Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 264 (2003) 1–14
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Mucoadhesive buccal patches of miconazole nitrate: in vitro/in vivo performance and effect of ageing

Noha A. Nafee, Fatma A. Ismail*, Nabila A. Boraie, Lobna M. Mortada

Department of Pharmaceutics, Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt

Received 15 October 2002; received in revised form 30 May 2003; accepted 25 June 2003

Abstract

Mucoadhesive patches containing 10 mg miconazole nitrate were evaluated. The patches were prepared with ionic polymers, sodium carboxymethyl cellulose (SCMC) and chitosan, or non-ionic polymers, polyvinyl alcohol (PVA), hydroxyethyl cellulose (HEC) and hydroxypropylmethyl cellulose (HPMC). Convenient bioadhesion, acceptable elasticity, swelling and surface pH were obtained. Patches exhibited sustained release over more than 5 h and the addition of polyvinyl pyrrolidone (PVP) generally enhanced the release rate. Optimum release behaviour was shown with patches containing 10% w/v PVA and 5% w/v PVP. Study of the in vivo release from this formulation revealed uniform and effective salivary levels with adequate comfort and compliance during at least 6 h. On the contrary, in vivo release of the commercial oral gel product resulted in a burst and transient release of miconazole, which diminished sharply after the first hour of application. Storage of these patches for 6 months did not affect the elastic properties, however, enhanced release rates were observed due to marked changes in the crystal habit of the drug.

Keywords: Mucoadhesive polymers; Patches; Miconazole nitrate; In vitro and in vivo release; Ageing

1. Introduction

Conventional formulations for local oral delivery are principally lozenges, mouthwashes, mouth paints, oral gels, pastes and suspensions. Release of drugs from these preparations involves an initial burst of activity, whose level rapidly declines to sub-therapeutic concentrations (Khanna et al., 1998).

Retentive buccal mucoadhesive formulations may prove to be a viable alternative to the conventional oral medications as they can be readily attached to the buccal cavity, retained for a longer period of time and removed at any time. Attempts have been made earlier to formulate various mucoadhesive devices including tablets (Ali et al., 1998), films (Kohda et al., 1997), patches (Nair and Chien, 1996), disks (Parodi et al., 1996), strips (Ilango et al., 1997), ointments (Bremecker et al., 1984), and gels (Shin et al., 2000). Buccal patches are highly flexible and thus much more readily tolerated by the patient than tablets. Patches also ensure more accurate dosing of the drug compared to gels and ointments.

Drug classes used topically in the mouth include antimicrobials (Senel et al., 2000), topical corticosteroids (Shin et al., 2000), local anaesthetics (Nair and Chien, 1996), antibiotics (Jones et al., 2000), and anti-dental caries drugs (Vivien-Castioni et al., 2000). Oral

* Corresponding author. Tel.: +20-3-4871317; fax: +20-3-4873273.
E-mail address: fatmaismail@yahoo.com (F.A. Ismail).

0378-5173/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/S0378-5173(03)00371-5

candidal infections require prolonged therapy with antifungal agents and hence it may be advantageous to deliver these drugs in a sustained manner. Previous reports have documented the use of buccal mucoadhesive devices for prolonged release of antifungal agents (Khanna et al., 1997).

Miconazole nitrate (MN) is a broad-spectrum antifungal agent that has been extensively applied for the management of dermal (Minghetti et al., 1999), buccal (Bouckaert and Remon, 1993), and vaginal (Mandal, 2000) candidiasis. Several buccal drug delivery devices containing miconazole were developed such as chewing gum (Pedersen and Rassing, 1991), oral gel and bioadhesive buccal tablets (Bouckaert et al., 1992).

The main aim in the present study was to develop buccal mucoadhesive patch to ensure satisfactory miconazole level in the mouth for prolonged periods. The performance of the prepared patch is to be compared to that of a commercial oral gel. In addition, the effect of ageing on the mucoadhesive performance of the prepared patches is to be investigated.

2. Materials

Miconazole nitrate BP93/USPXXIII (Madex Pharmaceuticals Limited, Ireland) and clotrimazole BP93/USPXXIII (Fabbrica Italiana Sintetici Viale, Italy) were both in the micronized form and were kindly supplied from Amriya Pharmaceutical Industries, Egypt. Chitosan, maximum granule size 0.2 mm, degree of acetylation $>$ 80%; (CarboMer, Inc., USA). Sodium carboxymethyl cellulose, SCMC (ADWIC, El-Nasr Pharmaceutical Chemicals Co., Egypt). Polyvinyl alcohol, PVA, Mowiol®40-88; (E.I. du-Pont de Nemours & Co., USA). Hydroxypropylmethyl cellulose 4000 cp, HPMC, Methocel® and hydroxyethyl cellulose 15000MPAS, HEC, Natrosol® (Alexandria Pharmaceutical Co., Egypt). Polyvinyl pyrrolidone, PVP, Povidone®, Kollidon®25 (BASF Aktiengesellschaft Ludwigshafen, Germany). Methanol, Chromasolv®, for HPLC (Riedel-De Haen Rdh Laborchemikalien Gmbh & Co. KG, Germany). Acetonitrile (Fisher chemicals for HPLC application, UK). Sodium acetate trihydrate (Riedel-De Haen AG Sleeze, Germany). Other chemicals were of analytical grade.

3. Methods

3.1. Preparation of mucoadhesive patches

The mucoadhesive patches were prepared using either ionic polymers (SCMC, chitosan) or non-ionic polymers (HEC, PVA, HPMC). To improve patch performance and release characteristics, a water-soluble hydrophilic additive, PVP, was added in two different concentrations, 1 and 5% w/v. For SCMC (4% w/v) and HEC (1.5% w/v) solutions, the calculated amount of the polymer was dispersed in 3/4 the volume of water with continuous stirring using mechanical stirrer and the final volume was adjusted with distilled water. According to Tsutsumi et al. (1994), PVA powder (10% w/v) was dissolved in hot water at approximately 80–100 °C while stirring. HPMC gel (3% w/v) was prepared as described by Kumar and Himmelstein (1995): a weighed quantity of the polymer was gradually added, with constant stirring, to 1/3 of the required volume of distilled water (90 °C) and the final volume is made up by adding cold water (5 °C). Chitosan was prepared according to Sawayanaga et al. (1982): 1 g was dissolved in 50 ml 1.5% v/v acetic acid with constant stirring for 48 h. The resultant viscous chitosan solution was filtered through gauze. 2% w/v of MN was incorporated in the polymeric solutions after levigation with 5% v/v glycerol, added as plasticizer. The medicated gels were left overnight at room temperature to ensure clear, bubble-free gels. The gels were cast into glass petri dish and allowed to dry in a levelled oven maintained at 40 °C (or at room temperature in case of chitosan) till a flexible film was formed. The dried films were cut into patches of 10 mm diameter and packed in aluminium foil and stored in glass containers maintained at room temperature, 58% relative humidity.

