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Transdermal application of bupivacaine-loaded poly(acrylamide(A)-co-monomethyl itaconate) hydrogels

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Abstract

Bupivacaine, an amide local anaesthetic agent of long-acting and intense anaesthesia, was incorporated into poly(acrylamide (A)-co-monomethyl itaconate (MMI)) hydrogels. The swelling behaviour of two gel compositions, without drug, 75A/25MMI and 60A/40MMI, through rabbit ear skin, mounted on a modified Franz diffusion cell, was studied. Both gel compositions reach the equilibrium swelling degree (88.9 ± 0.7 wt.% for 75A/25MMI and 92.5 ± 0.1 wt.% for 60A/40MMI). The swelling kinetics was in accordance with the second Fick's Law; diffusion coefficients indicate faster swelling for gels with lower amount of monomethyl itaconic acid. The skin flux of bupivacaine solution through rabbit ear skin was 105 ± 24 μg/cm^2/h, the effective permeability coefficient was $26 \times 10^{-3} \pm 9 \times 10^{-3}$ cm/h, and 77 ± 15% of bupivacaine was permeated. Bupivacaine-loaded gels allow the drug was permeated through the skin. 47 ± 4% and 36 ± 3% of the drug amount included in 75A/25MMI and 60A/40MMI hydrogels, respectively, was permeated. The skin flux of the drug was between 90 ± 5 and 16 ± 7 μg/cm^2/h depending on the amount of bupivacaine included in the gel and the gel composition. Skin flux increases with the drug load of the gels. Furthermore, as more MMI in the gel slower skin flux of the drug due to bupivacaine-gel interactions.
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1. Introduction

The delivery of drugs through the skin to effect a pharmacological action or actions at a location or locations remote from the site of action is named transdermal delivery. Transdermal therapy can be regional or systemic as opposed to topical therapies wherein pharmacological action is preferably desired within and confined to the skin tissues (Ramachandran and Fleisher, 2000). Topical drug delivery, for either dermatological or transdermal therapy, depends a lot on the nature of the skin (Walters, 2002). The stratum corneum is the external relatively impermeable layer of dead cells of the skin. This layer is a highly rigid, insoluble ectoskeleton which is very selective to permeability of water and other electrolytes and is considered to be the principal barrier to transport of molecules into and across skin. Absorption of substances into and across skin takes place by passive diffusion through the lipid domains of the stratum corneum. It is believed that polar drugs traverse the stratum corneum through the transcellular route while non-polar drugs penetrate through the intercellular route (Barry, 1987). The other major pathway of drug transport is the transfollicular route via the pilosebaceous units and shunts (Ramachandran and

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Fleisher, 2000). Drugs administered via transdermal or topical routes must possess specific physicochemical properties. They must be highly hydrophobic and oil-soluble, and their molecular weight must be small, in general lower than 500 Da. (Ramachandran and Fleisher, 2000).

The above-mentioned characteristics are shown by bupivacaine, an amide local anaesthetic agent of long-acting and intense anaesthesia (Aps and Reynolds, 1976); its partition coefficient (*n*-heptane/buffer pH 7.4) is 28, which means it is highly soluble in lipids and so very potent; it exhibits a pK_a of 8.1, and it causes an intermediate onset for nerve block anaesthesia; bupivacaine binds in a great manner to proteins (95%) and so it causes a long anaesthesia; the rapid half-life of bupivacaine in adult male is 0.045 ± 0.030 h (Tucker and Mather, 1979). Local anaesthetics are widely used in surgical, obstetric and dental patients. They are also used in the control of postoperative pain and in the therapy of chronic pain (Dahm et al., 2000). Bupivacaine, due to its anaesthetic characteristics, plays a valuable role in the overall management of surgical and postoperative pain associated with dental care (Dunsky and Moore, 1984; Danielsson et al., 1986; Moore, 1990; Saxen and Newton, 1999). This drug is considered one of the most toxic local anaesthetic with a maximum tolerated dose of 1.5 mg/kg i.v. in humans, resulting in a plasma level of 0.8–2.7 μg/ml (Feldman, 1994). Because of its high lipophility its adverse effects are focused on the central nervous system (Reynolds, 1987).

