Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 286 (2004) 27–39
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Formulation and evaluation of diclofenac sodium buccoadhesive discs

M.S. El-Samaligy*, S.A. Yahia, E.B. Basalious

Department of Pharmaceutics, Faculty of Pharmacy, Cairo University, Kasr El-aini Street, Cairo, Egypt

Received 3 January 2004; received in revised form 9 June 2004; accepted 30 July 2004

Abstract

Twenty diclofenac sodium buccoadhesive discs containing Cp974p, polycarbophil, PEO, SCMC-medium viscosity (SCMC-MV), SCMC-ultrahigh viscosity (SCMC-UHV) or their combinations were prepared. These buccoadhesive discs were evaluated for release pattern, swelling capacity, surface pH, mucoadhesion performance, and in vitro permeation of diclofenac sodium through buccal membranes. In vivo testing of mucoadhesion time, strength of adhesion, irritation, bitterness due to drug swallowing and disc disintegration in the buccal cavity were also performed. Drug bioavailability of a selected diclofenac sodium buccoadhesive product was then compared with that of Voltarin® 100 SR tablet. The percentage relative bioavailability of diclofenac sodium from the selected buccoadhesive disc 50 mg was found to be 141.31%.

Keywords: Diclofenac sodium; Buccoadhesive disc; Relative bioavailability

1. Introduction

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient. However, peroral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Drug buccal administration, on the other hand, is highly acceptable by patients and the oral mucosa is relatively permeable with a rich blood supply. Furthermore, oral transmucosal drug delivery avoids first pass effect and provides facile removal of dosage form in case of need. Within the oral mucosal cavity, delivery of drugs is classified into three categories: (1) sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth; (2) buccal delivery, which is drug administration through mucosal membranes lining the cheeks (Buccal mucosa); and (3) local delivery, which is drug delivery into the oral cavity.

Two of the major limitations associated with buccal route of administration are the lack of dosage form

* Corresponding author. Tel.: +20 106 079123/202 3800680.
E-mail address: samaligy@hotmail.com (M.S. El-Samaligy).

0378-5173/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2004.07.033

retention at the site of absorption and the low flux, which results in low drug bioavailability. Consequently, bioadhesive polymers have extensively been employed in buccal drug delivery systems in the form of adhesive patches (Li et al., 1998), adhesive films (Khoda et al., 1997), adhesive tablets (Nozaki et al., 1997) and buccal gels (Shin et al., 2000). For those drugs that penetrate the oral mucosal membranes slowly or incompletely, one strategy can be used, that is the coadministration with a penetration enhancer (Aungst and Rogers, 1989).

Buccoadhesives have long been employed to improve the bioavailability of drugs undergoing significant hepatic first-pass metabolism (Choi and Kim, 2000; Choi et al., 2000) and control the release of drugs from hydrophilic matrices (Singh and Ahuja, 2002).

Diclofenac sodium is an example of drugs, which are subject to first pass metabolism, since only 50–60% of the drug reaches the systemic circulation in the unchanged form (Sweetman, 2002). Moreover, peroral administration of diclofenac sodium results in gastrointestinal disturbances ranging from abdominal discomfort, nausea, vomiting to serious gastrointestinal bleeding or peptic ulcers (Sweetman, 2002).

The main objective in this work is to formulate diclofenac sodium buccoadhesive discs that could be applied to the buccal mucosa giving systemic effects to decrease gastric irritation and avoid the first pass effect. The products prepared were evaluated through in vitro release and in vivo testing of their adhesive properties.

2. Materials and methods

2.1. Materials

Hydroxypropylmethyl cellulose (HPMC, Methocel K4M, Tama, Tokyo, Japan), carbopol 974p (Cp974p, BF.Goodrich, USA), hydroxypropyl cellulose (HPC, molecular wt. 300,000, Aldrich chemical Co., USA), polyethylene oxide (PEO, molecular wt. 7,000,000), polycarbophil (Noveon AA-A, Goodrich Chemicals, England), carboxymethyl cellulose sodium salt, medium viscosity (SCMC-MV), diclofenac sodium, potassium dihydrogen phosphate and disodium hydrogen phosphate (El Nasr chemical company, Egypt), ethyl cellulose (ethoxy content 49%), polyvinyl pyrrolidone k90, carboxymethyl cellulose sodium salt, ultra high viscosity (SCMC-UHV) (Fluka Chemie GmbH CH-9471 Buchs). Sodium taurocholate (STC) 67% (Difco lab, Detroit, MI, USA). Sodium deoxycholate (SDC), sodium taurodeoxycholate (STDC), L-menthol, methanol, HPLC grade (Romil Chemicals, England), ketoprofen (kindly supplied by Minapharm Company, Egypt), acetonitrile, HPLC grade (Sigma Chemical Company, USA) and glacial acetic acid (analytical grade).

2.2. Preparation of diclofenac sodium buccoadhesive discs

Formulae of buccoadhesive discs containing diclofenac sodium are listed in Tables 1 and 2. The buccoadhesive discs formulations are classified as follows:

(a) Discs containing Cp974p and/or polycarbophil as the bioadhesive polymers (Table 1).
(b) Discs containing PEO and/or SCMC as the bioadhesive polymers (Table 2).

Discs were prepared by directly compressing the polymer powder or polymer powder mixture with 50 mg diclofenac sodium after thorough mixing at a pressure of 49,000 N for 15 s using a hydraulic press. All the discs have a diameter of 13 mm.