3.2. Evaluation of the prepared patches

Assessment of weight, thickness and drug content uniformity was performed on 10 patches. The mean and the standard deviation were calculated.

3.2.1. Surface pH

Buccal patches were left to swell for 2 h on the surface of an agar plate. The surface pH was measured by means of a pH paper placed on the surface

of the swollen patch. A mean of two readings was recorded.

3.2.2. Swelling study

After determination of the original patch weight and diameter, the samples were allowed to swell on the surface of agar plate kept in an incubator maintained at 37 °C. Increase in the weight and diameter of the patches ($n = 3$) was determined at preset time intervals (1–5 h). The percent swelling, %S, was calculated using the following equation:

$$\%S = \frac{X_t - X_o}{X_o} \times 100$$

where X_t is the weight or diameter of the swollen patch after time t, and X_o is the original patch weight or diameter at zero time.

3.2.3. Determination of the in vitro residence time

The in vitro residence time was determined using a locally modified USP disintegration apparatus, based on the apparatus applied by Nakamura et al. (1996). The disintegration medium was composed of 800 ml pH 6.75 isotonic phosphate buffer (IPB) maintained at 37 °C. A segment of rabbit intestinal mucosa, 3 cm length, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive patch was hydrated from one surface using 15 μl pH 6.75 IPB and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the patch from the mucosal surface was recorded (mean of triplicate determinations).

3.2.4. In vitro release study

The USP 24 dissolution apparatus type 1 was used. Patches were fixed to the central shaft using cyanoacrylate adhesive. The dissolution medium consisted of 900 ml pH 6.75 IPB. The release was performed at 37 ± 0.5 °C with a rotation speed 50 rpm. At predetermined time intervals, the remaining patch was removed from the dissolution flask and assayed for the amount of drug remaining using two-phase titration technique. The release study was carried out for 5 h. One patch was used for each interval. The percent MN released was determined by difference. The data presented were the mean of three determinations.

Miconazole nitrate was assayed using a two-phase titration as described by Massaccesi (1986). The medicated patch was placed in a 100-ml beaker and soaked with 10 ml distilled water till complete disintegration. Then, 10 ml of 1 M sulphuric acid, 25 ml of dichloromethane and 1 ml of dimethyl yellow (as indicator) were added. The mixture was titrated 0.01 M sodium dodecyl sulphate solution with vigorous magnetic stirring until a colour change from yellow to pink was observed in the organic phase at the end-point. The upper aqueous layer remained colourless throughout the titration. A reagent blank prepared in the same way was titrated and any necessary corrections were calculated. The sensitivity and linearity of the assay were checked over a concentration range from 1 to 30 mg ($y = 0.281x$; $r^2 = 0.9999$). Inter-day precision ($n = 9$) at the concentration of 5 mg had a coefficient of variation of 2.55%.

3.2.5. In vivo evaluation of selected miconazole patches

Formulated patches containing 10 mg miconazole nitrate and having selective mucoadhesive and release characteristics were evaluated in vivo and compared to a commercial brand oral gel Daktarin® (Janssen, Belgium). Five adult healthy volunteers, four females and one male (age range 30–50 years) were enrolled in a crossover study. At 8 a.m., a standard breakfast was given then the subjects were advised to brush their teeth. At 8.30 a.m., the volunteers were requested to place the patch on the buccal mucosa between the cheek and gingiva in the region of the upper canine with slight pressure for 30 s. During the study, no eating or drinking was allowed. The subjects were asked not to touch the patch with their tongue. Blank saliva samples were taken before patch installation. At fixed intervals, 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 h, saliva samples were collected and kept frozen at −18 °C until analysis. One week later, the volunteers were asked to place a fixed dose of Daktarin®, Janssen oral gel (1/4 spoonful) at the same place of the patch. The same precautions were carefully considered. Blank as well as saliva samples were collected.

The collected samples were treated as described by Bouckaert et al. (1996). An internal standard solution

40 μl, containing 1 mg/ml clotrimazole in methanol, and 160 μl methanol were added to 800 μl saliva sample. After vortexing for 1 min, 1 ml acetonitrile was added. The mixture was vortexed again for 1 min and centrifuged twice for 2 min, next, 20 μl supernatants were analysed using HPLC (Shimatzu). The assay was performed on a reversed phase column (μ Nova-Pack C_{18}, 39 mm × 150 mm, Waters, Ireland). The mobile phase consisted of 70% methanol, 20% acetonitrile, and 10% acetate buffer pH 5. The column flow rate was set at 1 ml/min. UV detection (model SPD-10A), was carried out at 220 nm. Linearity of the calibration curve was obtained in a concentration range from 5 to 40 μg/ml ($y = 0.0832x$; $r^2 = 0.9999$). The intra-day and inter-day precision ($n = 10$) at a concentration of 15 μg/ml had coefficient of variation of 1.3 and 0.58%, respectively. From the measured salivary MN concentration, the following parameters were calculated for the formulated patch and the commercial products: C_{max}, the peak salivary concentration, T_{max}, the time of peak concentration; $T^{>MIC}$, the time period above the minimum inhibitory concentration (MIC) value for miconazole nitrate against *Candida albicans* ATCC no. 10231 (5 μg/ml); $AUC_{0–6\,h}$, the area under the salivary concentration time curve from 0 to 6 h.

3.2.6. Effect of ageing

Optimized medicated patches were subjected to accelerated stability testing. Patches were packed in glass petri dish lined with aluminium foil and kept in an incubator maintained at 37 ± 0.5 °C and 75 ± 5% RH, for 6 months. The change in the appearance, physical properties and/or release behaviour of the stored bioadhesive patches was investigated after 1–6 months. The data presented were the mean of three determinations. Fresh and aged medicated patches were investigated using a Jeol, JSM-5300 scanning electron microscope. The patches were coated with gold using a direct current sputter technique.