Different devices have been designed to obtain controlled release of bupivacaine. The drug has been included in poly(lactide) and poly(lactide-co-glycolide) microspheres (Le Corre et al., 1997; Malinovsky et al., 1997); in a comatrix of bupivacaine-loaded albumin microspheres in a poly(lactide-co-glycolide) film (Blanco et al., 1999; Bernardo et al., 2000); also it has been included in lipospheres, which are drug-containing solid-filled vesicles made of triglyceride with a phospholipid outer covering (Masters and Domb, 1998), as well as in lipid–protein–sugar particles (Kohane et al., 2000).

On the other hand, hydrogels can be used in transdermal devices (Roy and Manoukian, 1995; Thacharodi and Rao, 1995) not only as a medium to load the drug but also to control the drug release (Sudo et al., 1998; Tsai et al., 1999). Furthermore, hydrogels have been used as wound dressing (Crokhill et al., 1989). Thus, the aim of this work has been the use of poly(acrylamide(A)-co-monomethyl itaconate) hydrogels as a base for dermal delivery of bupivacaine in order to obtain a bupivacaine-loaded formulation that could be used as a topical device for buccal cavity or as a dressing against wound pain, since local anaesthetics like lidocaine have potent anti-inflammatory effects, and they can significantly reduce experimental oedema formation in burns (Cassuto et al., 1990).

2. Materials and methods

2.1. Materials

Itaconic acid (methylene succinic acid) [Merck], acrylamide [Merck], *N,N′*-methylenbisacrylamide (NBA) [Merck], ammonium peroxodisulfate [$(NH_4)_2S_2O_8$] [Merck], sodium disulfite ($Na_2S_2O_5$) [Merck], sodium chloride [Panreac], hydrochloric acid [Panreac], methanol [Panreac], acetyl chloride [Merck], dichloromethane [Panreac], sodium hydroxide [Panreac], anhydrous sodium sulphate [Merck], toluene [Panreac], dipotassium monohydrogen phosphate (K_2HPO_4) [Panreac], potassium dihydrogen phosphate (KH_2PO_4) [Panreac], were used as received.

Bupivacaine ($C_{18}H_{28}N_2O$) was kindly supplied by Laboratorios Inibsa S.A. (Spain); Milli-Q® (Millipore, Madrid, Spain) water was used.

2.2. Methods

2.2.1. Synthesis of poly(acrylamide(A)-co-monomethyl itaconate) hydrogels

Monomethyl itaconate (MMI) was obtained by esterification of itaconic acid with methanol (Katime et al., 1993; Blanco et al., 1996). Two different acrylamide(A)-monomethyl itaconate (MMI) compositions were studied: 75A/25MIM and 60A/40MIM (wt./wt.). In the feed mixture the monomer-to-water ratio was 60/40 (wt.%). The crosslinking agent was *N,N′*-metilenbisacrylamide (NBA) (2 wt.%) and the initiator was the redox pair $(NH_4)_2S_2O_8$ (1 wt.%)/ $Na_2S_2O_5$ (0.4 wt.%); their contents were based on the total mass of the monomers. The mixture was weighted out and degassed with nitrogen. The teflon moulds were sealed and placed in an oven at 313 K,

the temperature increasing slowly up to 333 K and then maintained for 2 h.

In order to obtain thin gel pieces, the amount of the feed mixture components was adjusted to be diluted with 0.5 ml of water in each teflon mould (1.3 cm × 1.6 cm). After polymerisation, the samples were maintained in the moulds for 15 h and then they were removed and were cut in four rectangular tablets, whose dimensions were determined with a micrometer: 8.7 ± 0.2 mm × 7.6 ± 0.6 mm × 3.1 ± 0.3 mm for 75A/25MIM and 8.7 ± 0.8 mm × 7.8 ± 0.5 mm × 3.1 ± 0.2 mm for 60A/40MIM.

2.2.2. *Bupivacaine inclusion in the copolymers*

Bupivacaine (Bp) was included in the feed mixture of polymerisation by dissolving it in the aqueous solution of the initiator. Tablets loaded with 2, 4, 6 and 8 mg of Bp (0.54, 1.08, 1.63 and 2.17 wt.% of the total formulation) for each copolymer composition were synthesised. After polymerisation the samples were optically transparent, showing complete solubility of Bp in the copolymer matrices. The maximum amount of Bp in the tablets (8 mg) was determined by the water amount in the feed mixture of polymerisation.

