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European Journal of Pharmaceutics and Biopharmaceutics 44 (1997) 137–142

European Journal of Pharmaceutics and Biopharmaceutics

Research paper

# Buccoadhesive oxycodone hydrochloride disks: plasma pharmacokinetics in healthy volunteers and clinical study

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Received 20 November 1996; accepted 30 April 1997

**Abstract**

The pharmacokinetics of oxycodone hydrochloride were investigated following a single 10 mg buccal dose administered to nine healthy volunteers. Plasma samples were collected up to 24 h after administration and analyzed by an original, sensitive and specific selected ion monitoring (SIM) gas chromatography/mass spectrometry (GC–MS) assay, after purification with a solid-phase extraction procedure. The limit of quantitation was 1 ng/ml using a 1 ml plasma sample. The $AUC_{0-\infty}$ and the $C_{max}$ data of oxycodone hydrochloride were similar to the values reported in the literature for conventional oral tablets. The $t_{max}$ data obtained seem greater for the buccoadhesive disks compared with other oral dosage forms. Mucoadhesion, mucosal irritation and comfort were assessed. No serious problems were encountered. The administration of the new dosage form to cancer patients produced effective pain control, allowing a reduction in the dosing frequency. © 1997 Elsevier Science B.V.

*Keywords:* Buccoadhesive disks; GC–MS assay; Mucoadhesion; Oxycodone; Pharmacokinetic

## 1. Introduction

Oxycodone is an opioid analgesic drug widely used for the management of post-operative and cancer related pain, administered both parenterally and orally [1]. Although the oral administration route is preferred for the treatment of chronic pain, this route is limited by the low oral bioavailability of the drug, due to extensive presystemic biotransformation [2,3]. The search for alternative routes of opioid administration in the treatment of mild to moderate pain in adult cancer patients in an advanced or terminal phase of illness has intensified in recent years [4,5].

In previous work [6], we described the development of a buccoadhesive dosage form of oxycodone hydrochloride that allows the mucosal absorption and avoids drug degradation by hepatic first-pass metabolism.

The aim of this study was to determine the single-dose pharmacokinetics of oxycodone hydrochloride administered by the buccal route to nine healthy volunteers. Several chromatographic methods for quantitation of oxycodone in human plasma have been reported, but each of them has methodological disadvantages. The main limitations are related to the large sample volume (5 ml) [7], to derivatization procedures resulting in different and unstable derivatives [8] and to the levels of quantitation [9].

The gas chromatography/mass spectrometry (GC–MS) method proposed in this work is specific, sensitive and requires only 1 ml of plasma without a derivatization procedure.

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*PII* S0939-6411(97)00081-7

A clinical evaluation of the analgesic effectiveness of the new oxycodone hydrochloride dosage form was carried out in cancer patients and the compliance was evaluated.

## 2. Materials and methods

### 2.1. Materials

Oxycodone hydrochloride (Salars, Como, Italy), flurazepam hydrochloride (Roche, Milan, Italy), gelatin (commercial type B), sorbitol, glycerol, methanol analytical grade, chloroform analytical grade, sodium hydroxide, RP-18 silica gel (Merck, Darmstadt, Germany) and distilled water were used.

### 2.2. Methods

The following apparatus were used: electronic balances (Sartorius AG, Goettingen, Germany), centrifuge model 4236A (ALC, Milan, Italy), HP 5890 Series II gas chromatograph (Hewlett Packard, Avondale, PA, USA) equipped with a HP programmable cool on column injector and a HP 5971A mass selective detector (Hewlett Packard, Avondale, PA, USA).

Levels of oxycodone in plasma were determined by a GC–MS method, with an internal standard, after extraction from the sample matrices by the solid-phase extraction (SPE) technique.

Primary stock solutions (1 mg/ml) of oxycodone hydrochloride and of an internal standard, flurazepam hydrochloride, were prepared by dissolving 10.0 mg in distilled water in separate 10 ml volumetric flasks. Working stock solutions of 100 ng/ml (oxycodone hydrochloride) and 500 ng/ml (flurazepam hydrochloride) were prepared and aliquots were added to plasma as standards. Chloroformic solutions of oxycodone (1 mg/ml) and flurazepam (1 mg/ml), appropriately diluted, were also prepared for the extraction recovery evaluation. All solutions were stored at 4°C.

