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Development and Characterization of a Buccoadhesive Dosage Form of Oxycodone Hydrochloride

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ABSTRACT

A buccoadhesive system for the delivery of oxycodone hydrochloride to the oral mucosa was prepared from a colloidal solution of gelatin used as a bioadhesive agent. An in vitro method for measuring the adhesion of release system to a substrate was developed by employing a modified balance. The effects of thickness and of the presence of the drug on swelling and mucoadhesion properties were evaluated. The in vitro release of the buccoadhesive formulation was studied by a USP paddle dissolution apparatus and the results were fitted to an empirical equation. In vivo compliance and permanence time in 10 healthy volunteers were estimated.

INTRODUCTION

Oxycodone (6-deoxy-7,8-dihydro-14-hydroxy-3-*O*-methyl-6-oxomorphine) is a semisynthetic narcotic with an analgesic potency close to that of morphine, used both parenterally and orally over 70 years. Oxycodone has pharmacological properties similar to those of codeine and is used in the treatment of the relief of postoperative pain and severe cancer pain (1). However, when given orally, the amount of oxycodone reaching the systemic circulation is reduced by first-pass metabolism. The development of a nonparenteral dosage form of oxycodone that avoids the first-pass metabolism should be a notable advantage for analgesic therapy.

In recent years, significant interest has been shown in the development of bioadhesive dosage forms for buccal mucosa delivery of drugs (2). This route is easily accessible, it has a good patient compliance, and avoids the first-pass metabolism, entering the drug directly into the systemic circulation. The close contact

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with the adhesion surface of the oral cavity increases the drug absorption and results in an enhanced drug bioavailability.

Several substances have been described as bioadhesive materials (3); gelatin is a natural, nonirritant hydrophilic polymer with good adhesive properties. Therefore its use is particularly convenient for application on damaged mucosae typical of cancer patients.

This paper describes the development and the characterization of a bioadhesive dosage form of oxycodone hydrochloride.

MATERIALS AND METHODS

Oxycodone hydrochloride (Salars, Como, Italy), gelatin (commercial type B), sodium alginate (Fluka Chemie AG, Switzerland), sorbitol, glycerol, disodium hydrogen phosphate dihydrate, potassium dihydrogen phosphate (Merck, Darmstadt, Germany), cellulose acetate membrane filter (Sartorius AG Goettingen, Germany), and demineralized water were used.

The following apparatuses were employed: Sotax AT7 dissolution tester (Sotax Ltd., CH Basel), diode array spectrophotometer 8452A (Hewlett Packard, Germany), electronic balance (Sartorius AG, Goettingen, Germany), pH meter (Orion Research, USA), peristaltic pump (2120 Varioperpex II Pump, Pharmacia LKB, Sweden), and ultrasonic bath (Branson 1200, USA).

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 (10 mg for each disk), by heating to 50°–60°C to dissolve gelatin. The air bubbles were removed by use of an ultrasonic bath. With a graduated syringe, a fixed volume (0.48 ml) of the warm solution was placed in a perforated plate whose holes measured 15 mm in diameter and 3 mm in depth. After gelation the disks were removed from the plate and dried at ambient conditions for 72 hr. The dimensions of the disks were 11 mm in diameter and 1.7 mm in thickness. Drug-free disks and disks of lesser thickness were also prepared.

Swelling Studies

The swelling index of the bioadhesive disks was determined. Four disks were weighed (W_2) and placed separately in beakers containing 4 ml of demineralized water. The beakers were stored at room temperature (22°C). At specific time intervals (0.5, 1, 2, and 4 hr) the disks were removed and the excess water on their surface was carefully absorbed using filter paper.

The swollen disks were weighed (W_1), and the index of swelling was calculated by the formula $(W_1 - W_2)/W_2$ (4).

Surface pH of the Disks

The surface pH of the disks was determined to evaluate the possible irritative effects of the formulation on the mucosae. The disks were left to swell for 2 hr in 4 ml of water (pH 5.62); after this time the pH was measured placing the electrode in contact with the surface of the disks (5).

Weight Uniformity

The weight (milligrams) of each of 10 individual disks was determined by placing it on an electronic balance. The weight data from the disks were analyzed for sample mean and standard deviation.

Content Uniformity

The content uniformity was calculated as follows. Each of 10 disks was put into a volumetric flask (100 ml) containing water, heated at 60°C, and stirred until complete dissolution was attained. After cooling the volume was adjusted up to the mark with water. The solution, after filtration through a 0.45 μm cellulose Millipore filter, was analyzed spectrophotometrically at 282 nm. The amount of the drug was determined by comparison with a standard solution prepared by dissolving 10.0 mg of oxycodone hydrochloride and a drug-free disk in a 100 ml volumetric flask in the same solvent. The data were analyzed for sample mean and standard deviation.

