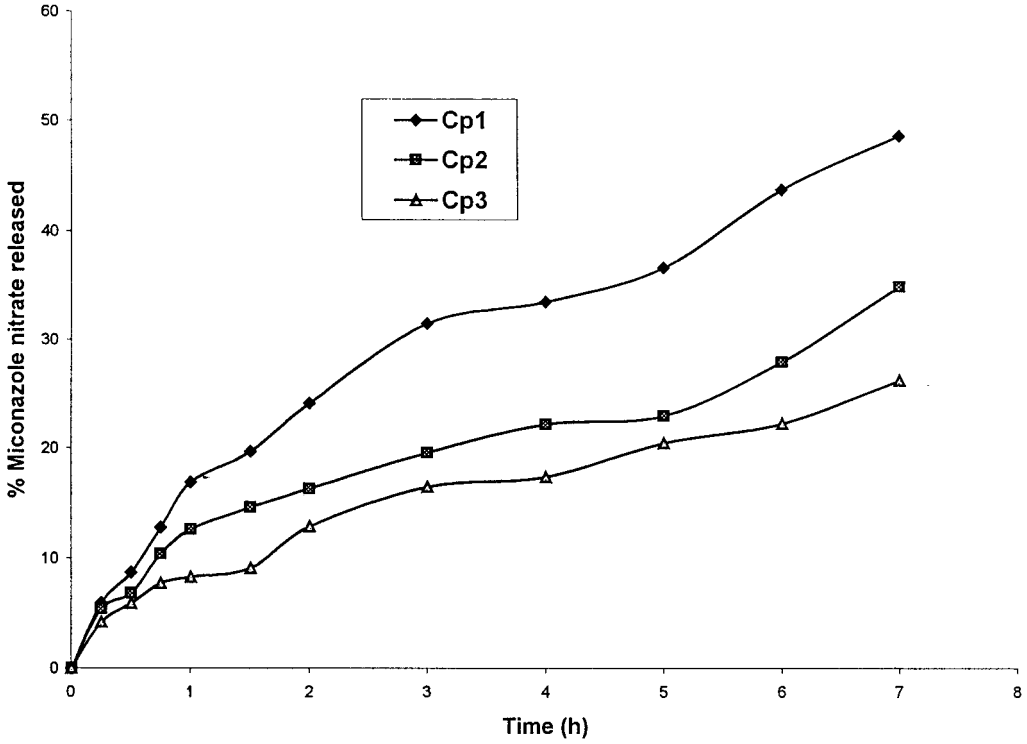

Figure 1. Release profiles of miconazole nitrate (into phosphate buffer, pH 6.8) from slow-release buccal bioadhesive tablets prepared with Cp/HPMC. Each point represents the mean of six determinations.

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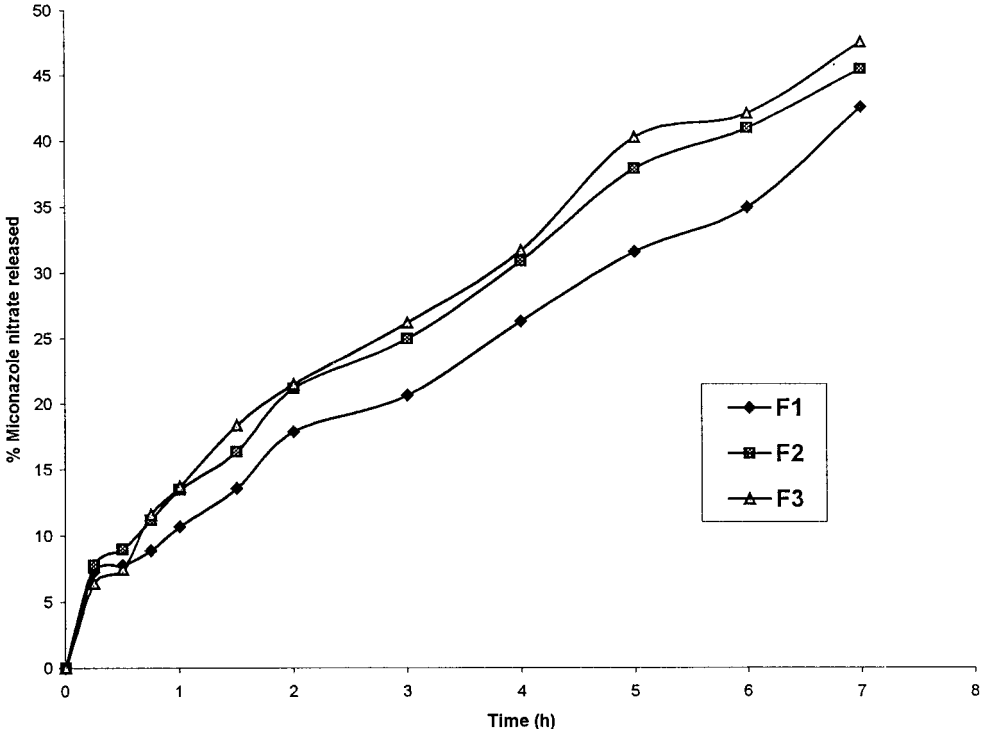

Figure 2. Release profiles of miconazole nitrate (into phosphate buffer, pH 6.8) from slow-release buccal bioadhesive tablets prepared with sodium alginate/NaCMC. Each point represents the mean of six determinations.