### 2.3. Standard and test samples preparation

Standard samples were prepared by adding 0.020, 0.040, 0.080, 0.160 and 0.240 ml of the oxycodone hydrochloride working stock solution and 0.18 ml of the internal standard working stock solution to 10 ml glass tubes containing 1.0 ml of blank human plasma. After the addition of 0.1 ml of 1 N NaOH, the volume in each tube was adjusted to 2.0 ml with distilled water.

Test samples were prepared by adding 0.18 ml of the internal standard working stock solution to 10 ml glass tubes containing 1.0 ml of collected plasma. After the addition of 0.1 ml of 1 N NaOH, the volume in each tube was adjusted to 2.0 ml with distilled water.

The sample preparation step involved the SPE technique using homemade glass columns (10 × 0.5 cm i.d.) packed with 100 mg RP-18 silica gel. SPE columns were conditioned by methanol and water. After loading the standard or test samples (2 ml), the columns were washed with 2 ml water. Then the columns were dried with a nitrogen stream for 1 min and eluted with 2 ml chloroform. The obtained solution was evaporated to dryness on a 40°C water bath by using a nitrogen stream. Then 0.5 ml of chloroform were added to the tube and vortexed for 30 s to dissolve any residue from the walls of the tube. After the evaporation of chloroform under nitrogen on a 40°C water bath, the residue was reconstituted with 50 $\mu$l of chloroform and 1 $\mu$l of this solution was injected.

### 2.4. Operating conditions

The initial oven temperature (50°C) was increased to 200°C at a rate of 30°C/min and from 200 to 250°C at a rate of 10°C/min. After 1 min at 250°C, the temperature was increased to 300°C at 30°C/min and held at this final value for 1.3 min. Helium was used as carrier gas at a flow rate of 1.6 ml/min. The on-column injector port temperature was on 'oven track' mode and the inlet pressure was 4.0 psi at 100°C, at constant flow. A HP cross-linked 5% methyl silicone capillary column, 25 m × 0.31 mm i.d., film thickness 0.17 $\mu$m (Hewlett Packard, Avondale, PA, USA) was used for chromatographic separations.

The mass spectrometer was operated in the electron-impact mode at 70 eV. Dwell time was set at 100 ms and electron multiplier was as tune setting. Selected ions were monitored (SIM) at $m/z$ 315.0, 316.2, 230.2 for oxycodone and $m/z$ 387.2, 315.1, 388.2 for flurazepam.

### 2.5. Preparation of buccoadhesive disks

Buccal disks were prepared from an aqueous colloidal solution containing 5.4% (w/w) glycerol, 3.8% (w/w) sorbitol, 23% (w/w) gelatin and 1% (w/w) oxycodone hydrochloride, by heating to 50–60°C [6]. A fixed volume (0.48 ml) of the warm solution was placed in each hole of a mould plate. After gelation the disks were removed from the plate and dried at room temperature. The final disks measured 11 mm in diameter and 1.7 mm in thickness.

### 2.6. Pharmacokinetics

#### 2.6.1. Human volunteers

Buccoadhesive disks containing oxycodone hydrochloride were administered in a single dose (10 mg) to nine healthy volunteers. The disks were placed between the gingiva and the cheek in the region of the

upper canine and pressed onto the mucosa for about 30 s [10]. The age of subjects (three females and six males) ranged between 27 and 55 years and their weights between 50 and 75 kg. All subjects were determined to be in good health. During the experiment the volunteers were allowed to eat and drink ad libitum from 60 min after administration of the disk.

*2.6.2. Sample collection*

Blood samples (6 ml) were collected in heparinized tubes (Vacutainer®) from the brachial vein via an indwelling butterfly cannula at predose and at 0.5, 1, 1.5, 2, 3, 4, 8, 12 and 24 h after disk application. The human plasma was immediately separated by centrifugation for 15 min at 2000 rpm and stored at −20°C until analysis.

*2.6.3. Data analysis*

The peak plasma concentration ($C_{max}$) and the time to reach maximum concentration ($t_{max}$) of oxycodone were experimentally determined. The elimination rate constant ($\beta$) was determined by linear regression of the terminal log–linear data and the elimination half-life ($t_{1/2}$) was calculated from the relationship: $t_{1/2} = 0.693/\beta$.

The area under the plasma concentration–time curve from time zero to infinity ($AUC_{0-\infty}$) was determined by the trapezoidal rule to the last measurable concentration ($Ct$) plus the additional area from time $t$ to infinity, calculated as $Ct/\beta$ [11]. All pharmacokinetic values are reported as mean ± standard deviation (S.D.).