2.3. Release of diclofenac sodium from different buccoadhesive discs

The release of diclofenac sodium from the prepared bioadhesive discs in simulated salivary fluid (phosphate buffer pH 6.8) at $37 \pm 0.5\,^{\circ}C$ was monitored through a 24-h period. A specially modified Levy method was adapted (Levy, 1963). Each bioadhesive disc was adhered to the side wall of a covered vessel (600 ml beaker). Adequate sink conditions were provided by placing 500 ml of phosphate buffer pH 6.8 in each covered vessel. Each covered vessel was fitted with a magnetic stirrer rotating at a rate of 150 rpm. After each of the time intervals of 0.5, 1, 2, 4, 6, 8, 10, 12, 18 and 24 h, 3 ml sample was withdrawn, filtered through a Millipore filter of 0.45 μm pore size and assayed spectrophotometrically after suitable dilution at 276 nm. Immediately after each sample withdrawal, a similar volume of phosphate buffer pH 6.8 was added to the release medium to maintain the volume in the vessel constant. The absorbance of the

Table 1
Buccoadhesive discs containing Cp974p and polycarbophil as bioadhesive polymers

Formulae	Diclofenac sodium (mg)	Polymer composition (mg)					
		Cp974p	Polycarbophil	HPMC	HPC	PVP	Total
1	50	90	–	10	–	–	150
2	50	66.7	–	33.3	–	–	150
3	50	10	–	40	–	–	100
4	50	66.7	–	–	33.3	–	150
5	50	50	–	–	–	50	150
6	50	–	50	–	–	50	150
7	50	–	16.7	33.3	–	–	100
8	50	33.3	33.3	33.3	–	–	150
9	50	50	33.3	16.7	–	–	150

polymeric additives was proved to be negligible and did not interfere with the drug absorbance. The percentage release was computed through a standard calibration curve of diclofenac sodium.

The release data were kinetically analyzed using different kinetic models (zero-order, first-order and Higuchi diffusion models) to determine the mechanism of diclofenac sodium release from the different bioadhesive systems.

2.4. Determination of disc hydration

The dimensional changes occurring during hydration of the discs containing hydrophilic polymer was performed by placing discs of formulae 20 in excess distilled water in petri dishes. Dynamics of gel layer thickness/movements were analyzed by photography of the fronts during swelling with QX3 Computer Microscope.

2.5. In vivo testing of the buccoadhesive discs

The buccoadhesive discs were tested in three healthy volunteers aged (25–50 years). After wipping off the excessive saliva, each disc was applied to the gingival mucosa above the canine tooth by pressing for 30 s onto mucosa (Save et al., 1994) and left for a period of 16 h.

The volunteers were asked to record:

(a) The adhesion time; time of detachment of disc from the buccal mucus membrane.
(b) The strength of adhesion (very adhesive, adhesive, slightly adhesive, unadhesive or slippery).
(c) Any local signs of irritation (severe, moderate, slight or non-irritant).
(d) Bitterness due to swallowing of diclofenac sodium (very, moderate, slight or non).
(e) The disintegration of the buccoadhesive disc in the buccal cavity (high, moderate, slight or non).

Table 2
Buccoadhesive discs containing SCMC and PEO as bioadhesive polymers

Formulae	Diclofenac sodium (mg)	Polymer composition (mg)				
		PEO	SCMC-MV	SCMC-UHV	HPMC	Total
10	50	100	–	–	–	150
11	50	66.7	–	–	33.3	150
12	50	–	100	–	–	150
13	50	50	50	–	–	150
14	50	16.7	33.3	–	50	150
15	50	33.3	33.3	–	33.3	150
16	50	–	50	–	50	150
17	50	–	33.3	–	66.7	150
18	50	–	66.7	–	33.3	150
19	50	–	–	100	–	150
20	50	–	–	33.3	66.7	150

2.6. Determination of the swelling index and the surface pH of the buccoadhesive discs in distilled water

The discs were coated on the lower side with ethyl cellulose (to avoid sticking to the dish) then weighed (W_1) and placed separately in Petri dishes containing 20 ml of distilled water. The dishes were stored at room temperature. After 30, 60 and 120 min, the discs were removed and the excess water on their surface was carefully removed using filter paper. The swollen discs were reweighed (W_2) and the index of swelling was calculated by the following formula:

$$\text{Swelling index} = \frac{W_2 - W_1}{W_1}$$

The discs used for determination of swelling index were used for determination of their surface pH using universal pH paper (Amin, 2000).

2.7. Determination of mucoadhesion performance of the buccoadhesive discs

The mucoadhesive performances of the medicated bioadhesive discs were evaluated by assessing the time for these discs to detach from chicken pouch membrane in a well-stirred beaker (Han et al., 1999). The chicken pouch membranes were fixed on the side of the beaker with cyanoacrylate glue. The discs were attached to the membrane by applying light force with finger tip for 30 s. The beaker was then filled with 500 ml phosphate buffer pH 6.8 at 37 °C. A stirring rate of approximately 150 rpm were used to simulate buccal and saliva movement.

2.8. Permeation of diclofenac sodium through chicken pouch membrane

Only the buccoadhesive disc(s), which gave the best results in the in vivo testing were subjected to permeation studies. The permeation of diclofenac sodium through chicken buccal membrane was carried out using glass tubes (1.3 cm diameter) opened from both ends. Each disc was pressed on the mucosa of chicken buccal membrane for 30 s and the loaded membrane was stretched over an open end of the glass tube and made water tight by rubber band forming donor chamber. Four milliliters phosphate buffer pH 6.8 was transferred to the donor chamber. The tube was suspended so that the membrane was just below the surface of 500 ml phosphate buffer pH 6.8 contained in 600 ml covered beaker and magnetically stirred at approximately 150 rpm in water bath maintained at 37 ± 0.5 °C. The diffusional surface area was 1.33 cm^2. Samples, each of 3 ml were withdrawn from the beaker at 0.5, 1, 2, 4, 6, 8, 10 and 12 h time intervals and replaced by equal volumes of fresh buffer. The concentration of diclofenac sodium in the samples was measured spectrophotometrically at λ_{max} 276 nm after appropriate dilutions on the basis of standard curve previously constructed.

The permeability of diclofenac sodium was also evaluated after inclusion of the permeation enhancers; sodium taurocholate (2%), sodium deoxycholate (2%) and sodium taurodeoxycholate (2%) and menthol (5%) in the disc.

The cumulative amount of permeated drug ($\mu g/cm^2$) was plotted versus time (h) and the flux ($\mu g\, cm^{-2}\, h^{-1}$.) was calculated from the slope of the line (Sloan et al., 1991). The straight line was extrapolated to obtain the lag time (h). The permeability coefficients (P) were calculated as follows (Bird et al., 2001).

$$P = \frac{(dQ/dt)}{A.C} = \frac{J}{C}$$

where dQ/dt is the permeation rate, the steady state slope of the cumulative flux curve; C is drug concentration in the donor chamber; A is the surface area of diffusion (1.33 cm^2); $(dQ/dt)/A = J$ = flux.