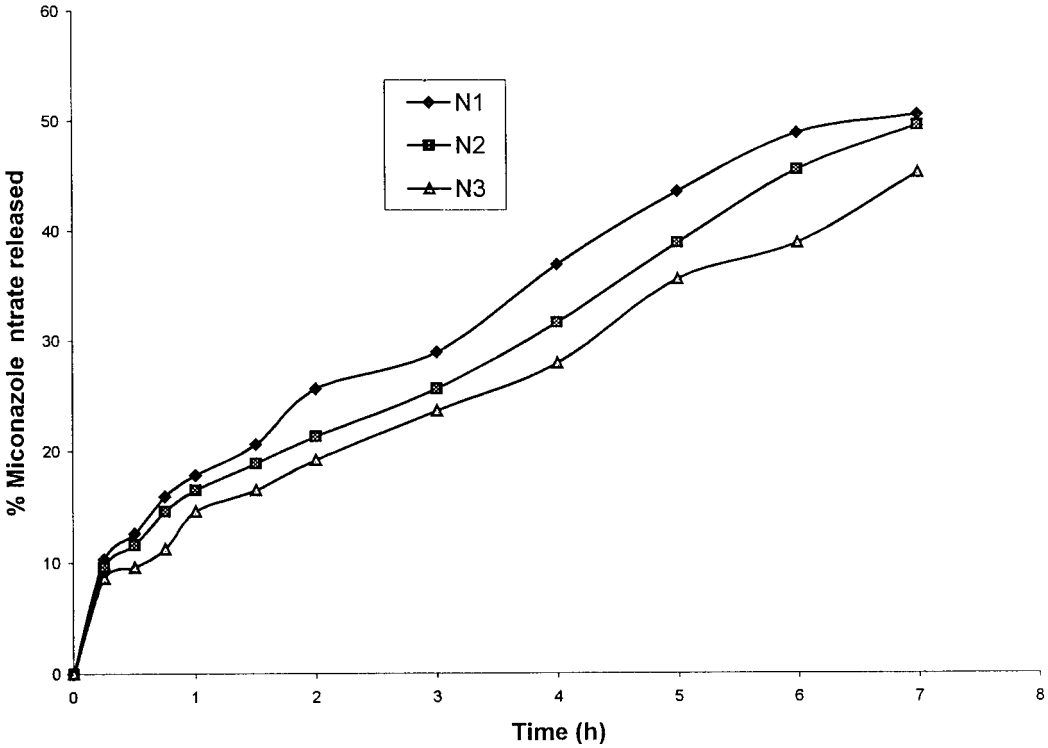

Figure 3. Release profiles of miconazole nitrate (into phosphate buffer, pH 6.8) from slow-release buccal bioadhesive tablets prepared with Cp/NaCMC. Each point represents the mean of six determinations.

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Table 5. Linear correlation coefficient (r), determination coefficients (r^2), kinetic release constants (K), and diffusion exponents (N) after fitting the release data of miconazole nitrate to the simple power law (Log M_t/M_o vs. Log t).

Formulation code	r	r^2	K (h^{-n})	n[a]
Cp1	0.994	0.988	14.80	0.619
Cp2	0.992	0.984	8.42	0.564
Cp3	0.994	0.988	8.62	0.539
F1	0.978	0.956	13.13	0.564
F2	0.991	0.982	14.29	0.563
F3	0.994	0.988	13.70	0.631
N1	0.992	0.985	18.42	0.501
N2	0.990	0.982	16.76	0.502
N3	0.990	0.980	14.49	0.517

[a]n = the diffusion release exponent, indicative of the release mechanism; $n = 0.5$ in case of the diffusion mechanism; $n = 1$ for zero-order release, n lies between 0.5 and 1.0 ($0.5 < n < 1$) for non-Fickian (anomalous) release and $n < 0.45$ for Fickian release mechanism.

Fickian diffusion, $n = 0.5$; for zero-order release (case II transport), $n = 1$, and for supercase II transport, $n > 1$.[16,25] The values of n as estimated by linear regression of log (M_t/M_∞) vs. log(t) of different formulations are shown in Table 5. The obtained values of n lie between 0.501 and 0.630 for the release of miconazole from all the prepared tablet formulations, indicating non-Fickian release kinetics, which is indicative of drug release mechanisms involving a combination of both diffusion and chain relaxation mechanisms.[28–34] Therefore, the release of the drug from the prepared tablets is controlled by swelling of the polymer, followed by drug diffusion through the swelled polymer, slow erosion of the polymer.[16,36] This behavior is dependent on the swelling properties of the used polymers, which also produced the slow dissolution of the systems.[35,36] However, similar release rates (patterns) obtained from all the prepared buccoadhesive tablet formulations of miconazole nitrate make more than a chance for possible use of the available buccoadhesive materials.