2.2.3. *In vitro skin permeation*

Skin of the inner side of the rabbit ear (New Zealand rabbits of 2.9–3.1 kg from Granja Conicular San Bernardo, Navarra, Spain), where pinna skin is located, was used for the skin permeation studies using modified Franz diffusion cells.

The animals were sacrificed and the ears were removed. The skin of the inner side of the ear (pinna skin) was peeled away from the underlying cartilage, then it was washed with saline solution (NaCl 0.9%) and frozen at −20 °C. The skin samples were allowed to equilibrate with buffer solution for 12 h before using for permeation studies.

The skin was mounted on a modified Franz diffusion cell and clamped carefully between the receiver and donor compartment. The active diffusion area was 3.8 cm^2 . The receiver compartment was filled with 25 ml of phosphate buffer (1 mM, pH 7.5) (containing 0.02 M sodium azide to arrest fungal growth). The diffusion cells were placed in a double walled vessel (7 cm × 5.5 cm i.d.), connected to a water recirculating thermostat to maintain a constant temperature of 37 °C. The receiver fluid was stirred continuously at approximately 500 revolutions/min (Velt multiposition electromagnetic stirrer, Italy).

2.2.3.1. *Swelling studies.*

Each gel tablet (without bupivacaine) was placed on the stratum corneum side of the skin. The donor compartment of the cell was covered with laboratory film (Parafilm®) to prevent dehydration of the gel. At predetermined times, the swelling degree (W_t) was obtained by withdrawing the tablet, lightly drying with filter paper and weighing quickly in a tared sample bottle by means of an electronic balance ($\pm 10^{-4}$ g), then the gel tablet was placed back in the receiver. W_t was calculated by using the expression (Allen et al., 1992; Blanco et al., 1994):

$$W_t = \frac{\text{weight of swollen tablet} - \text{weight of dry tablet}}{\text{weight of swollen tablet}} \times 100 \qquad (1)$$

The extent of equilibrium swelling of the hydrogel (W_∞) was reached when the weight of the swollen tablet was constant. The fluid volume of the receiver department was maintained constant by addition of phosphate buffer. All experiments were performed in triplicate ($n = 3$).

2.2.3.2. *Permeability of bupivacaine.*

The donor compartment was charged with 2 ml of bupivacaine solution (4 mg/ml in phosphate buffer 1 mM, pH 7.5) and covered with laboratory film (Parafilm®). At specific intervals, 100 μl of receiver solution was withdrawn from the receiver compartment and replaced with fresh phosphate buffer. The drug concentration in the receiver solution samples was assayed by HPLC (Spectra-Physics SP 8800 HPLC pump, SP 100 UV detector and SP 4400 computing integrator). The stationary phase was Lichrosorb RP8 5 μ (15 μm × 0.46 μm; Teknokroma). The eluent was 0.01 M dihydrogen sodium phosphate with acetonitrile (70:30 v/v) pH 2.1 (Le Guévello et al., 1993). The flow rate was set at 1.5 ml/min and the detector wavelength was 205 nm. Bp standards of 1–1000 μg/ml were run for external standardisation and linear curves with a correlation coefficient of 0.999 were generated from the area under the peak measurements. The reproducibility of bupivacaine measurements at a concentration of 100 μg/ml was 3.2% (CV% = S.D. × 100/mean) ($n = 5$). The

Bp retention time was 5.5 ± 0.2 min. Permeability measurements were performed in triplicate ($n = 3$).

2.2.3.3. Skin permeation of bupivacaine from gel tablets. Each bupivacaine-loaded gel tablet was placed on the stratum corneum side of the skin, and the donor department was covered with laboratory film (Parafilm®). The surface area of hydrogel tablets was the active diffusion area. At specific intervals, 100 μl of receiver solution was withdrawn from the receiver compartment and replaced with fresh phosphate buffer. The drug concentration in the receiver solution samples was assayed by HPLC. The concentration of bupivacaine in the receiver medium was always less than 10% of the maximum solubility of Bp (45 mg/ml in phosphate buffer), thus sink conditions were maintained (Song et al., 1981; Lee, 1983). All experiments were performed in triplicate ($n = 3$).