The efficacy of the different enhancers was determined by comparing specific permeation parameters of diclofenac sodium in the presence or absence of enhancer. This ratio was defined as the enhancement factor (EF), which was calculated using one of the following equations (Senel et al., 1998; Shojaei et al., 1998; Shin and kim, 2000).

$$\text{EF} = \frac{\begin{array}{c}\text{diclofenac permeation rate at steady} \\ \text{state in the presence of enhancer}\end{array}}{\begin{array}{c}\text{diclofenac permeation rate at steady} \\ \text{state in the absence of enhancer}\end{array}} \quad \text{(a)}$$

$$\text{EF} = \frac{P(\text{enhanced})}{P(\text{control})} \quad \text{(b)}$$

where P(enhanced) is permeability coefficient obtained for tablets containing enhancer; P(control) is

permeability coefficient obtained for tablets without enhancer.

$$EF = \frac{Q_{enhanced}}{Q_{control}} \quad (c)$$

where $Q_{enhanced}$ is cumulative permeated amount of diclofenac in presence of enhancer at end of permeation period, $Q_{control}$ is cumulative permeated amount of diclofenac in absence of enhancer at end of permeation period.

2.9. Bioavailability assessment of diclofenac sodium from selected buccoadhesive disc

The bioavailability of diclofenac sodium was determined from the selected disc prepared according to formulation 20 in comparison to that of the commercially available Voltarin® 100 SR tablet (Novartis).

The selected formulation was flavored to be as follows:

Diclofenac sodium (mg)	50
SCMC-UHV (mg)	34
HPMC (mg)	66
Saccharin (mg)	10
Menthol (mg)	10
Strawberry flavor (mg)	5

2.9.1. Dosing and plasma sampling

Four healthy male volunteers, aged between 20 and 30 years participated in this study. The selected buccoadhesive formulation of diclofenac sodium was pressed to the gingival mucosa above the canine tooth of two healthy human volunteers for 30 s and Voltarin® 100 SR tablet was administered perorally with 200 ml water to the two other healthy human volunteers. After 1 week of washout period, the volunteers were cross-overed to receive the other formulation. The volunteers were fasted overnight and continued fasting for 3 h after drug administration. Blood samples were collected at time intervals of 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12 and 16 h after drug administration into heparinized tubes. The blood samples were centrifuged at 3000 rpm for 10 min and the plasma of each was collected in labeled tubes. The plasma samples were frozen at −20 °C until analyzed.

2.9.2. Assay of diclofenac sodium in plasma

A modified HPLC method of El-Sayed et al., 1988 for the determination of diclofenac sodium in plasma was used. The method involved the addition of aliquots of the internal standard (ketoprofen) to 1 ml plasma samples. after vortexing for 1 min, precipitation of plasma protein was accomplished by addition of 1 ml acetonitrile. After vortexing for 30 s and centrifugation for 10 min at 3000 rpm, the upper layer was transferred to another tube, filtered through 0.45 μm Millipore filter. Twenty microliters were injected into the HPLC column for analysis using mobile phase composed of acetonitrile:water (50:50%, v/v) adjusted to pH 3.3 with glacial acetic acid. The mobile phase flow rate was 1 ml/min and the detection wavelength was 275 nm.

2.9.3. Pharmacokinetic analysis

Peak plasma concentrations (C_{max}) and the corresponding times at which these are reached (T_{max}) were obtained by inspection of the plasma concentration–time profile of each volunteer. The area under the plasma concentration–time curve was calculated by trapezoidal rule.

3. Result and discussion

Through initial trials on bioadhesive polymers, eight polymers namely, Cp974p, sodium alginate, SCMC, PEO, xanthan gum, polycarbophil, HPMC, HPC were investigated for the choice of the bioadhesive polymers having both optimum adhesion properties and release pattern for diclofenac sodium. The adhesion properties (detachment force and work of adhesion) were measured using an apparatus previously designed and reported in our laboratory (El-Samaligy et al., 2001). It was found that the bioadhesive polymers differ in their adhesion properties and can be arranged in descending order as follows: polycarbophil ∼ Cp974p > PEO ∼ Xanthan gum > SCMC > Na alginate ∼ HPMC ∼ HPC. The high bioadhesive strength of polycarbophil and Cp974p may be due to formation of secondary bioadhesion bonds with mucin due to their rapid swelling and interpenetration of the polymer chains in the interfacial region while the other polymers only undergo superfacial bioadhesion (Nair and Chien, 1996). The diclofenac sodium release rates from

the different bioadhesive systems can be arranged in descending order as follows: Cp974p ∼ SCMC > Na alginate > polycarbophil > PEO ∼ HPMC > xanthan gum ∼ HPC. Thus, Cp974p, polycarbophil, PEO and SCMC have shown optimum adhesion properties and diclofenac release patterns. So these polymers or their combinations may be useful for formulation of diclofenac buccoadhesive discs.

Tables 1 and 2 show the formulations prepared as buccoadhesive diclofenac sodium discs. They were subjected to the following investigations:

3.1. Release of diclofenac sodium from different buccoadhesive discs

Drug release from hydrophilic matrices is dependent on factors like swelling and dissolution of the polymers, giving rise to mass erosion of the system, concomitantly with dissolution and diffusion of drug. Initially, the matrix thickness increases due to hydration and swelling of polymer then the matrix thickness decreases and finally disappear due to polymer dissolution as well as dissolution of the drug. This phenomenon has been referred to as "swellable soluble matrix" (Chattaraj and Das, 1996).

Fig. 1 shows the release profile of diclofenac sodium from buccoadhesive discs containing Cp974p and polycarbophil. It can be seen that changing drug polymer ratio from 1:2 (formulations 1 and 2) to 1:1 (formulation 3) did not affect the release rate of diclofenac sodium remarkably. Replacement of HPMC (formulation 2) with HPC (formulation 4) or PVP (formulation 5) showed faster drug release rates. It is obvious that replacement of Cp974p (formulation 5) with polycarbophil (formulation 6) showed an increase in release of diclofenac sodium. Combination of polycarbophil and Cp974p as bioadhesive polymers with HPMC (formulations 8 and 9) showed sustained drug release.