$T_{50\%}$ and $T_{90\%}$ Release of Miconazole Nitrate

The times for 50% ($T_{50\%}$) and 90% ($T_{90\%}$) release of miconazole nitrate from the prepared buccoadhesive tablets were estimated by linear regression of log (M_t/M_∞) vs. log(t) of different formulations and are shown in Table 6. For Cp1, Cp2, and Cp3, the $T_{50\%}$ values were 7.13, 15.91, and 25.61 hr, respectively. For N1, N2, and N3, the $T_{50\%}$ values were 7.33, 8.99, and 10.92, respectively (Table 6). These results clearly indicate increasing the half-life ($T_{50\%}$) of miconazole release from the prepared tablets by increasing the concentration of carbopol. For F1, F2, and F3, the ($T_{50\%}$) values were 12.24, 9.17, and 7.77, respectively (Table 6). These results indicate that rate of release of miconazole nitrate was markedly affected by the proportions of both sodium alginate and NaCMC in the tablets (Table 1). Statistical analysis of $T_{50\%}$ and $T_{90\%}$ showed significant differences between all the tested formulations (Table 7). The values of $T_{50\%}$ were decreased in the following order: Cp3 > Cp2 > F1 > N1 > F2 > N2 > F3 > N3 > Cp1 (Table 7).

Table 6. Time (hr) for 50% and 90% miconazole nitrate release from the prepared buccal bioadhesive tablet formulations of miconazole nitrate.

Formulation code	$T_{50\%}$	$T_{90\%}$
Cp1	7.13	18.41
Cp2	15.91	47.51
Cp3	25.61	75.51
F1	12.24	34.59
F2	9.17	25.90
F3	7.77	19.75
N1	7.33	23.69
N2	8.99	29.28
N3	10.92	33.98

Each value represents the mean of six determinations.

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Table 7. PC-Stat one-way analysis of variance of the time (hr) for 50% and 90% miconazole nitrate release from the prepared buccal bioadhesive tablet formulations of miconazole nitrate.

$T_{50\%}$			$T_{90\%}$		
Code	Mean	Grouping[a]	Code	Mean	Grouping[a]
CP3	25.61	A	CP3	75.51	A
CP2	15.91	B	CP2	47.51	B
F1	12.24	C	F1	34.59	C
N3	10.92	D	N3	33.98	D
F2	9.17	E	N2	29.28	E
N2	8.99	F	F2	25.90	F
F3	7.77	G	N1	23.69	G
N1	7.33	H	F3	19.75	H
CP1	7.13	H	CP1	18.41	I

[a]Means with the same letter are not significantly different ($p < 0.05$).

IR Absorption Spectroscopy

Figure 4 shows the IR spectra of pure miconazole nitrate (Fig. 4A) and its physical mixtures (1:1) with NaCMC (Fig. 4B), sodium alginate (Fig. 4C), HPMC (Fig. 4D) and Cp (Fig. 4E). The IR spectra did not show any significant difference from those obtained for their physical mixtures. These obtained results indicate that there was no positive evidence for the interaction between miconazole nitrate and the utilized buccoadhesive materials more than hydrogen bonding (if any), which may have occurred between donating and accepting groups of both the drug and the utilized buccoadhesive materials. These results clearly indicate the usefulness of the utilized buccoadhesive materials for preparation of slow-release buccoadhesive tablets of miconazole nitrate.

DSC

Figure 5 shows the DSC thermograms of pure miconazole nitrate (Fig. 5A) and its physical mixtures (1:1) with NaCMC (Fig. 5B), sodium alginate (Fig. 5C), HPMC (Fig. 5D) and Cp (Fig. 5E). The DSC thermograms of the physical mixtures of miconazole nitrate and the utilized buccoadhesive materials (Figs. 4 B–E) did not show any significant difference from that obtained for pure miconazole nitrate (Fig. 5A). However, the disapperance of the endothermic peak in the physical mixture with NaCMC (Fig. 5B) could be attributed to the possible interaction of miconazole nitrate and NaCMC during the fusion process. This was confirmed by the absence of any significant differences in the IR spectrum of miconazole nitrate and its physical mixture with NaCMC (Fig. 4B). These obtained results indicate that there was no positive evidence for the interaction between miconazole nitrate and the utilized buccoadhesive materials.

In Vivo Buccoadhesion Time

All the prepared buccoadhesive tablets were generally well accepted by the volunteers and did not cause any irritation or hinderance to the volunteers; their taste was acceptable. No side effects, such as taste alteration, dry mouth, or excessive salivation, were observed with all tablets. All the prepared buccoadhesive tablets were eroded completely, and none were removed because of irritation. Tablets prepared with NaCMC/Carbopol (N1, N2, and N3) or sodium alginate/NaCMC (F1, F2, and F3) were especially more preferred by the volunteers than those prepared with carbopol/HPMC (Cp1, Cp2, and Cp3) which could be attributed to the better microenvironment pH values (Table 3). The mean buccoadhesion times for Cp1, Cp2, and Cp3 were 3.27 ± 0.74, 2.80 ± 0.57 and 2.45 ± 0.34 hr, respectively (Table 8). Thus, increasing carbopol concentration from Cp1 to Cp3 led to a decrease in the buccoadhesion time, which could be attributed to weakening of the polymer–polymer interactive forces because of increased hydration and swelling of the system. This caused rupture, rapid erosion, and detachment of the tablets from the mucosal surface.[5,35] The mean buccoadhesion time values for F1, F2, and F3 were 3.65 ± 0.35, 2.75 ± 0.27 and 2.50 ± 0.25 hr, respectively (Table 8). Therefore, increasing concentration of sodium alginate relative to NaCMC (F1, F2, and F3) was found to decrease the swelling index