3. Results and discussion

The mammalian stratum corneum is a dual-compartment system of lipid-depleted corneocytes embedded in an extracellular matrix of non-polar, lipid-enriched lamellar bilayers (Elias, 1991). The greatest obstacle for drug administration by dermal and transdermal routes is the stratum corneum, the thin, outermost and least permeable layer of the skin. Morphological studies of the stratum corneum indicate that the pasive route of chemical penetration across this barrier layer is intercellular (Potts et al., 1991), although transcellular as well as transfollicular routes are also significant. Other interesting route for drug administration is the oral route. Thus, when buccal route is used, drugs penetrate the mucous membrane of the mouth by simple diffusion and are carried in the blood into the systemic circulation via the jugular vein. Small unionized molecules tend to cross the lipid membranes of the oral mucosa with relative easy (McElnay and Hughes, 2002).

Mostly of the in vitro permeation experiments are carried out using skin of different mammalian species, rabbit (Thacharodi and Rao, 1995), rat (Tsai et al., 1999; Fang et al., 1999), mouse (Gokhale et al., 1992), porcine (Ceschel et al., 1999), and human (Roy and Manoukian, 1995; Tanojo et al., 1997). In this kind of experiments, Franz diffusion cells are mainly used, and mammalian skin is mounted on the receptor compartment with the stratum corneum side facing upwards into the donor compartment. In our experiments, the pinna skin of the inner side of the rabbit ear was chosen in order to determine bupivacaine permeation through the stratum corneum of the skin; two reasons were considered for the election, a priori stratum corneum is a greater obstacle than mucous membrane, and also it is easier to obtain in enough amount for permeation experiments. Furthermore, all of the common laboratory rodents have keratinized oral epithelium on all regions of their oral mucosa, and are, therefore, not suitable models for the study of human mucosal permeability (Hoogstraate and Wertz, 1998).

Swelling studies of the copolymer hydrogels of acrylamide (A)/monomethyl itaconate (MMI) crosslinked with *N*,*N*′-methylenbisacrylamide (NBA) through the ear skin of rabbits were carried out. The equilibrium swelling degree (W_∞) (Table 1) of both gel compositions, 75A/25MMI and 60A/40MMI, was so high of that obtained when they are immersed in phosphate buffer solution (Bernardo et al., 2002), although the time needed to obtained it was almost 1.7 times longer for 75A/25MMI and 0.75 times longer for 60A/40MMI. The swelling kinetic of the gels through the skin was in accordance with second Fick's Law. To characterise the various types of solute diffusion in polymers, the following equation can be used (Kim et al., 1992):

$$\frac{M_t}{M_\infty} = Kt^n \tag{2}$$

where M_t and M_∞ are the mass of water or aqueous solution taken up at t and infinite time in sorption experiments; K is a constant incorporating character-

Table 1
Equilibrium swelling degree (W_∞), time needed to obtain W_∞, and diffusion coefficient (D_s) for phosphate buffer (1 mM, pH 7.5) uptake into two compositions (75A/25MMI and 60A/40 MMI) of poly(acrylamide(A)-co-monomethyl itaconate (MMI)) hydrogels through rabbit ear skin

Hydrogel	W_∞ (wt.%)	Time (h)	D_s 10^{11} (m^2/s)
75A/25MMI	88.9 ± 0.7	169 ± 2	5.4 ± 0.3
60A/40MMI	92.5 ± 0.1	160 ± 12	1.3 ± 0.2

Mean ± S.D. of three experiments ($n = 3$).

istics of the macromolecular network system, and n is the diffusional exponent, which is indicative of the transport mechanism. Eq. (2) is valid for the first 60% of the fractional swelling or release. For $n > 0.5$, non-Fickian diffusion is observed, while $n = 0.5$ represents Fickian diffusion mechanism. The case $n = 1$ provides the Case II transport mechanism.