Fig. 2 shows the release profile of diclofenac sodium from buccoadhesive discs containing PEO, SCMC-MV and SCMC-UHV as bioadhesive polymers. It can be seen that addition of HPMC to PEO discs (formulation 11) decreased the release rate of diclofenac sodium. Combination of SCMC-MV with PEO (formulations 13–15) slightly increased the release rate of diclofenac sodium from these matrix discs. It is observed that addition of HPMC to SCMC discs decreased the release rate of diclofenac sodium (formulations 16–20). This can be explained on the basis that the combination of anionic SCMC with nonionic HPMC produced a synergistic increase in viscosity. This was attributed to the stronger hydrogen bonding between the carboxyl groups of SCMC and hydroxyl groups of HPMC leading to stronger cross linking between the two gums (Madhusudan et al., 2001). SCMC-UHV discs (formulation 19) sustained the release of diclofenac sodium releasing the drug in more than 18 h. However, those containing SCMC-MV (formulation 12) released the

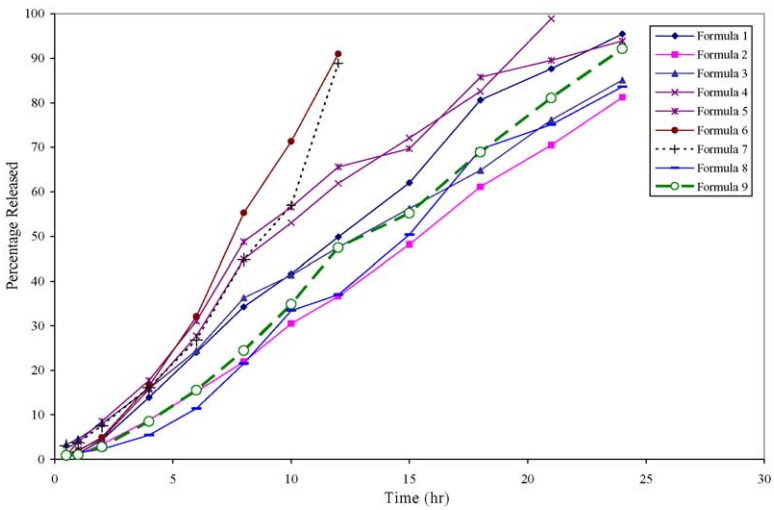

Fig. 1. Release profile of diclofenac sodium from buccoadhesive discs containing Cp974p and polycarbophil as bioadhesive polymers.

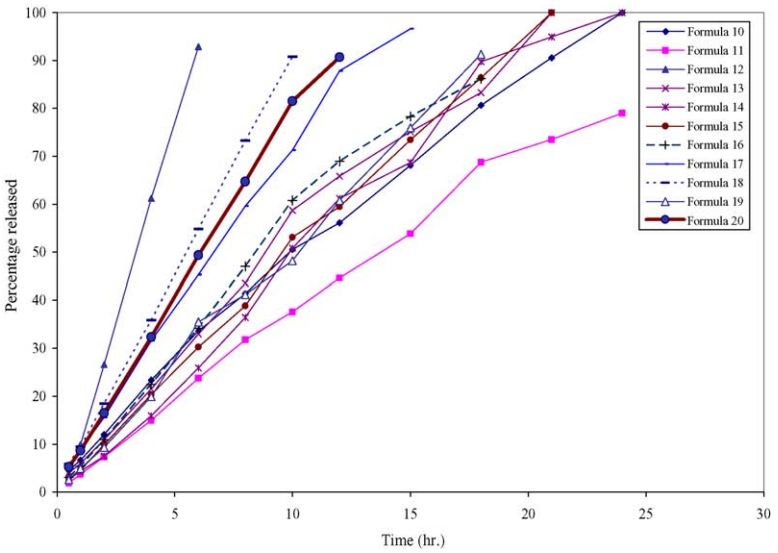

Fig. 2. Release profile of diclofenac sodium from buccoadhesive discs containing SCMC and PEO as bioadhesive polymers.

drug in more than 6 h. Replacement of SCMC-MV (in formulation 17) with SCMC-UHV (in formulation 20) did not alter the release of diclofenac sodium remarkably.

Photographs of the buccoadhesive disc (formulation 20) after swelling for different time intervals are shown in Fig. 3. It is clear that swelling and matrix hydration occurred gradually with time. The release mechanism and dynamics of the macroscopic and microscopic molecular changes associated with hydrophilic polymer matrix is complex. It was reported (Durrani et al., 1994) that the drug release mechanism from hydrophilic polymer matrix is swelling controlled system. The swelling of drug/polymer disc is due to diffusion of water into the polymer matrix, which results in the lowering of the glass transition temperature (T_g) of the polymer. The presence of water causes relaxation of the polymer chains, which is manifested macroscopically as the swelling of polymer matrix. The drug is released from the swollen system, which gradually erodes and finally completely dissolves.

3.2. Kinetic analysis of diclofenac sodium in vitro release data

The kinetic analysis of the in vitro release data of diclofenac sodium from buccoadhesive discs are presented in Table 3. The in vitro release data are in favor of zero-order release kinetic except in case of formulations 4, 5, 13 and 16. For all the test formulations, the values of n on fitting the simple power equation (Peppas, 1985) $M_t/M_\infty = Kt^n$ were around one indicating case II transport where drug release involves polymer relaxation and chain disentanglement (Peppas, 1985). The last finding was verified by the smaller values of k_1/k_2 through applying the following equation (Kim and Fassihi, 1997) $M_t/M_\infty = K_1 t^{1/2} + K_2 t$. The time for 50% released ($t_{50\%}$) was in range from 3.34 h (formulation 12) to 15.9 h (formulation 8).