*2.7. Clinical study*

The analgesic effectiveness and the compliance of the new oxycodone hydrochloride dosage form were tested in 11 cancer patients (four males and seven females) allowed domiciliary palliative care service. All patients were opioid-naive at the time of the study. The age ranged between 50 and 78 years; the exclusion criteria included a known hypersensitivity to oxycodone. Medications that had been taken routinely by patients before the study were permitted (e.g. ketorolac 30 mg was available as a rescue medication on request). Oxycodone hydrochloride (10 mg) was administered by the buccal route, twice a day, for 7 days. The indications for using this formulation were: inadequate analgesia with oral non-steroidal anti-inflammatory drugs (NSAID) (four patients), severe opioid-related unwanted effects (three patients), difficulty in swallowing due to cancer site (four patients). Primary cancer sites were: lung–pleura (27.3%), stomach (36.3%), endometrial (9.1%), breast (9.1%) and genito-urinary tract (18.2%). Pain intensity was assessed by the visual analogue scale (VAS) score and global rating of pain control by verbal scale (excellent, good, fair, poor).

The clinical study was approved by the local committee.

## 3. Results and discussion

### *3.1. Analytical method*

*3.1.1. Selectivity and resolution*

The retention times for oxycodone and flurazepam were 9.6 and 11.5 min, respectively. Representative chromatograms obtained from a blank human plasma, a standard sample and a test sample after buccal administration of oxycodone hydrochloride are shown in Fig. 1. Under the chromatographic conditions used, no endogenous components from human plasma were

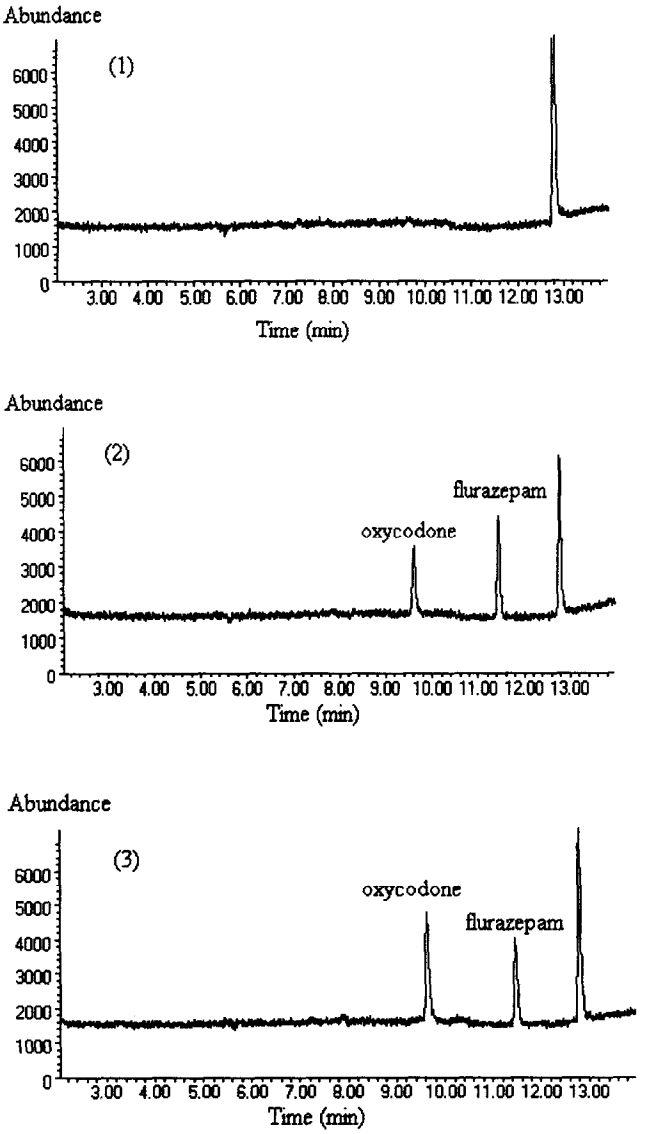


Fig. 1. GC chromatograms of oxycodone assayed in plasma: (1) blank plasma; (2) blank plasma spiked with oxycodone hydrochloride and flurazepam hydrochloride; and (3) test sample.