4. Results and discussion

Tables 1 and 2 summarize the physical characteristics as well as the bioadhesive performance of the formulated patches. Patch thickness ranged from 0.5 to 1 mm, with a weight range from 50 to 130 mg. Patches had a surface pH of 5–6. The effect of miconazole nitrate on the swelling behaviour and the residence time of the mucoadhesive polymers are presented in Figs. 1 and 2, respectively. In general, the medicated patches had higher swelling values compared to plain

Table 1
Characteristics of mucoadhesive miconazole-containing patches based on ionic polymers

Characteristics	SCMC (anionic)			Chitosan (cationic)		
	0% PVP	1% PVP	5% PVP	0% PVP	1% PVP	5% PVP
Patch thickness (mm)	0.49 (0.28)[a]	0.55 (0.137)	0.52 (0.341)	0.72 (0.902)	0.69 (0.377)	0.78 (0.709)
Patch weight (mg)	129 (0.771)	116 (1.86)	119 (2.63)	77 (1.57)	91 (2.42)	88 (1.13)
% Swelling						
Weighing method (2 h)	351.38 (3.21)	589.32 (5.185)	437.02 (2.615)	49.17 (1.443)	38.92 (0.525)	119.12 (1.727)
Diameter method (5 h)	60.14 (1.352)	79.36 (1.845)	51.85 (2.548)	4.17 (0.09)	9.09 (0.408)	20 (0.496)
In vitro residence time (h)	2.5[b] (0.559)	2.5[b] (0.721)	3[b] (0.908)	3[b] (0.263)	2[b] (0.746)	1.25[b] (1.054)
% MN released after						
1 h	10.11 (1.051)	9.05 (0.913)	7.15 (0.004)	4.36 (1.749)	30.49 (0.609)	2.71 (0.82)
5 h	39.65 (2.84)	51.04 (2.11)	24.17 (0.987)	35.17 (0.442)	67.63 (0.768)	30.74 (1.445)
Release kinetics						
n	0.811	1.093	0.877	1.295	0.467	0.955
K	9.63	8.633	6.57	4.813	28.37	2.68
r	0.998	0.998	0.998	0.998	0.995	0.999

[a] Values between brackets indicate the standard deviation.
[b] The time at which patches were detached from the membrane before complete erosion.

Table 2
Characteristics of mucoadhesive miconazole-containing patches based on non-ionic polymers

Characteristics	PVA			HEC			HPMC		
	0% PVP	1% PVP	5% PVP	0% PVP	1% PVP	5% PVP	0% PVP	1% PVP	5% PVP
Patch thickness (mm)	0.98 (0.36)[a]	0.83 (0.544)	0.99 (0.742)	0.57 (0.116)	0.6 (0.256)	0.52 (0.309)	0.73 (0.12)	0.84 (0.142)	0.77 (0.096)
Patch weight (mg)	117 (1.74)	126 (1.932)	122 (2.044)	57 (1.56)	66 (0.927)	69 (2.15)	53 (0.633)	52 (1.091)	60 (0.882)
% Swelling									
Weighing method (2 h)	172.1 (2.603)	120.64 (1.375)	111.51 (2.356)	576.83 (4.737)	591.28 (3.805)	415.39 (3.714)	297.73 (2.148)	232 (1.754)	192.19 (1.923)
Diameter method (5 h)	28.67 (1.428)	26.01 (1.575)	25.41 (1.238)	36.36 (2.854)	40.91 (1.561)	33.56 (1.443)	40 (1.749)	31.67 (1.147)	30 (1.129)
In vitro residence time (h)	3.25 (0.087)	3.75 (0.109)	1.25 (0.192)	10 (0.156)	7 (0.248)	6 (0.525)	6 (0.144)	3 (0.2)	0.5[b] (0.082)
% MN released after									
1 h	18.71 (1.033)	26.66 (3.19)	29.185 (1.842)	9.99 (1.044)	7.33 (0.565)	9.04 (1.207)	3.25 (0.185)	2.69 (0.947)	2.59 (0.895)
5 h	65.15 (3.142)	68.49 (0.95)	86.33 (3.25)	45.74 (0.776)	30.79 (0.867)	40.57 (1.218)	21.62 (1.68)	30.41 (3.27)	26.29 (1.271)
Release kinetics									
n	0.778	0.675	0.718	0.921	0.895	0.916	1.135	1.46	1.45
K	19.67	28.03	29.185	10.46	6.68	9.12	3.68	2.27	2.76
r	0.993	0.997	0.993	0.996	0.998	0.999	0.993	0.997	0.996

[a] Values between brackets indicate the standard deviation.
[b] The time at which patches were detached from the membrane before complete erosion.

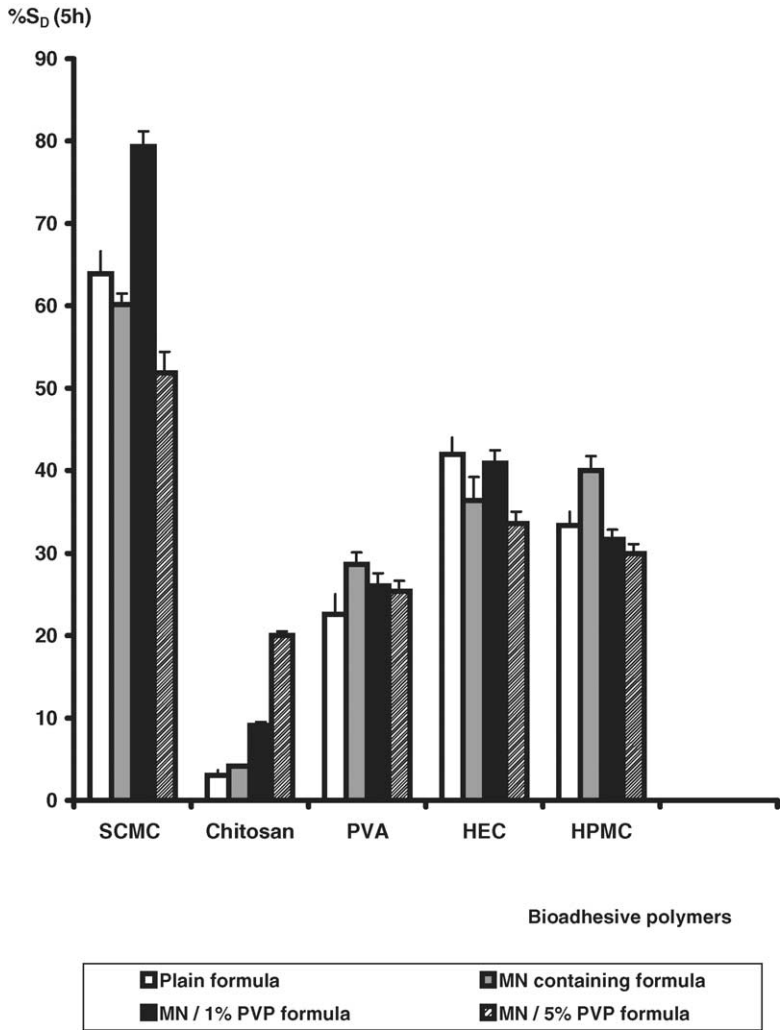

Fig. 1. The effect of miconazole nitrate and PVP (1 and 5% w/v) on the radial swelling of the mucoadhesive patches.

patches (Fig. 1). The addition of the water-insoluble drug increased the water uptake by the dosage form. The micronized drug particles may exist in between the polymer chains allowing each chain to hydrate freely, which may result in weak hydrogen bonding areas around the miconazole molecules. These areas may increase the strength of the swollen layer followed by an obvious increase in the amount of penetrated water (Panomsuk et al., 1996). Indomethacin, a practically water-insoluble drug, was found to increase the swelling behaviour of HPMC matrices (Panomsuk et al., 1996), while lower swelling indices were observed when the same drug was added to Gantrez-169 compressed matrix (El-Khodairy, 2001). The influence of drug on the swelling properties of polymer matrices is primarily dependent on the substituted groups of the polymer. The hydroxyl group in the molecules plays an important role in the matrix integrity of the swollen hydrophilic cellulose matrices. The amount and properties of the incorporated drug determine matrix integrity.