3.3. In vivo testing of the buccoadhesive delivery systems

Several trials were done to choose the best site for application of buccoadhesive discs. The gingival mucosa below the canine tooth was first tried, but it was found that the presence of food affected greatly the adhesion of the disc in this place. Consequently, the gingival mucosa above the canine tooth was chosen, as the effect of food was minimal in this place. Trials to determine the effect of impermeable backing of the disc on drug release were unsuccessful. The discs were coated on all sides except one with ethyl cellulose (10% solution in ethanol) and left to dry. The uncoated side

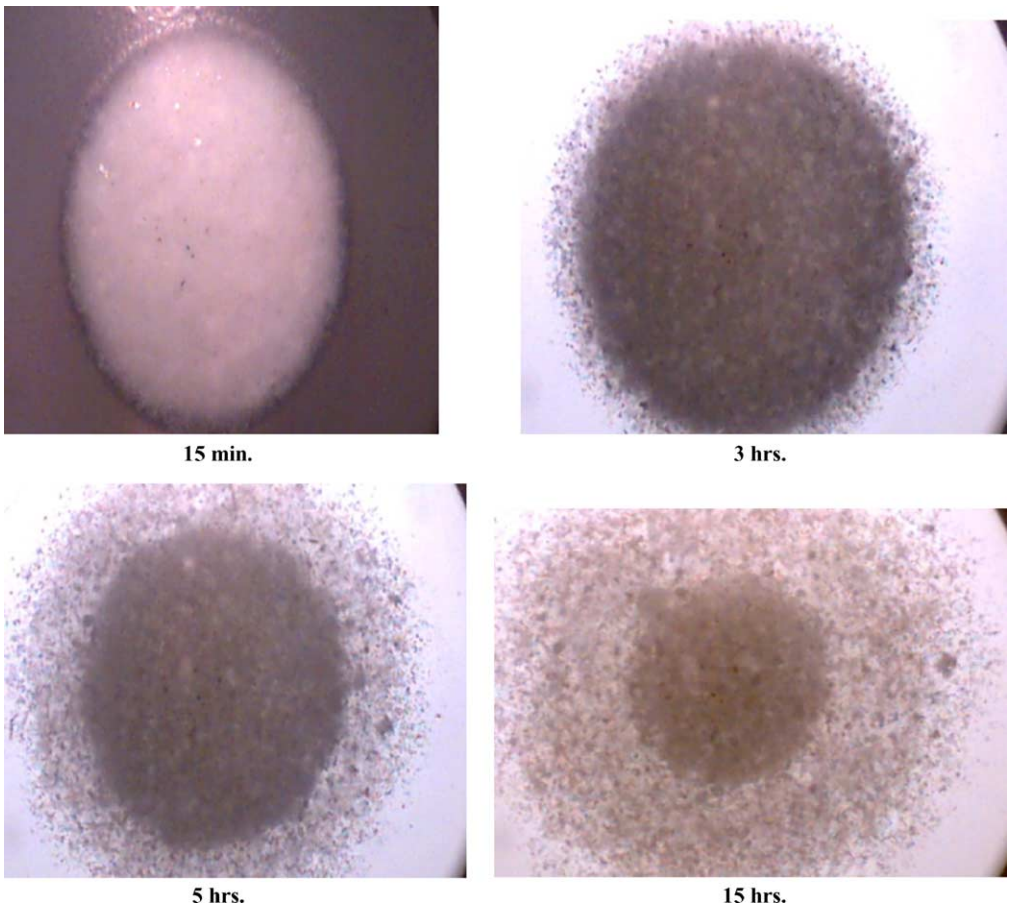

Fig. 3. Photographs of the buccoadhesive disc of formulation 20 (10×) after swelling 15 min, 3, 5 and 15 h in distilled water.

was pressed onto the mucosa for 30 s. It was found that the release of drug from the bioadhesive matrix was very low due to the lower amount of saliva available to hydrate the disc and dissolve the drug. Hence, it was preferred to press the bioadhesive disc to the gingival mucosa above the canine tooth for 30 s then the other side of the disc gradually adhered to the buccal mucosa due to the effect of saliva. This is in agreement with Yukimatsu et al. (1994). They developed a transmucosal controlled release device applied to the buccal and gingival mucosae for systemic delivery of isosorbide dinitrate where the drug is gradually dissolved in saliva and absorbed through the mucus membrane.

Table 4 shows the response answers of the adhesion time, the strength of adhesion, irritation, bitterness and disintegration of the buccoadhesive discs applied in vivo to three healthy volunteers. Most of the products up to formulation 16 suffered from certain problems including long adhesion time, irritation, bitterness and disintegration. Product prepared according to formulation 17 started to show the best parameters (adhesive, no irritation, slight bitterness and no disintegration) but suffered only from short adhesion time (6 h). Replacement of SCMC-MV (in formulation 17) with SCMC-UHV (in formulation 20) increased the adhesion time to 9 h so that it is obvious that formulation 20 is considered to be the best buccoadhesive disc regarding its in vivo adhesion properties, zero-order release kinetic and optimum release rate ($t_{50\%}$ = 6.26 h).

Table 3
Kinetic analysis of the release data of diclofenac sodium from buccoadhesive discs

Formulae	R^2			Release order	K	n	R^2	t_{50}% (h)	K_1	K_2	K_1/K_2	Main transport mechanism
	Zero-order	First-order	Diffusion									
1	0.9945	0.9013	0.9639	Zero	0.0135	1.530	0.9936	10.5	−0.009	0.0416	0.0224	Case II
2	0.9965	0.9382	0.9329	Zero	0.0157	1.258	0.9877	15.6	−0.037	0.0294	0.8846	Case II
3	0.9909	0.9572	0.9757	Zero	0.0510	0.884	0.9913	13.1	0.0314	0.0480	1.0680	Anomalous
4	0.9794	0.9881	0.9716	First	0.0182	1.480	0.9949	9.3	0.0001	0.0292	0.0028	Case II
5	0.9548	0.9729	0.9828	Diffusion	0.0302	1.293	0.9877	8.7	0.0657	0.1091	2.2507	Fickian
6	0.9809	0.8496	0.9078	Zero	0.0256	1.378	0.9689	8.6	−0.119	0.0957	1.0970	Case II
7	0.9475	0.7573	0.8569	Zero	0.0455	1.026	0.9672	10.3	−0.102	0.0476	1.0710	Case II
8	0.9808	0.9333	0.8977	Zero	0.0129	1.320	0.9772	15.9	−0.054	0.0483	1.1407	Case II
9	0.9943	0.8914	0.9344	Zero	0.0144	1.333	0.9772	14.1	−0.044	0.0308	0.9228	Case II
10	0.9936	0.9353	0.9822	Zero	0.0728	0.830	0.9959	10.16	0.0566	0.0300	1.83	Fickian
11	0.9912	0.9798	0.9738	Zero	0.0373	1.009	0.9995	13.09	0.0226	0.1885	0.73	Case II
12	0.9993	0.9134	0.9748	Zero	0.0998	1.333	0.9989	3.34	−0.078	0.0396	0.41	Case II
13	0.9826	0.9848	0.9771	First	0.0649	0.909	0.9907	9.43	0.0406	0.0418	1.02	Anomalous
14	0.9915	0.8933	0.9544	Zero	0.0452	1.002	0.9871	11	0.0156	0.0465	0.37	Case II
15	0.9975	0.9432	0.9692	Zero	0.0483	1.020	0.9991	9.94	0.0094	0.0413	0.20	Case II
16	0.9798	0.9842	0.9808	First	0.0573	1.004	0.9977	8.65	0.0420	0.0551	1.01	Case II
17	0.9909	0.8950	0.9794	Zero	0.0927	0.8802	0.9988	6.76	0.0485	0.0891	0.879	Case II
18	0.9998	0.9091	0.9689	Zero	0.1024	0.908	0.9952	5.73	0.0053	0.0492	0.06	Case II
19	0.9961	0.8894	0.9627	Zero	0.0500	1.010	0.9965	9.77	0.0053	0.0438	0.10	Case II
20	0.9968	0.9408	0.9759	Zero	0.0919	0.9226	0.9972	6.26	0.0225	0.0716	0.31	Case II