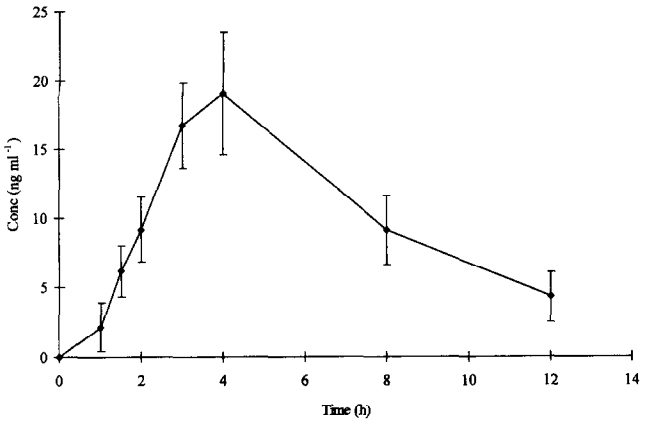


Fig. 2. Mean ± S.D. plasma concentrations of oxycodone after buccal administration of 10 mg to healthy volunteers ($n = 9$).

found to interfere with any of the analyzed compounds. The peak with a retention time of 12.8 min observed in the chromatograms was identified as cholesterol.

*3.1.2. Linearity*

The standard curves in human plasma were linear in the range 2–30 ng/ml ($r^2 = 0.997$). Intercepts of the calibration curves were not significantly different from zero ($P > 0.05$).

*3.1.3. Precision and accuracy*

Precision and accuracy were evaluated by spiking blank plasma with oxycodone hydrochloride ($n = 6$) at three concentration levels: 2, 8 and 16 ng/ml. The coefficients of variation (CVs) for the intra-day precision were: 5.8% at 2 ng/ml, 5.0% at 8 ng/ml and 2.4% at 16 ng/ml. The CVs for day-to-day precision were: 7.5% at 2 ng/ml, 6.5% at 8 ng/ml and 3.8% at 16 ng/ml. The relative error, determined by comparing the measured concentrations to the expected concentrations, was less than 10%.

*3.1.4. Recovery and sensitivity*

Absolute recovery, in the studied concentration range, was measured by direct comparison of chloroformic standard solutions versus standard samples. The recovery of oxycodone was 79.5 ± 5.2% (mean ± S.D.).

The limit of quantitation, defined as the lowest concentration with respect to acceptable precision and accuracy [12], was 1 ng/ml.

*3.2. Pharmacokinetics*

The buccal disks were readily retained in the oral mucosa with a mean residence time of 2.7 ± 0.3 h. No signs of local irritation were observed in any subject and no trouble at all was indicated [6].

Fig. 2 shows the oxycodone plasma concentration–time curve (mean ± S.D.) after buccal administration of mucoadhesive disks to nine healthy volunteers. The pharmacokinetic parameters for each volunteer (mean ± S.D.) are reported in Table 1.

The peak concentration of oxycodone ($C_{max}$) was 19.9 ± 3.8 ng/ml and was reached after 3.7 ± 0.5 h ($t_{max}$). Plasma concentrations of oxycodone at 24 h after administration were below the limit of the assay. The $AUC_{0-\infty}$ was 185 ± 54 ng/ml per h and the half life ($t_{1/2}$) was 3.9 ± 1.1 h.

The $AUC_{0-\infty}$ and $C_{max}$ values obtained with our formulation are comparable to those indicated in the literature [13] for conventional tablets of similar dosage, while the $t_{max}$ value seems to be greater for the buccal disk. This is confirmed, in the clinical study, by the reduction in the dosing frequency and, therefore, in the total amount of drug administered daily.

The mechanism of buccal absorption of several drugs has been the subject of a number of reviews and original papers [14–17]. In common with drug transport across other epithelia, there are two main routes of possible permeation pathways through the oral mucosa: the polar and non-polar routes.

Since the surface pH value of hydrated disks was 4.57, the oxycodone ($pK_a$ 8.53) was present almost exclusively in the ionized form, which was consistent with an aqueous pathway for buccal transport [18], as already proposed by some authors [19], in contrast with the conventional theory that only the unionized species can permeate through the buccal mucosa.

The absorption lag time observed between the $t_{max}$ value (3.7 ± 0.5 h) and the mean residence time of the disk on the oral mucosa (2.7 ± 0.3 h) may reflect depletion of the oxycodone from a buccal tissue depot. This is in accordance with some investigations showing, for hydrophilic drugs, a slow onset of appearance of permeant in the systemic circulation and a depot-like behaviour attributed to some form of binding within the oral mucosa [20].

*3.3. Clinical results*

The results obtained from the pharmacokinetic study in healthy volunteers were in accordance with the clinical responses in cancer patients. Fig. 3 shows the mean VAS scores at 24, 48, 72 and 168 h after starting the study. At the end of the study, the global rating of pain control was judged excellent for 27% of patients, good for 45%, fair for 18% and poor for 9%.