The incorporation of the drug induced significant reduction of the residence time of the studied formulae (*t*-test, $P < 0.05$) except for HEC patches (Fig. 2). The enhanced erosion rate observed with the non-ionic polymers PVA and HPMC may correlate with the

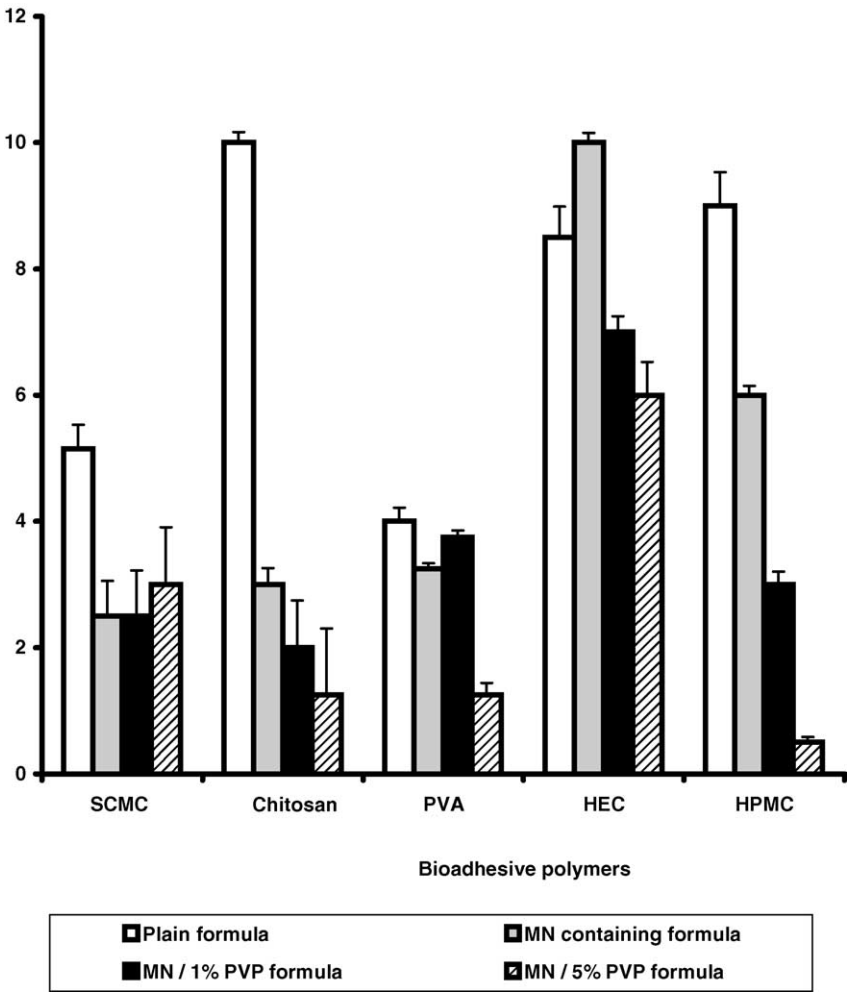

Fig. 2. The effect of miconazole nitrate and PVP (1 and 5% w/v) on the residence time of the mucoadhesive patches.

increase in swelling behaviour when the drug was added (Fig. 1). As the particle swells, the matrix experiences intra-matrix swelling force promoting disintegration and leaching of the drug leaves behind a highly porous matrix. Water influx weakens the network integrity of the polymer, the structural resistance of the swollen matrices is thus greatly influenced and erosion of the lose gel layer is more pronounced (Wan et al., 1995). The early dislodgement of the patch from the mucosal surface was more distinct with the ionic polymers chitosan and SCMC (Fig. 2). At pH 6.8, MN is ionized, hence, it may interfere with the charge density on the mucoadhesive polymers and/or may compete with the glycoproteinic molecules by binding to the functional groups on the mucoadhesive polymers, leading to weaker bioadhesive performance. The patch was then easily detached from the membrane (Table 1).

The addition of PVP predominantly decreased the swelling characteristics of the medicated patches, except for chitosan and SCMC (Tables 1 and 2). The water-soluble hydrophilic additive dissolves rapidly introducing porosity. The void volume is thus expected to be occupied by the external solvent diffusing into the film and thereby accelerating the dissolution of the gel (Samuelov et al., 1979). A remarkable increase in swelling properties was observed in the case of chitosan patches. The weak aqueous solubility of the

cationic polymer limited the swelling of the patches but the addition of certain amounts of the hydrophilic polymer PVP increased surface wettability and consequently water penetration within the matrix. Additional shortening in the residence time was observed when a higher percentage of PVP was added to the patches. The increase in water-soluble content promotes faster dissolution of the patch (Korsmeyer et al., 1983).

4.1. In vitro release of miconazole nitrate

From Fig. 3, marked differences in the MN release are seen between PVA and the other cellulose derivatives. During dissolution, PVA swelled forming a gel layer on the exposed patch surfaces. The loosely bound polymer molecules were easily eroded, allowing the release of MN in a higher rate compared to the other cellulosic derivatives (Korsmeyer et al., 1983). SCMC and HEC showed comparable release behaviour. Referring to the swelling data, both polymers exhibited high swelling; the patch weight increased by 350–580% from the original weight within 2 h (Tables 1 and 2). Although the marked increase in surface area during swelling can promote drug release, the increase in diffusional pathlength of the drug may paradoxically delay the release. In addition, the thick gel layer formed on the swollen patch surface is capable of preventing matrix disintegration and controlling additional water penetration (Rodriguez et al., 2000). SCMC is characterized by a higher dissolution rate compared to HEC; however, the use of SCMC in a higher concentration (4% w/v) than HEC (1.5% w/v) resulted in a comparable release rate for the two polymers.

The release of MN from HPMC patches was slower than SCMC and HEC. Recently, the release of the poorly water-soluble drug, theophylline, from hydrophilic matrices based on HPMC and HEC was studied (Rodriguez et al., 2000). The difference in release was attributed to differences in polymer dissolution, HEC is more hydrophilic and has high polymer dissolution whereas HPMC has slow erosion rate. This can be explained in terms of the differences between the polymer disentanglement concentration, which is defined as the concentration at which polymer chains detach from the matrix and traverse the boundary diffusion layer toward the bulk dissolution medium. According to Rodriguez et al. (2000), HEC detach from the matrix at a higher concentration leading to a higher transfer flux. HEC is thus more prone to chain disentanglement and thus to erosion than HPMC with the probable result of more rapid drug release. In addition, the polymer concentration was doubled in the case of HPMC (3% w/v) compared to HEC (1.5% w/v), which may contribute to the slower release rate describing HPMC patches.