Table 4
In vivo bioadhesion properties of diclofenac sodium buccoadhesive delivery systems

Formulae	Adhesion time (h)	Adhesion strength	Irritation	Bitterness	Disintegration
1	>16	Very	Severe	Non	Moderate
2	>16	Very	Severe	Non	Moderate
3	4	Slightly	Non	Non	Moderate
4	>16	Very	Moderate	Non	High
5	7	Adhesive	Non	Slight	Moderate
6	9	Adhesive	Non	Slight	Slight
7	>16	Adhesive	Non	Non	High
8	>16	Very	Severe	Non	High
9	>16	Very	Moderate	Non	High
10	10	Adhesive and slippery	Moderate	Non	Non
11	12	Adhesive and slippery	Severe	Non	Non
12	3	Slightly	Non	Very	Moderate
13	5	Adhesive and slippery	Non	Slight	Non
14	8	Adhesive and slippery	Non	Slight	Non
15	6	Adhesive and slippery	Non	Slight	Non
16	6	Adhesive	Non	Moderate	Non
17	6	Adhesive	Non	Slight	Non
18	5	Adhesive	Non	High	Non
19	4	Slightly	Non	Very	Moderate
20	9	Adhesive	Non	Slight	Non

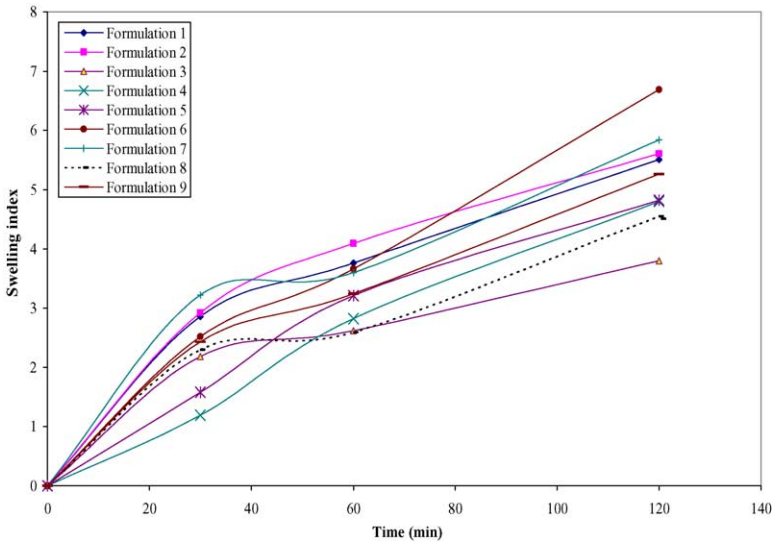

Fig. 4. Swelling index vs. time profiles of bioadhesive discs containing Cp974p and polycarbophil as bioadhesive polymers in distilled water.

3.4. Swelling capacity and surface pH of diclofenac sodium buccoadhesive discs in distilled water

The degree of swelling of bioadhesive polymers is an important factor affecting adhesion. Adhesion occurs shortly after the beginning of swelling but the bond formed is not very strong (Peh and Wong, 1999). Uptake of water results in relaxation of the originally stretched entangled or twisted polymer chains, resulting in exposure of all polymer bioadhesive sites for bonding to occur. The faster the swelling of the polymer, the faster the initiation of diffusion and formation of adhesive bonds resulting in faster initiation of bioadhesion (Anlar et al., 1993).

Fig. 4 shows the swelling indices of diclofenac sodium buccoadhesive discs containing Cp974p and polycarbophil as bioadhesive polymers. The study of swelling capacity of buccoadhesive discs confirmed the results obtained in the in vivo testing, where the discs with high swelling index were those showed long adhesion time and good adhesion strength e.g. formulations 1, 2 and 4.

Fig. 5 shows the swelling indices of diclofenac sodium buccoadhesive discs containing SCMC and PEO as bioadhesive polymers. The swelling capacity of these formulations was less than that of the formulations containing Cp974p and polycarbophil and this may explain the shorter adhesion time and the lower adhesion strength observed for these formulations. Formulation 19 containing SCMC-UHV gave higher swelling capacity compared to formulation 12 containing SCMC-MV. Formulation 20 containing SCMC-UHV and HPMC in the ratio 1:2 gave better swelling capacity for adhesion to occur. These findings could be confirmed by the swelling rate values shown in Table 5. These values illustrated the increase in disc weight in mg/min calculated as absorbed water.

The surface pH values of all discs containing Cp974p and polycarbopil as bioadhesive polymers were in the range 4–5 which may cause slight irritation to the mucus membrane on which it is applied. The surface pH values of all discs containing SCMC and PEO as bioadhesive polymers were found to be around the neutral pH and hence these discs did not cause any irritation to the mucus membrane when applied.

Studies of the mucoadhesion performance of the buccoadhesive discs showed that all discs attached well to the chicken pouch membrane until complete dissolution of the buccoadhesive discs demonstrating that all these bioadhesive polymers have good mucoadhesion performance.