The most common side-effect reported over 48 h after the first dose administered was mild drowsiness followed by nausea. Severe transient sweating accompanied by hot flushes was reported by only one patient (in this case the treatment was discontinued). Fig. 4 shows the incidence of side effects over 48 h after first drug administration of buccal oxycodone. The intensity of the side-effects was assessed by verbal rating scores (none, mild, moderate, severe).

Table 1
Pharmacokinetics of oxycodone after buccal administration of 10 mg to nine healthy volunteers

| Parameters | Values of parameters for volunteer | | | | | | | | | Mean | S.D. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | | |
| $AUC_{0-\infty}$ (ng/ml per h) | 159 | 189 | 264 | 140 | 136 | 205 | 261 | 112 | 196 | 185 | 54 |
| $t_{1/2}$ (h) | 3.2 | 3.6 | 5.9 | 3.4 | 3.1 | 4.2 | 4.9 | 4.2 | 2.4 | 3.9 | 1.1 |
| $t_{max}$ (h) | 4.0 | 4.0 | 4.0 | 3.0 | 3.0 | 4.0 | 4.0 | 3.0 | 4.0 | 3.7 | 0.5 |
| $C_{max}$ (ng/ml) | 20.1 | 22.8 | 17.3 | 19.2 | 21.0 | 20.1 | 21.9 | 11.9 | 25.6 | 19.9 | 3.8 |

The clinical results reported above were obtained with a dose regimen of 10 mg oxycodone every 12 h by the buccal route versus 10 mg oxycodone every 4–5 h by classical oral administration, in the same group of patients.

## 4. Conclusions

Pain control with oxycodone hydrochloride in cancer patients was investigated by several authors who have, however, explored 'common' routes of administration, particularly oral and intravenous. The new buccal adhesive disks for the transmucosal release of oxycodone hydrochloride showed blood drug concentrations sufficient to induce the complete remission of cancer pain. However, an erodible disk without any backing layer was used and the loss of drug due to swallowing was not controlled. Therefore, additional studies are required to provide unidirectional release of the drug into the mucus layer, thus minimizing loss of drug to the saliva and maximizing concentration gradient of the drug to the mucosa.

On the basis of pharmacokinetic values and clinical results, the mucoadhesive buccal disks can be considered convenient for the reduction in the total amount of analgesic required, for patients who have either nausea or vomiting problems, difficulty of swallowing, and for unconscious patients. Irritation to the oral mucosa was low and acceptable.

The GC–MS method employed in the analysis of oxycodone hydrochloride in human plasma was rapid, sensitive and specific. This analytical method is capable of quantitating plasma concentrations as low as 1.0 ng/ml of drug after a SPE procedure.

The results of this study suggest that the buccal route of administration of oxycodone is a suitable safe alternative to the use of other opioid analgesics in the management of chronic severe pain in advanced cancer. However, a better understanding of the clinical use of this opioid is needed for further reliable clinical trials.

## Acknowledgements

This work was partially supported by a MURST grant (Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome, Italy).

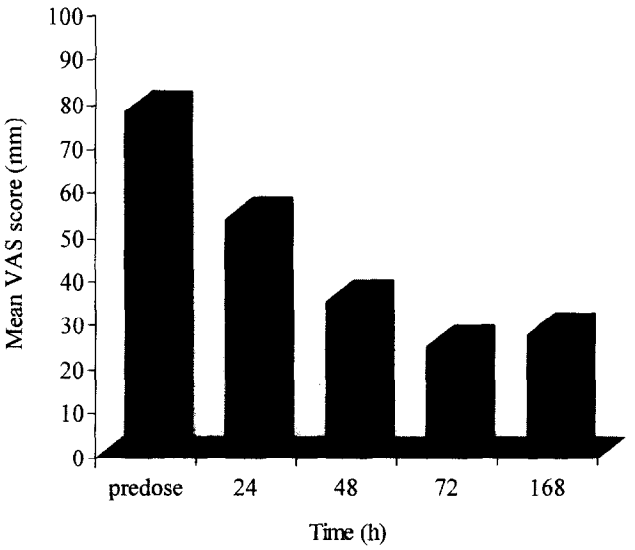


Fig. 3. Mean visual analogue scale scores.