Chitosan-containing patches produced sustained release in all formulations (Fig. 3). The minimum release rate was observed from the system containing 5% w/v PVP where only 2.71% MN was released in the first hour and slowly progressed to 30.74% after 5 h. This formula exhibited a higher swelling profile and slower erosion rate compared to other chitosan-based patches. The subsequent increase in diffusional path length and low attrition may be responsible for the distinct low release profile.

Patches containing SCMC, HEC and HPMC, respectively (Tables 1 and 2) show a zero-order release. Lee (1980) provided analytical solution for erodible swelling systems, where zero-order release is achieved when the movements of the diffusion front (solid drug—drug solution interface) and the eroding front (rubbery polymer—solvent interface) are synchronized, so that the diffusional pathlength for drug diffusion remained fairly constant. Later, Peppas and Franson (1983) proposed the concept of swelling-controlled release systems, where constant release is observed when the solvent penetration is much slower than drug diffusion in the swollen gel. In the case of PVA patches, where $0.5 < n < 1$ (Table 2), anomalous release could be observed. The release rate was higher for systems containing 5% w/v PVP. Due to the viscoelastic properties of the polymer, a relative contribution of drug diffusion, polymer relaxation and matrix erosion to drug release could be identified. The drug release control is obtained by diffusion of molecules through the gel layer that can dissolve or erode. As far as the dependence of the exponent n on drug solubility is concerned, many authors have generally observed that n departs from Fickian diffusion for very poorly soluble drugs and that the rate-limiting factor for release is the erosion of the hydrophilic matrix (Colombo et al., 2000).

It was concluded that formulations containing 10% w/v PVA and 5% w/v PVP are characterized by

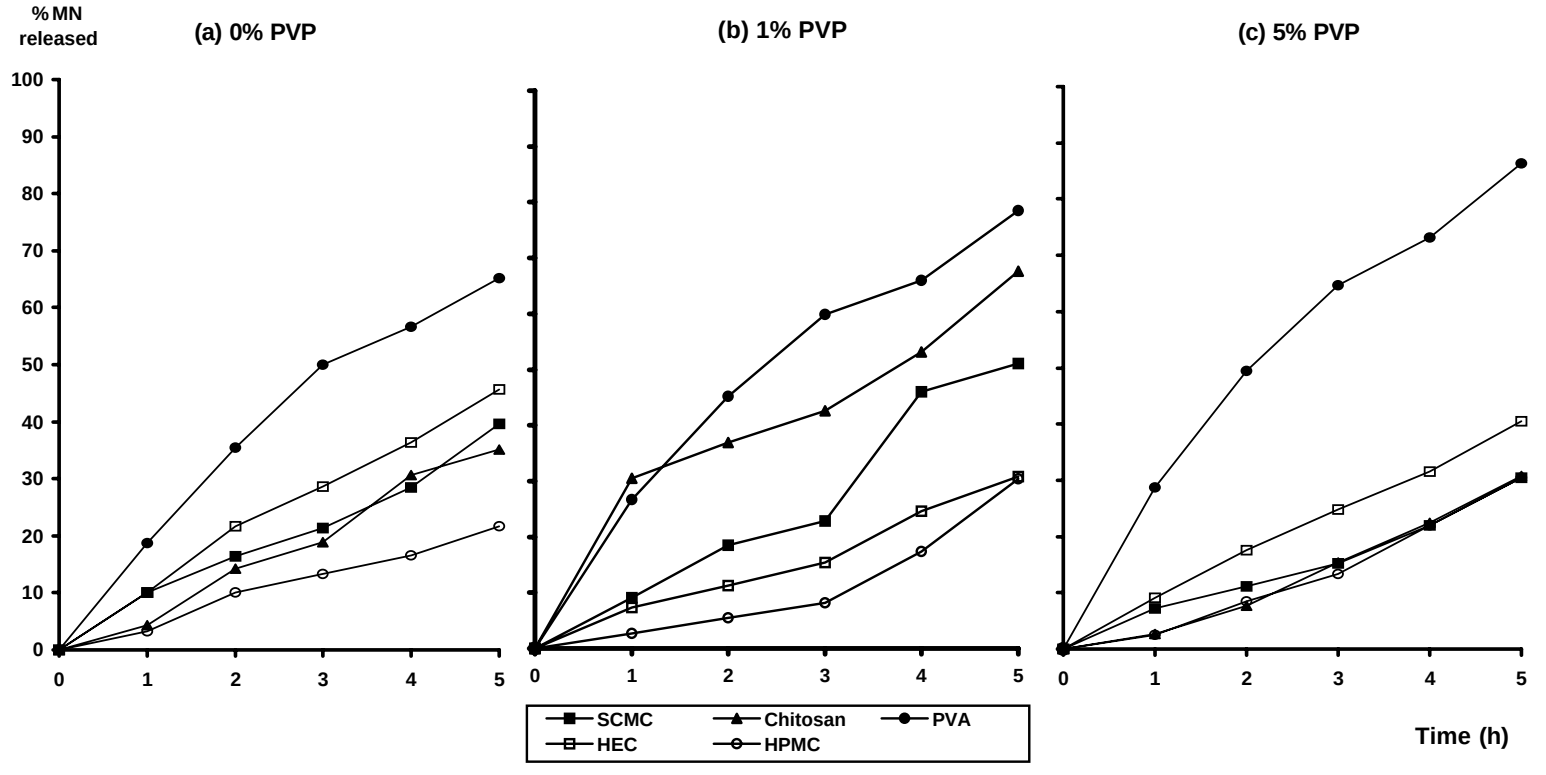

Fig. 3. The release profiles of miconazole nitrate from: (a) patches without PVP, (b) patches containing 1% w/v PVP, (c) patches containing 5% w/v PVP.

moderate swelling, a convenient residence time as well as adequate drug release. This formula was thus selected for investigation of in vivo performance and study of the effect of ageing on the formula.