Disk Thickness

The thickness of 10 disks was measured using a caliper. The data were analyzed for sample mean and standard deviation.

In Vitro Determination of Bioadhesion

The force required to separate the sample disk from a model substrate was measured using a modified two-

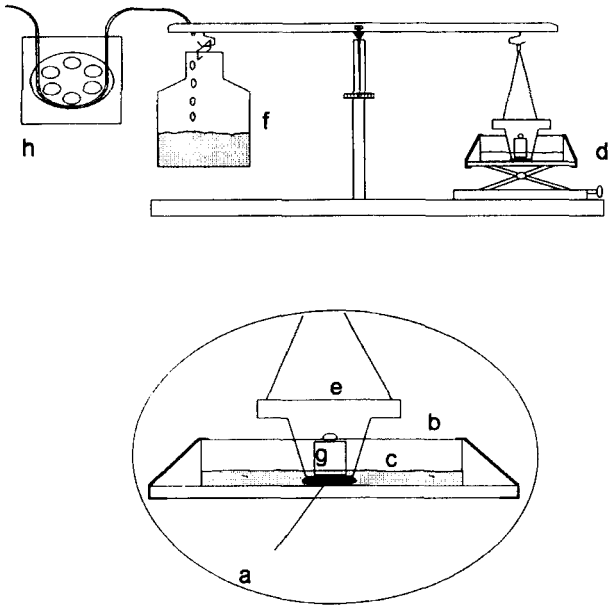

Figure 1. a, disk; b, glass beaker; c, gel; d, moving platform; e, stopper; f, counterbalance; g, preload; h, pump.

arm balance (Fig. 1). The disk (a) was fixed to the base of a glass beaker (b) with a cyanoacrylate adhesive, covered with a model gel (c), and left for a period of time to hydrate.

The beaker was placed on a moving platform (d). A flat polypropylene stopper (substrate) (e) was suspended above the disk and counterbalanced with a plastic container (f). The beaker was then slowly raised until the substrate came in contact with the disk. A preload (g) of 50 g was placed into the stopper for 6 min (preload time) so that the adhesion bonding could be established. After this time, the preload was removed and water was added in the plastic container, by the peristaltic pump (h), at a constant rate of 90 mg/sec. The addition was stopped as soon as the detachment of the two surfaces was obtained. The equipment was located in an air-conditioned room at 22°C and 60% relative humidity. The model gel used was a 1% (w/w) colloidal solution of sodium alginate as already proposed by Smart et al. (3).

The experimental conditions for adhesion measurements are reported in Table 1.

In Vivo Evaluation of Adhesive Behavior

The buccoadhesion of the drug-free disks was tested in 10 healthy volunteers (5 male, 5 female; ages ranging from 26 to 51 years). The disk was placed between the gingiva and the cheek in the region of the upper canine, and pressed onto the mucosa for about 30 sec (6). Then the disk and the inner upper lip were moistened with saliva to prevent the sticking of the disk to the lip.

The duration of mucosal adhesion was the time required for the complete wash-off of the disk. The volunteers were asked to record the time of detachment or of complete erosion of the disk, and to monitor for side effects, e.g., irritation, hindrance, bad taste, dry mouth or increase of salivary flux, mucosal lesions.

Table 1

Experimental Conditions for In Vitro Adhesion Measurements

Model Gel	Sodium Alginate 1% (w/w) (V = 10 ml)
Hydration time (min)	6
Preload (g)	50
Preload time (min)	6

Table 2

Physical Parameters of Different Formulations

Physical Tests	n	Thick Disks with Drug (mean ± SD)	Thick Disks (mean ± SD)	Thin Disks (mean ± SD)
Uniformity of weight (mg)	10	190.7 ± 4.7	178.0 ± 4.4	97.3 ± 6.2
Uniformity of content (mg)	10	9.34 ± 0.41	—	—
Surface pH	4	4.57 ± 0.02	4.32 ± 0.03	4.41 ± 0.01
Thickness (mm)	10	1.70 ± 0.01	1.67 ± 0.01	1.02 ± 0.06

In Vitro Release of Oxycodone Hydrochloride from Disks

The drug release was determined using a dissolution apparatus which, according to USP method II (paddle), consisted of seven polycarbonate vessels placed in a water bath thermostated at 37° ± 1°C and stirred at a rate of 50 rpm. Sink conditions were maintained throughout the study.