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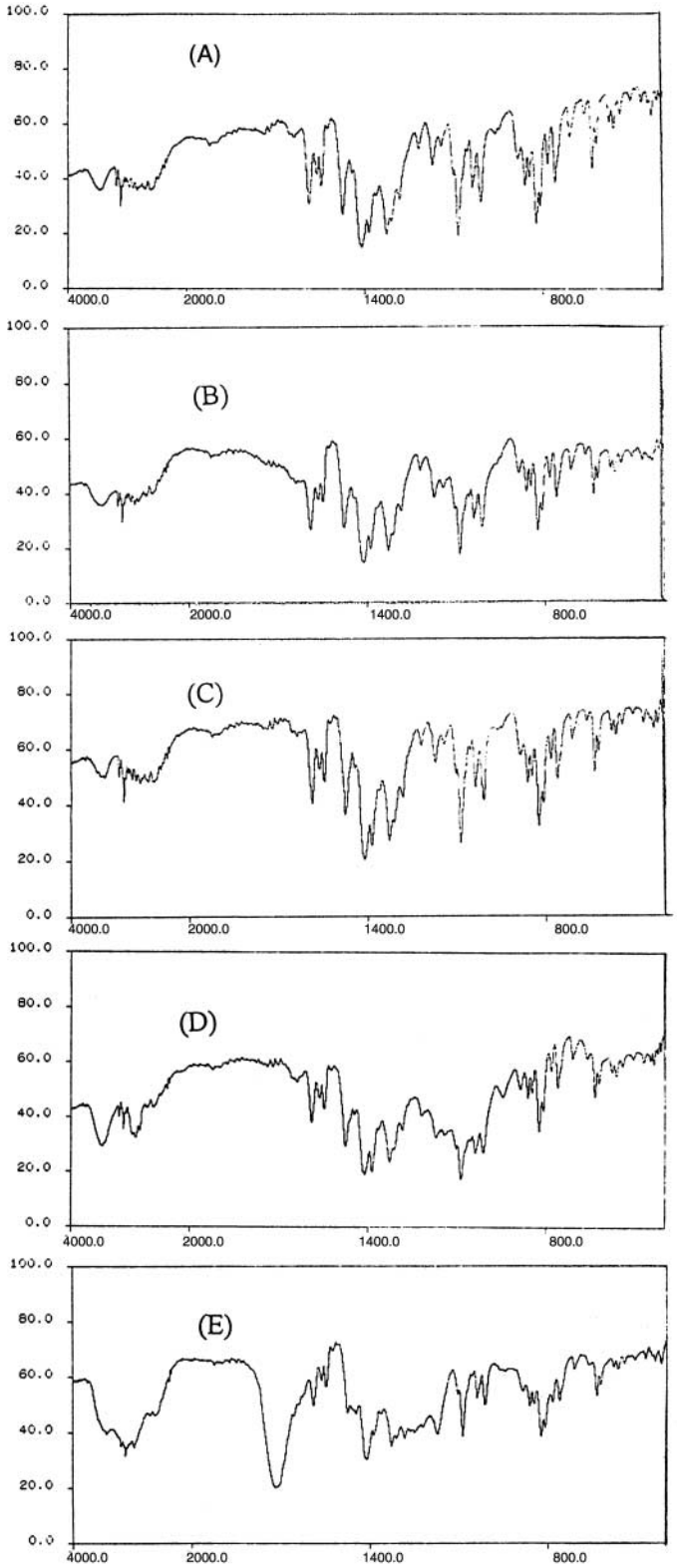

Figure 4. Typical IR spectra of: (A) pure miconazole nitrate, (B) physical mixture (1:1) with NaCMC, (C) physical mixture (1:1) with sodium alginate, (D) physical mixture (1:1) with HPMC, and (E) physical mixture (1:1) with Cp.