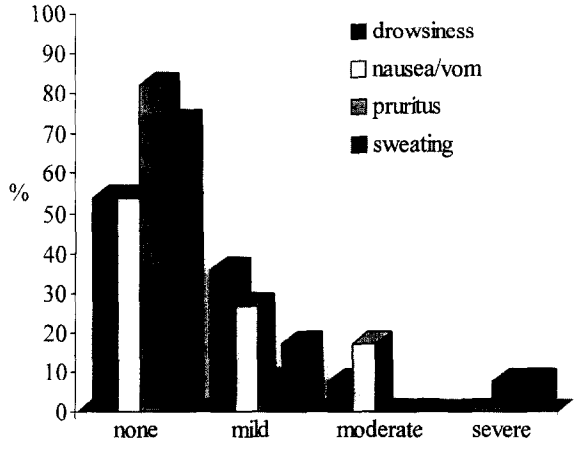


Fig. 4. Incidence of side effects over 48 h after first dose administration of buccal oxycodone to adult cancer patients.

## References


[1] E. Kalso, A. Vainio, Morphine and oxycodone hydrochloride in the management of cancer pain, Clin. Pharmacol. Ther. 47 (1990) 639–646.

[2] W.T. Beaver, S.L. Wallenstein, A. Rogers, R.W. Houde, Analgesic studies of codeine and oxycodone in patients with cancer. I. Comparisons of oral with intramuscular codeine and of oral with intramuscular oxycodone, J. Pharmacol. Exp. Ther. 207 (1978) 92–100.

[3] W.T. Beaver, S.L. Wallenstein, A. Rogers, R.W. Houde, Analgesic studies of codeine and oxycodone in patients with cancer. II. Comparisons of intramuscular oxycodone with intramuscular morphine and codeine, J. Pharmacol. Exp. Ther. 207 (1978) 101–108.

[4] C. Ripamonti, D. Polastri, L. Saita, Sublingual, buccal, inhalatory and intranasal route of opioids administration, Algos 10 (1993) 14–19.

[5] H.H. Withmann, Sublingual morphine: a novel route of narcotic administration, Am. J. Nurs. 84 (1984) 939–940.

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

[7] N.L. Renzi Jr., J.N. Tam, Quantitative GLC determination of oxycodone in human plasma, J. Pharm. Sci. 68 (1979) 43–45.

[8] S.H. Weinstein, J.C. Gaylord, Determination of oxycodone in plasma and identification of a major metabolite, J. Pharm. Sci. 68 (1979) 527–528.

[9] M.T. Smith, J.A. Watt, G.P. Mapp, T. Cramond, Quantitation of oxycodone in human plasma using high-performance liquid chromatography with electrochemical detection, Ther. Drug Monit. 13 (1991) 126–130.

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

[11] J.L. Hinson, I.D. Hind, D.J. Weidler, Pharmacokinetics, safety and tolerability of flosequinan in patients with hepatic dysfunction, J. Pharm. Sci. 83 (1994) 382–385.

[12] J.P. Laugier, C. Surber, H. Bun, J.M. Geiger, K.P. Wilhelm, A. Durand, H.I. Maibach, Determination of acitretin in the skin, in the suction blister, and in plasma, J. Pharm. Sci. 83 (1994) 623–628.

[13] K.P. Leow, M.T. Smith, J.A. Watt, B.E. Williams, T. Cramond, Comparative oxycodone pharmacokinetics in humans after intravenous, oral, and rectal administration, Ther. Drug Monit. 14 (1992) 479–484.

[14] A.H. Beckett, A.C. Moffat, Kinetics of buccal absorption of some carboxylic acids and the correlation of the rate constants and *n*-heptane: aqueous phase partition coefficients, J. Pharm. Pharmacol. 22 (1970) 15–19.

[15] T. Nagai, R. Konishi, Buccal/gingival drug delivery systems, J. Control. Release 6 (1987) 353–360.

[16] K. Knuth, M. Amiji, J.R. Robinson, Hydrogel delivery systems for vaginal and oral applications, Adv. Drug Del. Rev. 11 (1993) 137–167.

[17] J.P. Cassidy, N.M. Landzert, E. Quadros, Controlled buccal delivery of buprenorphine, J. Control. Release 25 (1993) 21–29.

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

[19] J. Zhang, C. Ebert, S. McJames, H.J. Gijsman, T.H. Stanley, Transbuccal permeability of isoproterenol—a dog model, Pharm. Res. 6 (Suppl) (1989) S135.

[20] G.S.M.J.E. Duchateau, J. Zuidema, F.W.H.M. Merkus, Bioavailability of propranolol after oral, sublingual, and intranasal administration, Pharm. Res. 3 (1986) 108–111.