In its logarithmic form, Eq. (2) was used to determine n. For the swelling process, n values were 0.48 ± 0.01 for 75A/25MMI and 0.51 ± 0.02 for 60A/40MMI, thus, these values are very close to the value 0.5, so that a Fickian diffusion can be considered. The solution of the differential form of the second Fick's Law, considering one-dimensional diffusion from a thin sheet and a constant diffusion coefficient D (Carnk, 1975) can be approached for early and moderate times of diffusion through the reduced expression (Lusting and Peppas, 1988; Allen et al., 1992):

$$\frac{M_t}{M_\infty} = 2\left(\frac{Dt}{\pi l^2}\right)^{1/2} \qquad \frac{M_t}{M_\infty} \leq 0.6 \tag{3}$$

where l is the sheet half-thickness. Thus, for a diffusion controlled process, the fractional swelling due to aqueous solution ($F_s = W_t/W_\infty$) may be expressed as:

$$F_s = \frac{W_t}{W_\infty} = 2\left(\frac{D_s t}{\pi l^2}\right)^{1/2} \tag{4}$$

where D_s is the diffusion coefficient for transport of a multicomponent species (i.e. phosphate buffer) into the hydrogel. One criterion of Fickian behaviour (Yean et al., 1990; Allen et al., 1992) holds that the plot of F_s versus $t^{1/2}$ should be linear up to 60% reduced sorption. When F_s values are plotted against $t^{1/2}$ for both polymers for first states of swelling ($F_s \leq 0.6$) a linear relationship is obtained between F_s and $t^{1/2}$ (Fig. 1); thus D_s can be obtained directly from the corresponding slopes (Table 1). A slower swelling process as the amount of MMI increases in the gel is observed.

The skin flux of bupivacaine was determined from Fick's law of diffusion using the following equations (Houk and Guy, 1988; Roy and Manoukian, 1995):

$$J_s = \frac{1}{A(\mathrm{d}M/\mathrm{d}t)} \tag{5}$$

$$P_e = \frac{J_s}{\Delta C} \tag{6}$$

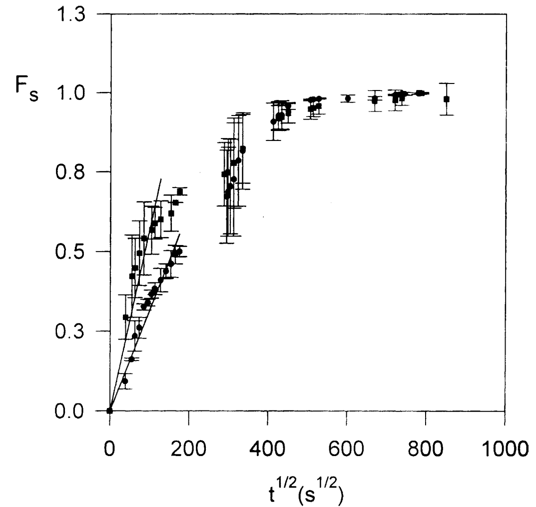


Fig. 1. Fractional swelling of poly(acrylamide(A)-co-monomethyl itaconate (MMI)) gels through rabbit ear skin. 75A/25MMI (■), 60A/40MMI (●). Mean ± S.D. of three experiments ($n = 3$).

where J_s is the skin flux (μg/cm²/h); dM/dt is the amount of drug permeated per unit time; A is the diffusion area (cm²); P_e is the effective permeability coefficient (cm/h), and ΔC is the concentration gradient across the skin. The skin flux was determined from the slope of the linear portion of a cumulative amount of bupivacaine per diffusion area–time plot.

In Fig. 2 the cumulative amount of permeated bupivacaine as a function of time for a bupivacaine solution (4 mg/ml in phosphate buffer 1 mM, pH 7.5) is shown. The bupivacaine amount permeated through the skin was $77 \pm 15\%$ of the initial one in the solution. The skin flux of bupivacaine through rabbit ear skin was 105 ± 24 μg/cm²/h, and the effective permeability coefficient was $26.5 \times 10^{-3} \pm 9.3 \times 10^{-3}$ cm/h. In vivo permeation studies of lidocaine (Tsai et al., 1996), a local anaesthetic similar to bupivacaine, through mouse skin show flux values between 0.2 and 1 mg/cm²/h, depending on the vehicle used.