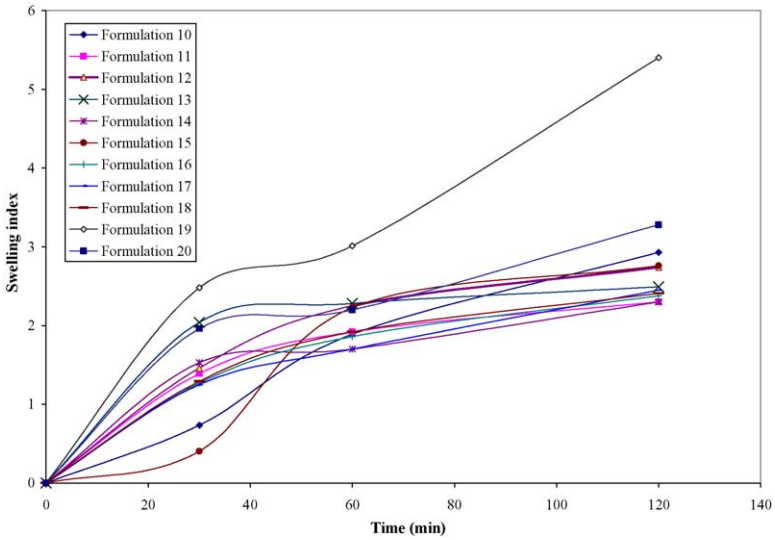

Fig. 5. Swelling index vs. time profiles of bioadhesive discs containing SCMC and PEO as bioadhesive polymers in distilled water.

3.5. Permeation of diclofenac sodium through chicken buccal membrane

Formulation 20 gave optimum adhesion time and adhesion strength with minimum irritation to volunteers. It showed zero-order release kinetic with optimum $t_{50\%}$. So that formulation 20 was used for further permeation and bioavailability studies.

Table 5
Swelling rates of buccoadhesive discs in distilled water

Formulae	Swelling rate (mg/min)
1	7.72
2	7.98
3	3.59
4	6.19
5	6.49
6	8.72
7	5.36
8	6.12
9	7.12
10	3.87
11	3.43
12	4.03
13	3.94
14	3.36
15	3.78
16	3.45
17	3.43
18	3.51
19	7.17
20	4.65

Because there is little information available on oral mucosal absorption enhancement, an attempt was made to demonstrate the degree of permeation of diclofenac sodium from its buccoadhesive product (formulation 20). The permeation enhancers, 2% sodium deoxycholate (SDC), 2% sodium taurocholate (STC), 2% sodium taurodeoxycholate (STDC) and 5% menthol have been incorporated separately in the selected formulation. A major benefit of using menthol as permeation enhancer is its safety profile. Furthermore, because of the pleasant taste associated with menthol and its ability to decrease the bitterness of diclofenac sodium, its use in a buccal delivery may increase patient acceptability (Robert and Gerard, 1997).

Table 6 presents the permeation parameters and enhancement factor of the penetration enhancers on the permeability of diclofenac sodium through chicken buccal membrane. The results indicated that diclofenac sodium can permeate easily the chicken buccal membrane with a steady state flux equal to 0.849 mg/cm^2 h and a short lag time equal to 4.22 min Cassidy et al. (1993) have demonstrated that diclofenac sodium from a hydrogel device was readily transported across the human buccal mucosa with a steady state flux calculated

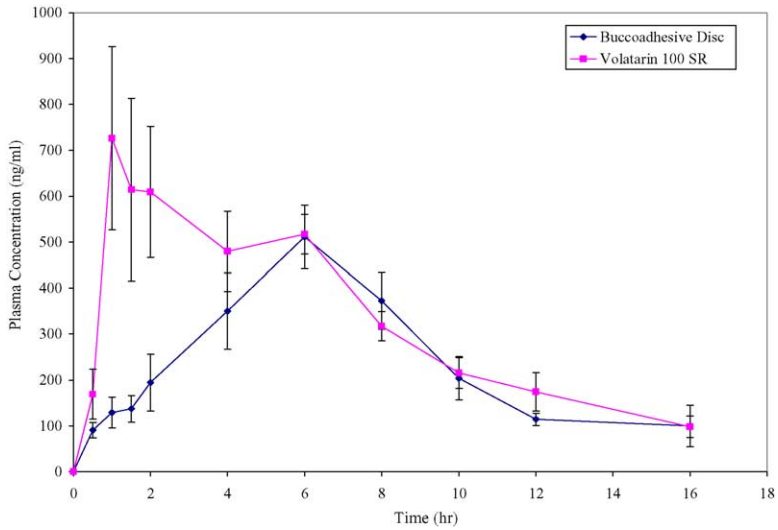

Fig. 6. Mean plasma concentration–time curve following the application of diclofenac sodium buccoadhesive disc and Voltarin® 100 SR to four volunteers.

to be $2.1 \pm 0.6\,mg/cm^2\,h$ and the large flux of this ionized drug indicated that the traditional lipoidal model of buccal permeation based on partition coefficient is inadequate.

The results indicted that the incorporation of any of the enhancers in the buccoadhesive formulation 20 had no remarkable effect on the flux of the drug but slightly decreased the lag time.

3.6. Bioavailability of diclofenac sodium from the selected buccoadhesive formulation

The mean plasma concentration–time curves of diclofenac sodium following the application of the stated buccoadhesive disc (50 mg) and Voltarin®100 SR tablet to four volunteers are shown in Fig. 6. The mean peak plasma concentrations were calculated to be 552.54 and 902.33 ng/ml attained after 6.5 and 1.25 h for buccoadhesive disc 50 mg and Voltarin® 100 SR tablet respectively. The mean area under the plasma concentration–time curve was found to be 4159.92 and 5887.67 ng h/ml, respectively. The percentage relative bioavailability of diclofenac sodium from the selected buccoadhesive disc 50 mg compared to that of the commercially available Voltarin® 100 SR tablet was found to be 141.31%.

As a conclusion, the buccoadhesive discs of diclofenac sodium can be a good way to bypass the extensive hepatic first pass metabolism and is expected to be less irritant to gastric mucosa.

Table 6
The permeation parameters of diclofenac sodium from discs of formula 20 with and without penetration enhancers through chicken pouch membrane

	J ($\mu g\,cm^{-2}\,hr^{-1}$)	Lt (min)	E.F. (%)
Formulation 20	849.53	4.22	1
STC	847.18	0.75	1.02
SDC	893.31	1.78	1.06
STDC	841.04	0.542	1.006
Menthol	849.25	3.7	1.04

J: steady state flux, Lt: lag time, E.F.: enhancement factor, STC: sodium taurocholate, SDC: sodium deoxycholate, STDC: sodium taurodeoxycholate.