4.2. In vivo evaluation of selected mucoadhesive patches

The in vivo miconazole nitrate concentration released from optimized mucoadhesive patches containing PVA 10% w/v and PVP 5% w/v and the commercial product Daktarin® oral gel (Janssen) in five healthy volunteers were compared (Fig. 4 and Table 3). The mean release curve, illustrated in Fig. 4, demonstrates a striking difference in release rate between the patch and the miconazole gel. Although high drug levels were observed for both formulations during the first 30 min of the experiment, a remarkable MN concentration was released from the patch after 4 h compared to traces of the drug obtained from the commercial gel (Table 3). Detectable MN concentrations were present in saliva even after the complete erosion of the patch (4–4.5 h). In a similar study, Pedersen and Rassing (1991) observed the

Table 3
In vivo release parameters of miconazole nitrate from mucoadhesive patch and Daktarin® oral gel

In vivo release parameters	Mucoadhesive patch (±S.D.)	Daktarin® oral gel (±S.D.)
C_{max} (μg/ml saliva)	120.275 (±17.23)	549.897 (±18.61)
T_{max} (h)	2.3 (±0.447)	0.08
$T^{>MIC}$	6.1 (±0.489)	1.313 (±0.325)
$AUC_{0–6\,h}$	370.29 (±15.156)	182.12 (±11.215)

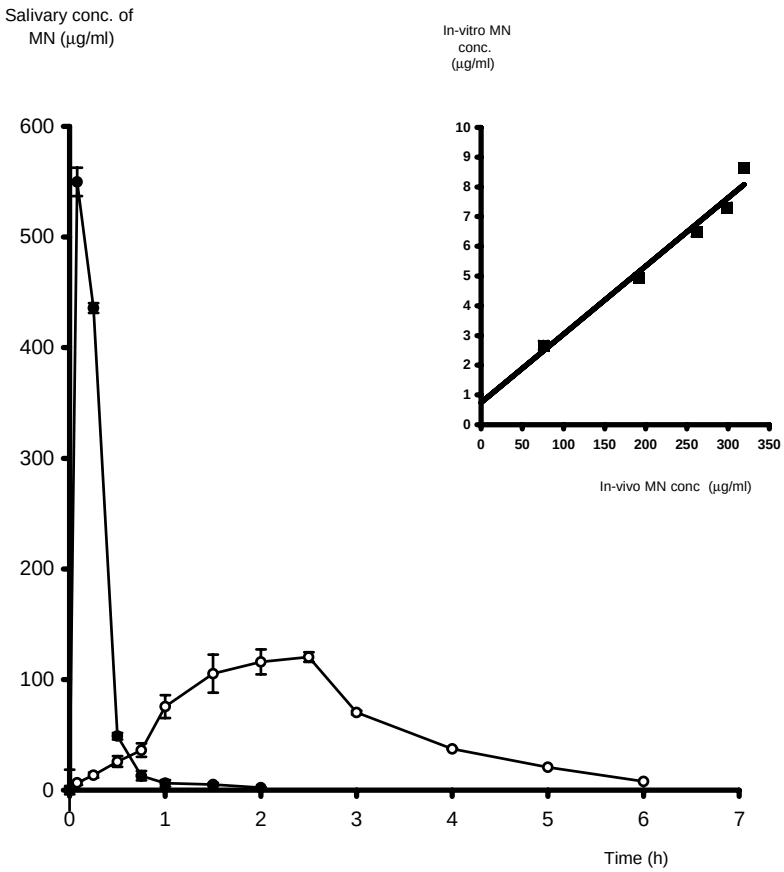

Fig. 4. Mean salivary miconazole concentration obtained in vivo with mucoadhesive patch (○) and Daktarin® oral gel (●). The insert represents correlation between in vitro/in vivo cumulative miconazole concentration (μg/ml) released from the mucoadhesive patch.

persistence of MN in the saliva 450 min after removal of the chewing gum from the oral cavity. The MIC for miconazole nitrate against *C. albicans* is 5 μg/ml; $T^{>MIC}$ is the time where the last salivary concentration is above the MIC. The recorded values of $T^{>MIC}$ were 1.313 and 6.1 h for Daktarin® oral gel and for mucoadhesive patch, respectively (Table 3). It is clear that the mucoadhesive patch has a greater ability to sustain an elevated MN concentration in saliva despite the administration of a smaller dose (10 mg) compared with the gel (25 mg). A buccal tablet formula based on carbopol was compared to the oral gel (Bouckaert et al., 1992); the amount of drug released via the bioadhesive tablet was six-fold lower than the gel, the salivary miconazole levels were higher and remained above the MIC value of *C. albicans* for more than 10 h. Bouckaert et al. (1993) studied the in vivo MN release from mucoadhesive tablets containing carbopol of different grades and thermally modified maize starch, the tablet adhered to the gingiva for 10.2 h and maximum MN level in saliva was 109–115 μg/ml after 4–5 h. The mucoadhesive buccal films of clotrimazole was evaluated in vivo; a maximum salivary concentration of 21.1 μg/ml was measured after 2 h and the release was maintained for 4 h (Khanna et al., 1997).

The high standard deviation values obtained from in vivo release (Table 3) can be explained by the difference in salivary flow from one subject to the other, which influenced patch hydration and clearance of solutes in the mouth. Many previous studies showed that salivary flow and cheek movement while speaking, eating, or drinking could play an important role in the adhesion time and drug release from the buccal

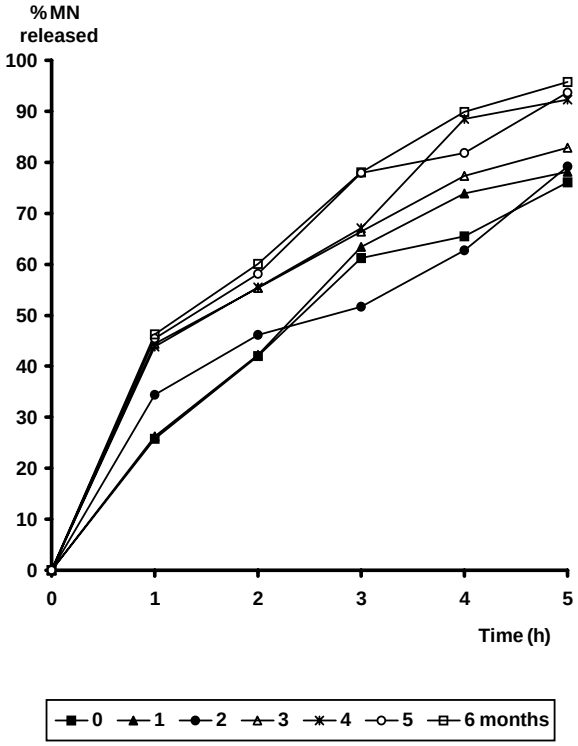

Fig. 5. Effect of ageing on the release profile of miconazole nitrate from mucoadhesive patches.

mucoadhesive formulation (Bottenberg et al., 1992). Analysis of variance test (ANOVA) revealed a significant difference ($P < 0.05$) between the in vivo release parameters for both the mucoadhesive patch and the commercial oral gel. The insert in Fig. 4 illustrates a plot of the cumulative concentration of mi-

Table 4
Short-term stability data of mucoadhesive patches containing miconazole nitrate stored at 37 °C/75% RH for 6 months