Each disk was fixed at a metallic support so that the drug could be released only from the upper face and immersed in the vessel containing 500 ml of 0.15 M phosphate buffer, pH 6.0 (1.42 g disodium hydrogen phosphate dihydrate, 7.99 g potassium dihydrogen phosphate made up to 1000 ml with demineralized water). Six disks were examined at the same time. A drug-free disk, used as a blank, was introduced in the seventh vessel. A standard curve was established before each series of measurements with solutions ranging from 1 to 30 μg/ml prepared from oxycodone hydrochloride in the phosphate buffer.

With the aid of a dissolution software, at regular intervals of time, aliquots of dissolution medium were drawn and the content of oxycodone was determined spectrophotometrically at 282 nm.

Table 3

In Vitro Evaluation of Disks Bioadhesion in 1% Sodium Alginate

Formulation	*n*	Weight Required for Detachment (g, mean value ± SD)
Thick disks	6	559 ± 24
Thick disks with drug	6	546 ± 6
Thin disks	6	473 ± 8

RESULTS AND DISCUSSION

Table 2 reports the physical parameters of the different formulations studied.

The data reported in Table 3 indicate that the addition of 10 mg oxycodone hydrochloride produces no effect on the in vitro mucoadhesion. The thickness of the disks influences their mucoadhesive properties: in fact, the thick disks show significantly higher values of the detachment force (analysis of variance—ANOVA, $p < 0.01$).

This behavior is connected with the swelling capacity. The swelling index of the formulation is considered to be an important factor for assessment of bioadhesiveness. The polymeric materials become adhesive with hydration: excessive swelling leads to reduced mucoadhesiveness, because water molecules bind to polymer groups required for adhesion (7).

The swelling values and the swelling curves of disks reported in Table 4 and in Fig. 2 show this correlation: thin disks swell significantly more than the other two, whose behavior is equivalent (ANOVA, $p < 0.05$).

The release data of each disk were analyzed by ordinary linear regression and the results were in accord with a mechanism of zero-order kinetics (r^2 ranging from 0.978 to 0.999, SY_x ranging from 0.146 to 4.832). An individual and the cumulative release profile are shown in Fig. 3.

To evaluate the possible differences in the drug release between and within batches, two-way ANOVA was applied: no significant difference in the dissolution rates ($p > 0.05$) was observed for two batches. The

Table 4

Index of Swelling in Water [$(W_1 - W_2)/W_2$]

Time (hr)	Index Mean Value ($n = 4$) ± *SE*		
	Thick Disks	Thick Disks with Drug	Thin Disks
0.5	0.82 ± 0.02	0.85 ± 0.01	1.46 ± 0.03
1	1.27 ± 0.04	1.22 ± 0.04	1.96 ± 0.02
2	1.89 ± 0.06	1.75 ± 0.07	2.58 ± 0.02
4	2.6 ± 0.1	2.38 ± 0.07	3.17 ± 0.02

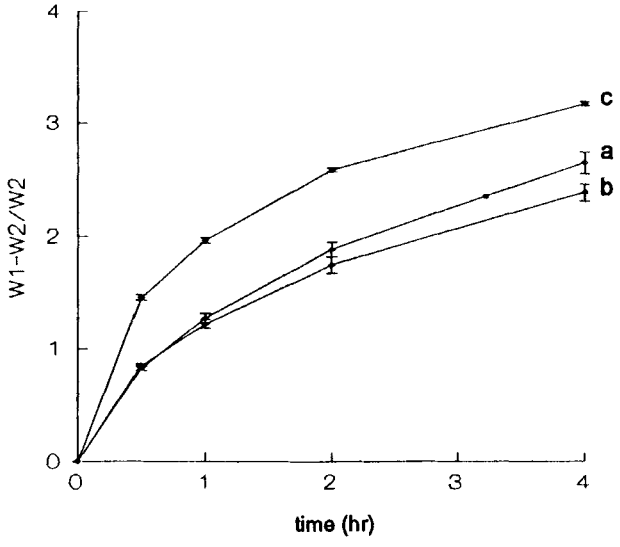

Figure 2. Swelling index of the bioadhesive disks: a, thick disks; b, thick disks with drug; and c, thin disks.

mean constant rate of oxycodone hydrochloride release was 0.833 ± 0.039 (95% confidence interval, CI) and the mean t_{50} (time for 50% drug release) was 53.1 ± 3.4 (95% CI).

On the other hand, the release data can be fitted to the exponential release model equation:

$$M_t/M_\infty = kt^n \quad (1)$$

where M_t/M_∞ is the fraction of drug released up to time t, n is a diffusional exponent and characterizes the type of release mechanism operative during the dissolution process, k is a constant which incorporates the properties of the macromolecular polymeric system and the drug, and M_∞ is the amount of drug incorporated in the disks, i.e., 10 mg (8).