References

Amin, S.Y., 2000. Development and characterization of a controlled release buccoadhesive dosage form of benzydamine hydrochloride. Egypt J. Biomed. Sci. 6.

Anlar, S., Capan, Y., Hincal, A., 1993. Physico-chemical and bioadhesive properties of polyacrylic acid polymers. Pharmazie 48, 285–287.

Aungst, B.J., Rogers, N.J., 1989. Comparison of the effects of various transmucosal absorption promoters on buccal insulin delivery. Int. J. Pharm. 53, 227–235.

Bird, A.P., Faltinek, J.R., Shojaei, A.H., 2001. Transbuccal peptide delivery: stability and in vitro permeation studies on endomorphin-1. J. Control Rel. 73, 31–36.

Cassidy, J., Berner, B., Chan, K., John, V., Toan, S., Holt, B., Rowland, M., 1993. Human transbuccal absorption of diclofenac sodium from a prototype hydrogel delivery device. Pharm. Res. 10, 126–129.

Chattaraj, S.C., Das, S.K., 1996. Effect of formulation variables on dissolution profile of diclofenac sodium from ethyl- and hydroxypropyl methylcellulose tablets. Drug Dev. Ind. Pharm. 22, 555–559.

Choi, H.G., Kim, C.K., 2000. Development of omeprazole buccal adhesive tablets with stability enhancement in human saliva. J. Control Rel. 68, 397–404.

Choi, H., Jung, J., Yong, C.S., Rhee, C., Lee, M., Han, J., Park, K., Kim, C., 2000. Formulation and in vivo evaluation of omeprazole buccal adhesive tablet. J. Control Rel. 68, 405–412.

Durrani, M.J., Andrews, A., Whitakers, R., Benner, S.C., 1994. Studies on drug release kinetics from carbomer matrices. Drug Dev. Ind. Pharm. 20, 2439–2447.

El-Samaligy, M.S., Yahia, S.A., Basalious, E.B., 2001. Improved design for in vitro measurement of adhesion parameters of bioadhesive pharmaceutical systems. Bull. Fac. Pharm. Cairo Univ. 39, 103–112.

El-Sayed, H.M., Abdel-Hameed, M.E., Suleiman, M.S., Najib, M.N., 1988. A rapid and sensitive high–performance liquid chromatographic method for the determination of diclofenac sodium in serum and its use in pharmacokinetic studies. J. Pharm. Pharmacol. 40, 727–729.

Han, R.Y., Fang, J.Y., Sung, K.C., Hu, O.Y., 1999. Mucoadhesive buccal disks for novel nalbuphine prodrug controlled delivery: effect of formulation variables on drug release and mucoadhesive performance. Int. J. Pharm. 177, 201–209.

Khoda, 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.

Kim, H., Fassihi, R., 1997. New ternary polymeric matrix system for controlled drug delivery of highly soluble drugs. Part 1. Diltiazem hydrochloride. Pharm. Res. 14, 1415–1421.

Levy, G., 1963. Effect of certain tablet formulation factors on dissolution rate of the active ingredients. J. Pharm. Sci. 52, 1039–1051.

Li, C., Bhatt, P.P., Johnston, T.P., 1998. Evaluation of a mucoadhesive buccal patch for delivery of peptides: in vitro screening of bioadhesion. Drug Dev. Ind. Pharm. 24, 919–926.

Madhusudan, R.Y., Krishna Veni, J., Jayasagar, G., 2001. Formulation and evaluation of diclofenac sodium using hydrophilic matrices. Drug Dev. Ind. Pharm. 27, 759–766.

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.

Nozaki, Y., Ohta, M., Chien, Y.W., 1997. Transmucosal controlled systemic delivery of isosorbide dinitrate: in vivo/in vitro correlation. J. Control Rel. 43, 105–114.

Peh, K.K., Wong, C.F., 1999. Polymeric films as vehicle for buccal delivery: swelling, mechanical and bioadhesive properties. J. Pharm. Pharmaceut. Sci. 2, 53–61.

Peppas, N.A., 1985. Analysis of Fickian and non Fickian drug release from polymers. Pharm. Acta Helv. 60, 110–111.

Robert, A., Gerard, M.K., 1997. Extended release buccal bioadhesive tablet. European Patent Number 769294Ai.

Save, T., Stah, M.U., Ghamande, A.R., Venkitachalam, P., 1994. Comparative study of buccoadhesive formulations and sublingual capsules of nifedipine. J. Pharm. Pharmacol. 46, 192–195.

Senel, S., Duchene, D., Hincal, A.A., Capan, Y., Ponchel, G., 1998. In vitro studies on enhancing effect of sodium glycocholate on transbuccal permeation of morphine hydrochloride. J. Control Rel. 51, 107–113.

Shin, S.C., Kim, J.Y., 2000. Enhanced permeation of triamcinolone acetonide through the buccal mucosa. Eur. J. Pharm. Biopharm. 50, 217–220.

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.

Shojaei, A.H., Berner, B., Li, X., 1998. Transbuccal delivery of acyclovir. Part 1. In vitro determination of routes of buccal transport. Pharm. Res. 15, 1182–1188.

Singh, B., Ahuja, N., 2002. Development of controlled-release buccoadhesive hydrophilic matrices of diltiazem hydrochloride: optimization of bioadhesion, dissolution, and diffusion parameters. Drug Dev. Ind. Pharm. 28, 431–442.

Sloan, K.B., Beall, H.D., Weimar, W.R., Villanueva, R., 1991. Effect of receptor phase composition on the permeability of hairless mouse skin in diffusion cell experiments. Int. J. Pharm. 73, 97–104.

Sweetman, S.C., 2002. Martindale: The Complete Drug Reference, 33rd ed. The Pharmaceutical Press.

Yukimatsu, K., Nozaki, Y., Kakumoto, M., Ohata, M., 1994. Development of a trans-mucosal controlled-release device for systemic delivery of antianginal drugs: pharmacokinetics and pharmacodynamics. Drug Dev. Ind. Pharm. 20, 503–534.