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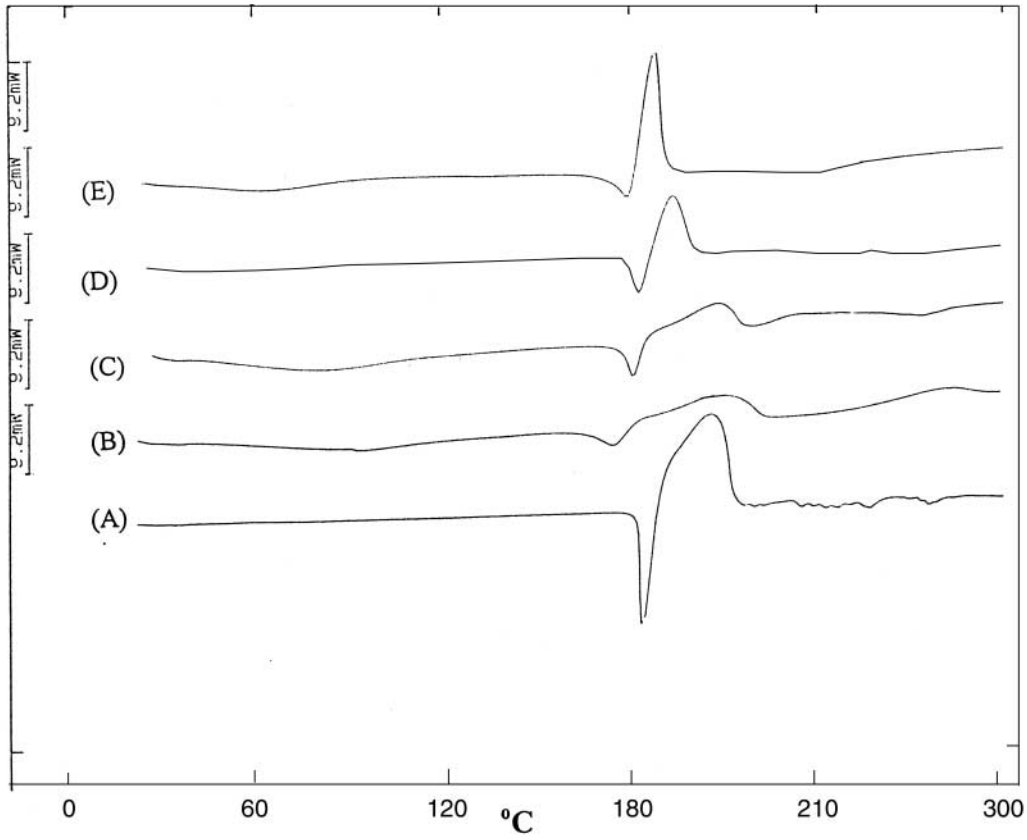

Figure 5. Typical DSC thermograms of: (A) pure miconazole nitrate, (B) physical mixture (1:1) NaCMC, (C) physical mixture (1:1) with sodium alginate, (D) physical mixture (1:1) with HPMC, and (E) physical mixture (1:1) with Cp.

Table 8. In Vivo characteristics of the prepared buccal bioadhesive tablet formulations of miconazole nitrate.

Formulation code	In vivo buccal bioadhesion time[a] (hr)	Pharmacokinetic parameters			Duration of activity ($T > MIC$)[b] (hr)
		C_{max} (μg/mL)	T_{max} (hr)	$AUC_{0\text{-}8h}$ (μg hr/mL)	
Cp1	3.27 ± 0.74	15.70 ± 1.50	1.75 ± 0.25	70.96 ± 6.77	> 8 hr
Cp2	2.80 ± 0.57	17.15 ± 2.30	1.50 ± 0.20	81.68 ± 10.36	> 8 hr
Cp3	2.45 ± 0.34	19. 21 ± 2.11	1.25 ± 0.35	97.42 ± 12.36	> 8 hr
F1	3.65 ± 0.35	17.11 ± 1.61	1.80 ± 0.25	92.64 ± 7.99	> 8 hr
F2	2.75 ± 0.27	18.11 ± 3.21	1.40 ± 0.26	99.33 ± 11.23	> 8 hr
F3	2.50 ± 0.25	20.91 ± 3.11	1.11 ± 0.31	102.9 ± 13.70	> 8 hr
N1	3.55 ± 0.62	25.60 ± 2.40	1.50 ± 0.25	109.2 ± 8.11	> 8 hr
N2	3.23 ± 0.31	18.80 ± 1.18	1.18 ± 0.454	108.77 ± 6.7	> 8 hr
N3	3.11 ± 0.45	20.69 ± 2.50	1.43 ± 0.40	91.03 ± 7.55	> 8 hr
Commercial gel (Daktaren gel)	0.35 ± 0.15[c]	30.01 ± 6.15[c]	0.08 ± 0.01[c]	25.88 ± 6.55[c]	3.50 ± 0.65[c]

[a]Mean ($n = 6$) buccal bioadhesion time.
[b]Time in which the saliva miconazole concentration is higher than the minimum inhibitory concentration (MIC).
[c]Statistical analysis was performed using one-way analysis of variance, ($p < 0.05$).

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Table 9. PC-Stat one-way analysis of variance of the in vivo characteristics of the prepared buccal bioadhesive tablet formulations of miconazole nitrate.

Buccal bioadhesion time (hr)			C_{max} (μg/mL)			T_{max} (hr)			$AUC_{0\text{-}8h}$ (μg hr/mL)		
Code	Mean	Grouping[a]	Code	Mean	Grouping[a]	Code	Mean	Grouping[a]	Code	Mean	Grouping[a]
F1	3.65	A	Com[b]	30.01	A	Com[b]	0.08	A	N1	109.2	A
N1	3.55	A	N1	25.60	B	F3	1.11	B	N2	108.7	A
CP1	3.27	B	F3	20.91	C	N2	1.18	B	F3	102.9	B
N2	3.23	B	N3	20.69	C	CP3	1.25	B	F2	99.33	C
N3	3.11	B	CP3	19.21	D	F1	1.40	C	CP3	97.42	D
CP2	2.80	C	N2	18.80	D	N3	1.43	C	F1	92.64	E
F2	2.75	C	F2	18.10	E	CP2	1.50	C	N3	91.03	F
F3	2.50	D	CP2	17.15	F	N1	1.51	C	CP2	81.68	G
CP3	2.45	D	F1	17.11	F	CP1	1.75	D	Cp1	70.96	H
Com[b]	0.35	E	CP1	15.70	G	F1	1.80	D	Com[b]	25.88	I

[a]Means with the same letter are not significantly different ($p < 0.05$).
[b]Commercial gel (Daktaren oral gel).