Permeation of bupivacaine from bupivacaine-loaded gels through the rabbit ear skin was studied for 75A/25MMI and 60A/40MMI gels loaded with 2, 4, 6 and 8 mg of the drug by tablet. The diffusion kinetic of bupivacaine from the gels through the skin shows a hyperbolic profile, an example for 60A/40MMI hydrogel loaded with 8 mg of bupivacaine is shown in Fig. 3. The amount of bupivacaine permeated per

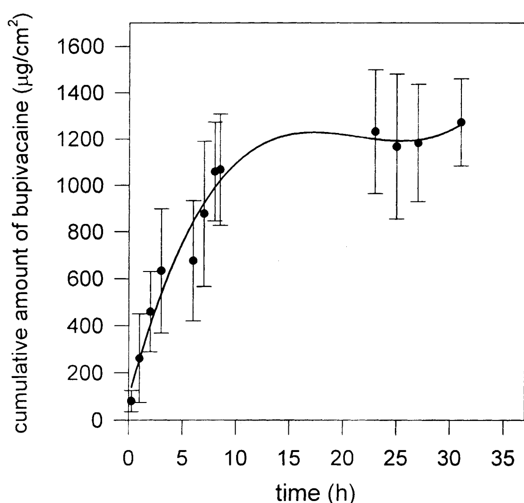


Fig. 2. Cumulative amount of permeated bupivacaine through rabbit ear skin from a drug solution (2 ml of 4 mg/ml in phosphate buffer 1 mM, pH 7.5) as a function of time. Mean ± S.D. of three experiments ($n = 3$).

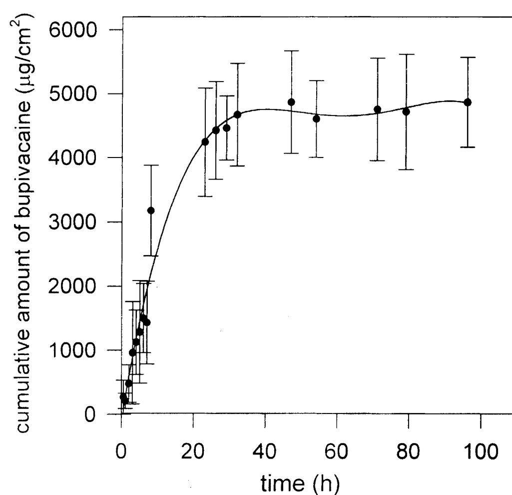
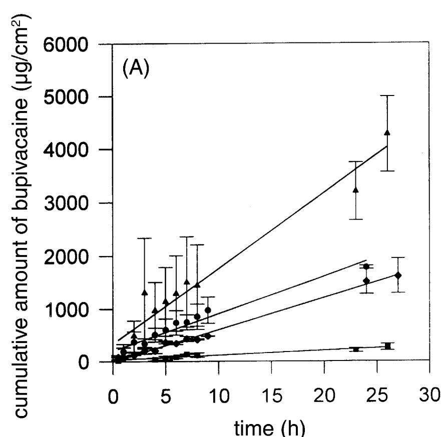


Fig. 3. Kinetic of bupivacaine permeation through rabbit ear skin from poly(acrylamide(A)-co-monomethyl itaconate (MMI)) gels. 60A/40MMI gel loaded with 8 mg of bupivacaine. Mean ± S.D. of three experiments ($n = 3$).

diffusion area as a function of time depends on the amount of the drug included in the gels for the two copolymeric compositions studied (Fig. 4). The skin flux of bupivacaine included in the gels through rabbit ear skin (Table 2) depends on the drug load of the gels, the flux decreases with the bupivacaine amount included in the hydrogels. In general, the flux is slower when the drug is released from 60A/40MMI gels. The reasons for this behaviour are that the swelling process of 60A/40MMI is slower, and also that bupivacaine interacts with the side carboxylic group of MMI, so more amount of MMI in the gel, greater is the interaction between bupivacaine and carboxylic groups. At neutral pH (7.5) the side groups of the monomers of the hydrogels are ionised, so repulsion among them is favoured. The pK_a of bupivacaine