Characteristics	Duration of storage (month)						
	0	1	2	3	4	5	6
In vitro residence time (h)	1.25 (0.385)	1.25 (0.167)	1.25 (0.401)	1.25 (0.366)	1.5 (0.097)	2 (0.156)	2 (0.283)
In vitro % released							
1 h	25.79 (0.191)	26.27 (0.275)	34.38 (0.377)	44.37 (0.713)	43.79 (0.655)	45.44 (0.491)	46.26 (0.389)
5 h	76.03 (0.476)	78.1 (0.254)	79.2 (0.151)	82.87 (0.286)	92.33 (0.202)	93.69 (0.405)	95.76 (0.41)
Release kinetics							
n	0.68	0.71	0.484	0.398	0.487	0.461	0.473
k	26.35	26.59	33.18	43.45	41.92	44.56	45.45
r	0.992	0.991	0.997	0.995	0.998	0.998	0.994

conazole released in vitro (μg/ml) against the cumulative concentration released in vivo (μg/ml). By comparison, higher drug concentrations were measured in saliva; this may be attributed to the large volume of the dissolution medium used in vitro (900 ml) relative to the salivary volume. The straight line and the high correlation coefficient value ($r = 0.975$) proved the good correlation between in vitro and in vivo release studies.

4.3. Effect of ageing

Optimized mucoadhesive patches containing 10 mg miconazole nitrate in PVA 10% and PVP 5% w/v were subjected to stability study maintained at $37 \pm 0.5\,^{\circ}C$ and $75 \pm 5\%$ RH for 6 months. No remarkable change in the physical characteristics was observed. The patches retained good flexibility and elastic properties. However, after 4 months, they were found to be considerably sticky and hygroscopic. This may be attributed to the well known hygroscopic nature of PVP included in the formula. In addition, a delay in the residence time of the stored patches is noticed; the time necessary for patch erosion increased from 1.25 h at zero time to 1.5 h after 4 months and finally 2 h after 5 and 6 months (Table 4). The formula exhibited excellent drug content over the period of 6 months. The release profiles, illustrated in Fig. 5, showed a gradual increase in release rate during storage. Patches stored for 6 months allowed the release of 46.26% MN in the first hour compared to 25.79% MN released from non-stored patches at the same interval.

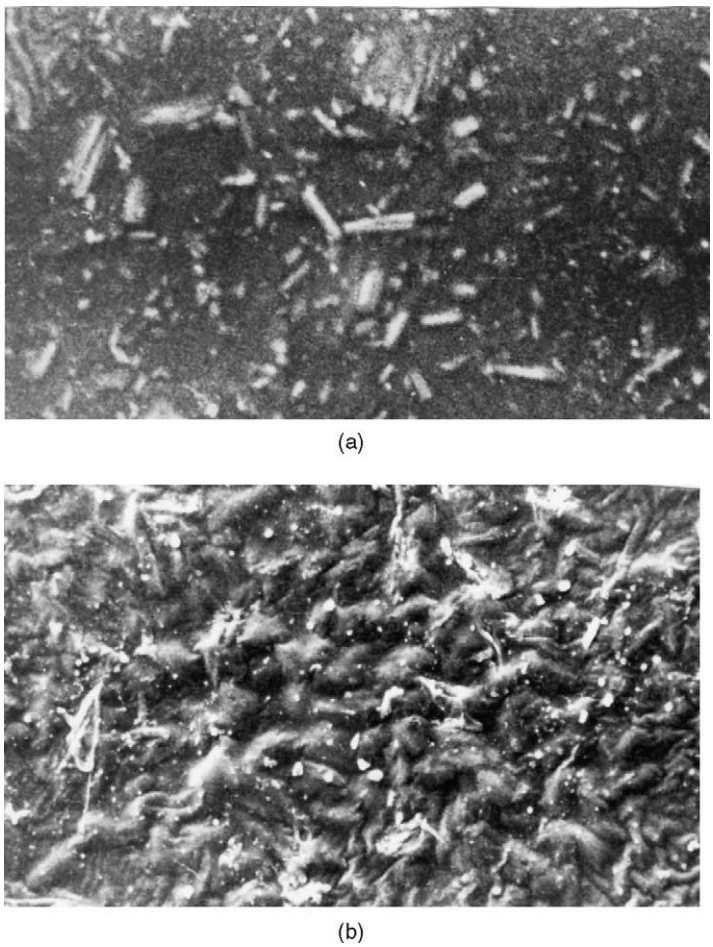

Fig. 6. Scanning electron micrograph of (a) fresh and (b) stored mucoadhesive patches containing miconazole nitrate, magnification 1000×.

The percent drug released after 5 h increased from 76.03%, at zero time, to 79.2, 92.33 and 95.76% after 2, 4 and 6 months, respectively. Fresh MN-containing patches as well as patches of the same composition stored for 1 year at 37 ± 0.5 °C and 75 ± 5% RH were examined using the electron microscope. Fig. 6a and b shows the electron micrographs of the fresh and stored patches, respectively. Fresh patches are characterized by well-defined crystals of the drug homogeneously dispersed in the polymer matrix. During the storage period, crystal solvation occurred where the drug slowly dissolved in the polymeric matrix to certain extent. By time, recrystallization, which is a dynamic process, resulted in the formation of minute amorphous drug crystals. It is suggested that the polymeric solution formed a protective coat around the minute drug particles, which may suppress regular crystal growth. The size reduction of drug crystals during storage may be the reason for the relatively enhanced release rate. The release kinetic parameters were calculated (Table 4). Values of the diffusional exponent *n* are 0.68 in the original patch slightly increasing to 0.71 after 1 month of storage indicating a non-Fickian release mechanism. However, after 2–6 months of storage, *n* is observed to range from 0.398 to 0.487 revealing a change in the release mechanism to be purely diffusion controlled.

5. Conclusion

Mucoadhesive patches containing miconazole nitrate using anionic (SCMC), cationic (chitosan) and non-ionic (PVA, HEC, HPMC) polymers showed satisfactory mucoadhesive characteristics. PVA patches improved uniform and effective miconazole levels in vitro and in vivo (>5 h) without being drastically influenced by ageing.

References

Ali, J., Khar, R.K., Ahuja, A., 1998. Formulation and characterization of a buccoadhesive erodible tablet for the treatment of oral lesions. Pharmazie 53, 329–334.

Bottenberg, P., Cleymaet, R., De Muyncha, C., Remon, J.P., Coomans, D., Slop, D., 1992. Comparison of salivary fluoride concentration after administration of a bioadhesive slow-release tablet and a conventional fluoride tablet. J. Pharm. Pharmacol. 44, 684–686.

Bouckaert, S., Schautteet, H., Lefebvre, R.A., Remon, J.P., van Clooster, R., 1992. Comparison of salivary miconazole concentrations after administration of a bioadhesive slow-release buccal tablet and an oral gel. Eur. J. Clin. Phamacol. 43, 137–140.