(Table 3), increase the microenvironment pH (Table 3) and decrease the in vivo buccal bioadhesion time (Table 8). The mean buccoadhesion time values for N1, N2, and N3 were 3.55 ± 0.62, 3.23 ± 0.31, and 3.11 ± 0.45 hr, respectivelly (Table 8).

Statistical analysis of the buccoadhesion time showed significant differences ($p < 0.05$) between the tested formulations and the commercial gel (Daktaren oral gel) (Table 9). The values of the buccoadhesion time were decreased in the following order: F1 > N1 > Cp1 > N2 > N3 > Cp2 > F2 > F3 > Cp3 > Commercial gel (Table 9). These data clearly indicate the more prolonged contact time and possible sustaining the antifungal activity of miconazole from the prepared tablets, compared with the commercial gel (Daktaren oral gel), mean buccoadhesion time of 0.35 ± 0.15 hr (Table 8).

In Vivo Salivary Concentration of Miconazole Nitrate

The mean salivary profiles of miconazole from the prepared buccal buccoadhesive tablets, in comparison with the commercial gel of miconazole, are shown in Figs. 6–8. Table 8 summarizes the important bioavailability parameters. The salivary profiles exhibited a sharp peak with a faster decline in the salivary concentration for the commercial gel of miconazole (Daktaren oral gel), but exhibited an absence of sharp peaks and more sustained salivary levels, at least until 8 hr, for all the prepared buccal buccoadhesive tablets (Table 8).

It has been observed that, by increasing the Cp content (Cp1, Cp2, and Cp3), C_{max} was decreased and T_{max} was increased (Table 8). The same results were observed with increasing sodium alginate (F1, F2, and F3). This could be attributed to the slower in vitro release of the drug by increasing the polymer concentration.

For Cp1, Cp2, and Cp3, the mean C_{max} values were 15.70 ± 1.50, 17.15 ± 2.30, and 19.21 ± 2.11 μg/mL, and the mean T_{max} value were 1.75 ± 0.25, 1.50 ± 0.20, and 1.25 ± 0.35 hr, respectively (Table 8), compared with C_{max} values of 17.11 ± 1.61, 18.11 ± 3.21, and 20.91 ± 3.11 μg/mL, and T_{max} values of 1.80 ± 0.25, 1.40 ± 0.26, and 1.11 ± 0.31 hr for F1, F2, and F3, respectively (Table 8). For Cp1, Cp2, and Cp3, the increased C_{max} with increasing carbopol concentration, could be attributed to increased hydration, swelling, and rapid erosion of the formed gel layer as the concentration of carbopol increased. This was confirmed by the reduction in the in vivo buccal bioadhesion time with increasing carbopol concentration (Table 8). The same results were obtained for F1, F2, and F3, in which the increasing sodium alginate concentration led to a rapid erosion of the gel layer and a reduction in the in vivo buccal bioadhesion time (Table 8), and, therefore, an increase in the C_{max} and a decrease in the T_{max} values (Table 8). For N1, N2, and N3, the mean C_{max} values were 25.60 ± 2.40, 18.80 ± 1.18 and 20.69 ± 2.50 μg/mL, and the mean T_{max} values