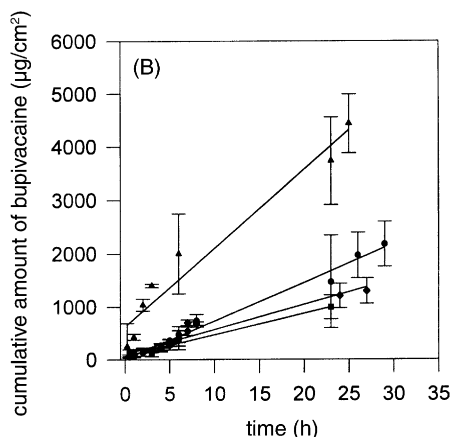


Fig. 4. Cumulative amount of permeated bupivacaine through rabbit ear skin from poly(acrylamide(A)-co-monomethyl itaconate (MMI)) gels as a function of time. 60A/40MMI (A), 75A/25MMI (B). Amount of bupivacaine by gel tablet: 8 mg (▲), 6 mg (●), 4 mg (◆) and 2 mg (■). Mean ± S.D. of three experiments ($n = 3$).

Table 2
Skin flux (J_s) (μg/cm^2/h) of bupivacaine released from 75A/25MMI and 60A/40MMI hydrogel tablets placed on rabbit ear skin

Drug amount/tablet		Hydrogels	
		75A/25MMI	60A/40MMI
Bupivacaine (mg)	8	88 ± 7	90 ± 5
	6	65 ± 7	45 ± 8
	4	44 ± 8	34 ± 2
	2	20 ± 3	16 ± 7

Mean ± S.D. of three experiments ($n = 3$).

(p$K_a = 8.16$) is larger than pH of the medium and the drug is as a cation (Skidmore et al., 1996), therefore, the drug can establish interactions with the ionised side groups of the hydrogels, which prevents bupivacaine release (Dhara et al., 1999; Kiatkamjornwong and Phunchareon, 1999). In all cases, the bupivacaine flux value is lower when the drug is included in the gels than when it is in solution, since the drug first must be released from the gel and then permeate the skin. The maximum amount of bupivacaine in the receiver compartment (Table 3) was 42–53% (average value: 47 ± 4%) and 33–42% (average value 36 ± 3%) of that included in the gels from 75A/25MMI and 60A/40MMI, respectively, and it was obtained at 56 ± 7 and 81 ± 22 h. In previous studies (Bernardo et al., 2002), we have determined the effect of the pH of the swelling medium on bupivacaine release from drug-loaded 75A/25MMI and 60A/40MMI hydrogels; the results indicated that when bupivacaine-loaded 75A/25MMI and 60A/40MMI gels were immersed in phosphate buffer (1 M, pH 7.5), only 52.21 ± 6.38% of the drug was released due to interactions between the drug and the carboxylic groups of these polymeric matrices, and it took place at 6 h. On the other hand, permeation studies of bupivacaine solutions from rabbit ear skin indicate that only 77 ± 15% of the drug is permeated, and it takes place at 26 ± 2 h. Thus, the experimental percentage of bupivacaine that permeates the skin from hydrogels is in accordance with that determined taking into account the percentage of drug released from the gels and the drug percentage that permeates the skin.

Table 3
Percentage of bupivacaine in the receiver compartment of Franz diffusion cell.

Drug amount/tablet		Bupivacaine in the receiver (%) Hydrogels	
		75A/25MMI	60A/40MMI
Bupivacaine (Bp) (mg)	8	53	42
	6	49	36
	4	45	35
	2	42	33

Drug released from 75A/25MMI and 60A/40MMI hydrogel tablets placed on rabbit ear skin. Mean of three experiments ($n = 3$).

The above results have demonstrated that bupivacaine could penetrate into and through the rabbit ear skin from bupivacaine-loaded poly(acrylamide(A)-co-monomethyl itaconate) gels due to the swelling process of these devices and the subsequent drug release. The skin flux of the drug depends on the copolymeric composition of the gels as well as the gel drug-load. These devices could be used as a dressing against wound pain or for example as a part of a topical and/or transdermal system in buccal cavity.

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