Bouckaert, S., Remon, J.P., 1993. In vitro bioadhesion of a buccal, miconazole slow release tablets. J. Pharm. Pharmacol. 45, 504–507.

Bouckaert, S., Lefebvre, R.A., Remon, J.P., 1993. In vitro/in vivo correlation of the bioadhesive properties of a buccal bioadhesive miconazole slow release tablet. Pharm. Res. 10, 853–856.

Bouckaert, S., Vakaet, L., Remon, J.P., 1996. Influence of the buccal application site of a bioadhesive slow-release tablet on the salivary miconazole concentrations in irradiated patients. Int. J. Pharm. 130, 257–260.

Bremecker, K.D., Strempel, H., Klein, G., 1984. Novel concept for a mucosal adhesive ointment. J. Pharm. Sci. 73, 548–552.

Colombo, P., Santi, P., Bettini, R., Brazel, C.S., 2000. Drug release from swelling controlled systems. In: Wise, D.L. (Ed.), Handbook of Pharmaceutical Controlled Release Technology, vol. 9. Marcell Dekker, New York, USA, pp. 183–209.

El-Khodairy, K.A., 2001. Effect of physicochemical properties of the hydrophilic Gantrez matrix. Alex. J. Pharm. Sci. 15, 35–40.

Ilango, R., Kavimani, S., Mullaicharam, A.R., Jayakar, B., 1997. In vitro studies on buccal strips of glibenclamide using chitosan. Ind. J. Pharm. Sci. 59, 232–235.

Jones, D.S., Woolfson, A.D., Brown, A.F., Coulter, W.A., Mc Clelland, C., Irwin, C.R., 2000. Design, characterization and preliminary clinical evaluation of a novel mucoadhesive topical formulation containing tetracycline for the treatment of periodontal disease. J. Control. Release 67, 357–368.

Khanna, R., Agarwal, S.P., Ahuja, A., 1997. Mucoadhesive buccal tablets of clotrimazole for oral candidiasis. Drug Dev. Ind. Pharm. 23, 831–837.

Khanna, R., Agarwal, S.P., Ahuja, A., 1998. Mucoadhesive buccal drug delivery: a potential alternative to conventional therapy. Ind. J. Pharm. Sci. 60, 1–11.

Kohda, Y., Kobayashi, H., Baba, Y., Yuasa, H., Ozeki, T., Kanaya, Y., Sagara, E., 1997. Controlled release of lidocaine hydrochloride from buccal mucosa-adhesive films with solid dispersion. Int. J. Pharm. 158, 147–155.

Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P., Peppas, N.A., 1983. Mechanisms of solute release from porous hydrophilic polymers. Int. J. Pharm. 15, 25–35.

Kumar, S., Himmelstein, K.J., 1995. Modification of in situ gelling behavior of carbopol solution by hydroxypropylmethyl cellulose. J. Pharm. Sci. 84, 344–348.

Lee, P.I., 1980. Diffusional release of a solute from a polymeric matrix: approximate analytical solutions. J. Membr. Sci. 7, 255–275.

Mandal, T.K., 2000. Swelling-controlled release system for the vaginal delivery of miconazole. Eur. J. Pharm. Biopharm. 50, 337–343.

Massaccesi, M., 1986. Two-phase titration of some imidazole derivatives in pharmaceutical preparations. Analyst 111, 987–989.

Minghetti, P., Cilurzo, F., Casiraghi, A., Molla, F.A., Montanari, L., 1999. Dermal patches for the controlled release of miconazole:

influence of the drug concentration on the technological characteristics. Drug Dev. Ind. Pharm. 25, 679–684.

Nair, M.K., Chien, Y.W., 1996. Development of anticandidal delivery systems. (II) Mucoadhesive devices for prolonged drug delivery in the oral cavity. Drug Dev. Ind. Pharm. 22, 243–253.

Nakamura, F., Ohta, R., Machida, Y., Nagai, T., 1996. In vitro and in vivo nasal mucoadhesion of soluble polymers. Int. J. Pharm. 134, 173–181.

Panomsuk, S.P., Hatanaka, T., Aiba, T., Katayama, K., Koizumi, T., 1996. A study of the hydrophilic cellulose matrix: effect of drugs on the swelling properties. Chem. Pharm. Bull. 44, 1039–1042.

Parodi, B., Russo, E., Caviglioli, G., Cafaggi, S., Bignardi, G., 1996. Development and characterization of a buccoadhesive dosage form of oxycodone hydrochloride. Drug Dev. Ind. Pharm. 22, 445–450.

Pedersen, M., Rassing, M.R., 1991. Miconazole chewing gum as a drug delivery system: test of release promoting additives. Drug Dev. Ind. Pharm. 17, 411–420.

Peppas, N.A., Franson, N.M., 1983. The swelling interface number as a criterion for prediction of diffusional solute release mechanisms in swellable polymers. J. Polym. Sci. Polym. Phys. 121, 983–997.

Rodriguez, C.F., Bruneau, N., Barra, J., Alfonso, D., Doelker, E., 2000. Hydrophilic cellulose derivatives as drug delivery carriers: influence of the substitution type on the properties of compressed matrix tablets. In: Wise, D.L. (Ed.), Handbook of Pharmaceutical Controlled Release Technology, vol. 1. Marcell Dekker, New York, USA, pp. 1–30.

Samuelov, Y., Donbrow, M., Friedman, M., 1979. Sustained release of drugs from ethyl cellulose-polyethylene glycol films and kinetics of drug release. J. Pharm. Sci. 68, 325–329.

Sawayanaga, Y., Nambu, N., Nagai, T., 1982. Permeation of drugs through chitosan membranes. Chem. Pharm. Bull. 30, 3297–3301.

Senel, S., Ikinci, G., Kasa, S., Yousefi-Rad, A., Sargon, M.F., Hincal, A.A., 2000. Chitosan films and hydrogels of chlorhexidine gluconate for oral mucosal delivery. Int. J. Pharm. 193, 197–203.

Shin, S.-C., Bum, J.-P., Choi, J.-S., 2000. Enhanced bioavailability by buccal administration of triamcinolone acetonide from the bioadhesive gels in rabbits. Int. J. Pharm. 209, 37–43.

Tsutsumi, K., Tahayama, K., Machida, Y., Ebert, C.D., Nakatomi, I., Nagai, T., 1994. Formulation of buccal mucoadhesive dosage form of ergotamine tartrate. S.T.P. Pharm. Sci. 4, 230–234.

Vivien-Castioni, N., Gurny, R., Baehni, P., Kaltsata, V., 2000. Salivary fluoride concentration following applications of bioadhesive tablets and mouthrinses. Eur. J. Pharm. Biopharm. 49, 27–33.

Wan, L.S.C., Heng, P.W.S., Wong, L.F., 1995. Matrix swelling: a simple model describing extent of swelling of HPMC matrices. Int. J. Pharm. 116, 168–195.