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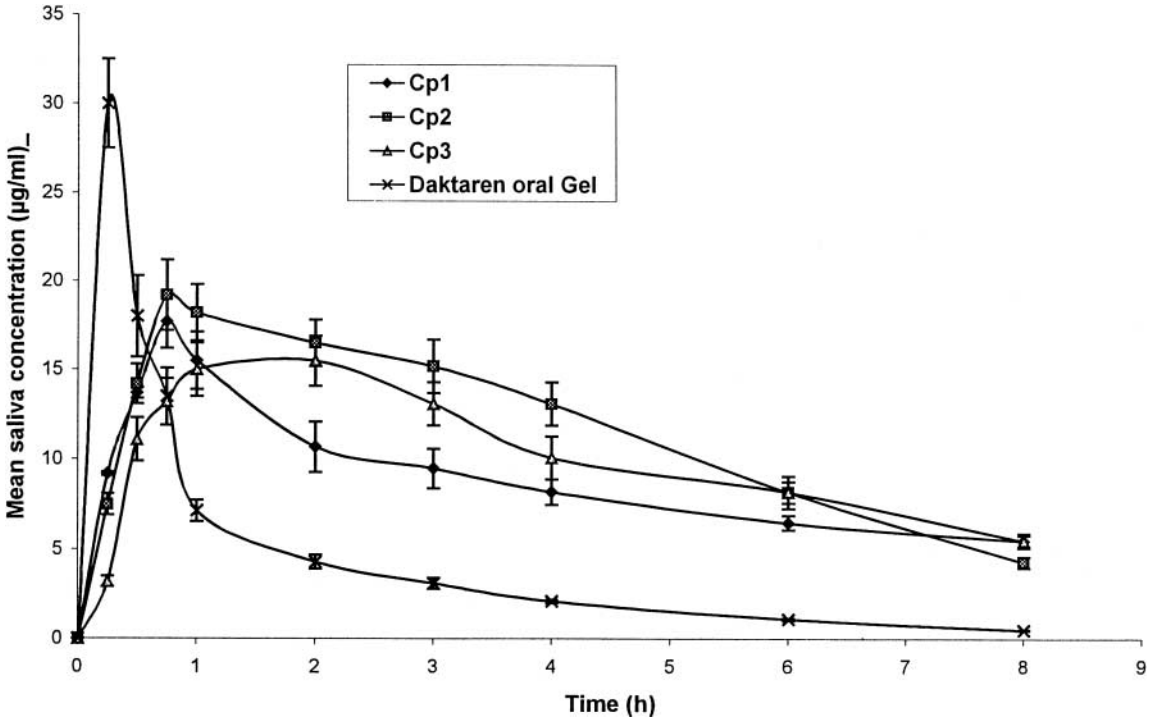

Figure 6. Mean ($n = 6$) salivary concentration of miconazole obtained after administration of the buccal bioadhesive tablets prepared with Cp/HPMC to six healthy volunteers in comparison with commercial miconazole nitrate gel (Daktaren oral gel).

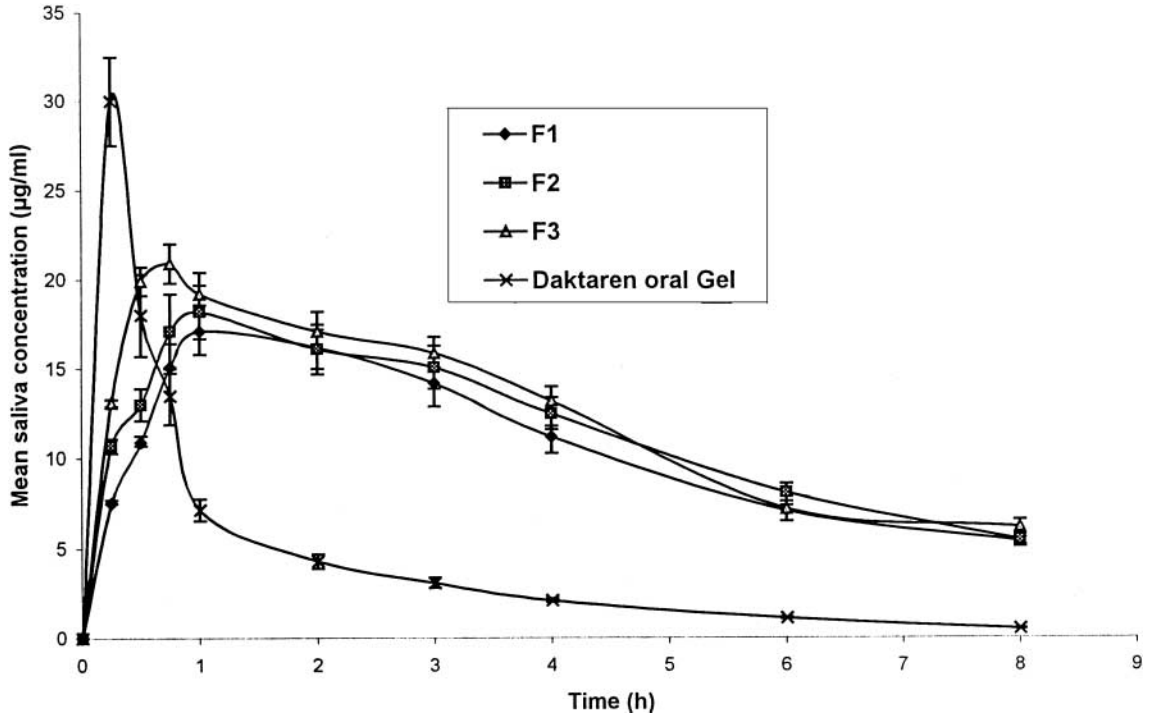

Figure 7. Mean ($n = 6$) salivary concentration of miconazole obtained after administration of the buccal bioadhesive tablets prepared with sodium aginate/NaCMC to six healthy volunteers in comparison with commercial miconazole nitrate gel (Daktaren oral gel).