In Table 5 the values of n and k for two different batches are reported. The mean value of n was 0.88 ± 0.13 (95% CI), in accordance with the proposed release mechanism based on zero-order kinetics.

The buccoadhesive formulation had an acceptable taste and was readily retained on the buccal mucosa. The mean residence time of the disks was 160 ± 20 min. They dissolved gradually and left no residue in the mouth. No signs of local irritation were observed in any subject and no trouble at all was indicated. A possible reason of the nonirritant properties of the formulation could be the surface pH, which value is in accordance with the data of Bottenberg et al. (5).

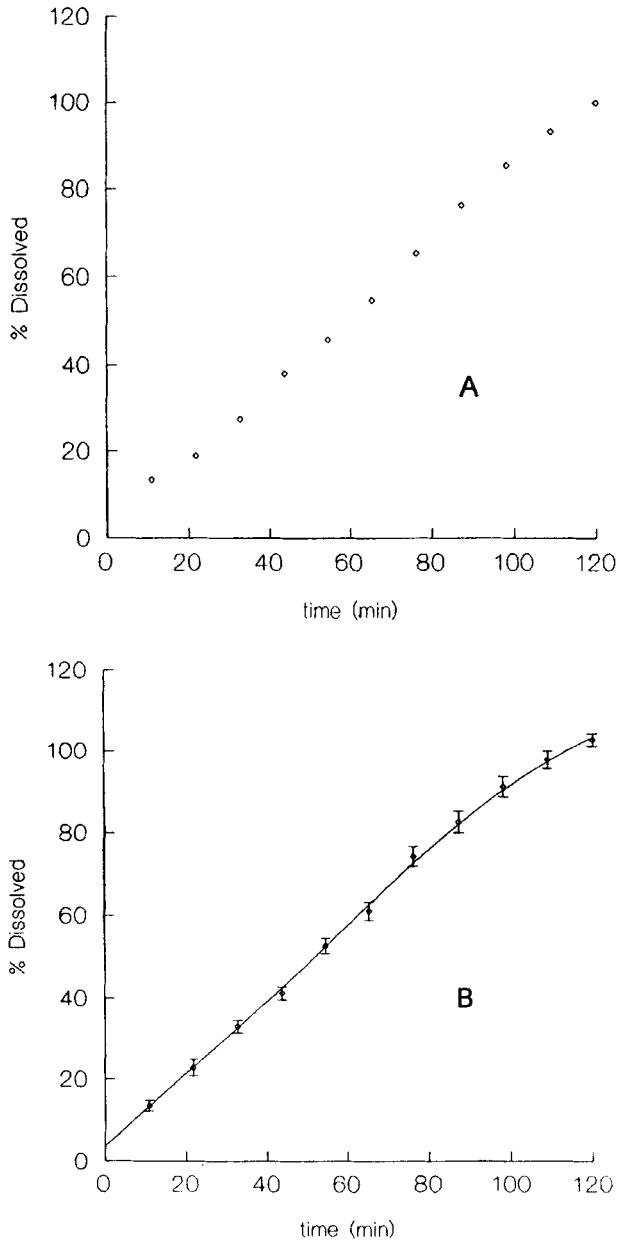

Figure 3. Release profiles of oxycodone hydrochloride disks: individual profile (A) and cumulative profile (mean value of 2 batches ± *SE*) (B).

CONCLUSIONS

A new buccoadhesive system for the release of oxycodone hydrochloride was proposed with gelatin as a mucoadhesive polymer. The drug delivery systems that are designed to remain in contact with the oral mucosa for prolonged periods have been a subject of growing

Table 5

Release Data of Oxycodone Hydrochloride from Two Different Batches of Disks According to Eq. (1)

Batch	Number of Disks	$k \pm SE$	$n \pm SE$
1	3	0.26 ± 0.02	0.86 ± 0.04
1	3	0.29 ± 0.01	0.90 ± 0.02
2	4	0.31 ± 0.01	0.77 ± 0.02
2	4	0.27 ± 0.01	0.98 ± 0.03

interest. As already reported in previous published data on mucoadhesion, gelatin shows satisfactory adhesive properties. The flexibility required for a good compliance of the disks is achieved employing glycerol and sorbitol, which help prevent desiccation of the formulation.

The oxycodone hydrochloride release from the studied matrix of gelatin appears to occur by a swelling-controlled mechanism. This type of mechanism, $n = 1$ in the model equation, is known as pseudo-case II solute transport, and it is characteristic of swelling-controlled drug delivery systems (9).

This formulation shows significant bioadhesive properties and could be useful for buccal administration of oxycodone hydrochloride.

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