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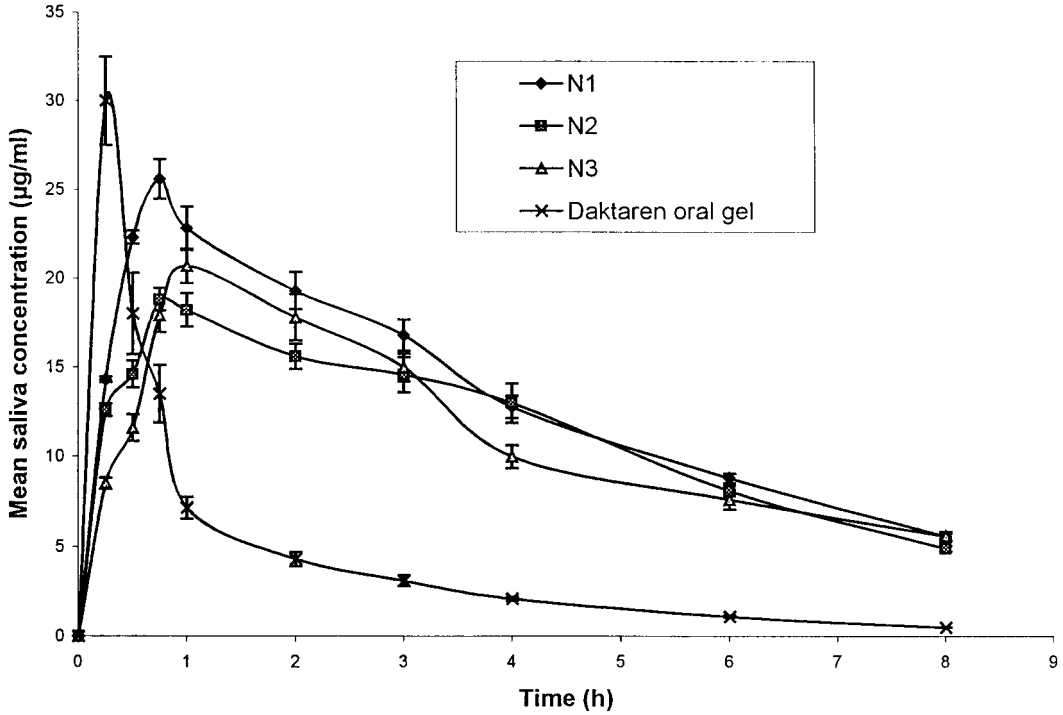

Figure 8. Mean ($n = 6$) salivary concentration of miconazole obtained after administration of the buccal bioadhesive tablets prepared with Cp/NaCMC to six healthy volunteers in comparison with commercial miconazole nitrate gel (Daktaren oral gel).

were 1.50 ± 0.25, 1.18 ± 0.45, and 1.43 ± 0.40 hr, respectively (Table 8). Thus, for N1, N2, and N3, C_{max} was decreased with increasing carbopol concentration from N1 to N3, which could be attributed to the slower release of the drug as the polymer concentration increased (Tables 1 and 8).

The mean C_{max} and T_{max} values for the commercial gel (Daktaren oral gel) were 30.01 ± 6.15 µg/mL and 0.08 ± 0.01 hr, respectively (Table 8).

The highest $AUC_{0\text{-}8h}$ values were obtained for tablets prepared with Cp/NaCMC (N1, N2, and N3), followed by those prepared with sodium alginate/NaCMC (F1, F2, and F3). This could be attributed to the relatively rapid release of the drug and to increased in vivo buccal bioadhesion time (Table 8).

Therefore, the obtained in vivo pharmacokinetic parameters (C_{max}, T_{max}, and $AUC_{0\text{-}8h}$) could be correlated to the in vitro release of miconazole nitrate, as well as the in vivo buccal bioadhesion time (Table 8).

Table 9 presents the statistical analysis of the obtained pharmacokinetic parameters. C_{max}, T_{max}, and $AUC_{0\text{-}8h}$ were significantly affected ($p < 0.05$) by the type and composition of the prepared buccoadhesive tablets (Table 9), which could be attributed to the difference in the in vitro release of the drug and/or difference in the contact time (in vivo buccal bioadhesion time) with mouth mucosa (Table 8).

CONCLUSIONS

All the prepared miconazole nitrate buccal bioadhesive tablets gave a reasonable buccoadhesive time (2.45–3.65 hr), which is important for prolonging the contact time of the drug with the buccal mucosa, thus improvement in the overall therapy of oral candidiasis. Increasing Cp concentration resulted in increasing the swelling index, decreasing the microenvironment pH (Table 3), and decreasing the in vivo buccal bioadhesion time. Increasing concentration of sodium alginate relative to NaCMC (F1, F2, and F3) was found to decrease the swelling index, increase the microenvironment pH, and decrease the in vivo buccal bioadhesion time. The prepared buccoadhesive tablets gave controlled and prolonged in vitro release of miconazole nitrate. Infrared spectroscopy and DSC studies revealed the absence of significant interactions between miconazole nitrate and the selected buccoadhesive materials. The salivary profiles exhibited a sharp peak, with a faster decline in the

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salivary concentration for the commercial gel of miconazole (Daktaren oral gel), but exhibited an absence of sharp peaks and more sustained salivary levels, at least for 8 hr, for all the prepared buccal buccoadhesive tablets. This would be important for better patient compliance. Duration of the antifungal activity of miconazole buccal bioadhesive tablets was markedly longer (> 8 hr) than that of the commercial miconazole gel (Daktaren oral gel). This would be important for better patient compliance because of the decrease in the frequency of administration.

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