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In Vitro Studies on Transdermal Permeation of Butorphanol

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ABSTRACT The influence of the donor vehicles pH and the addition of laurocapram or transkarbam 12 as permeation enhancers on the transdermal permeation of butorphanol through human skin were examined with the aim of finding out about its possible use in the transdermal delivery system. As the pH of the donor vehicles rises, the mean value of butorphanol skin fluxes declines; an exponential relationship of the means of butorphanol flux values against the pH of the buffered aqueous donor vehicles has been demonstrated. The presence of 1% of transkarbam 12 (T12) or 5% of laurocapram (LC), respectively, in an isopropylmyristate (IPM) donor vehicle increased transdermal fluxes of butorphanol almost 2.5 times (58.1 ± 5.7 μg cm^{-2} hr^{-1}) or 1.5 times (36.4 ± 7.0 μg cm^{-2} hr^{-1}), respectively, when compared to blank donors. Considering clinical and pharmacokinetic data on butorphanol, it is possible to expect that a transdermal preparation sized 20 cm^2 and possessing flux values ranging between 5.1 and 15.3 μg cm^{-2} hr^{-1} should be sufficient to achieve effective butorphanol transdermal fluxes, namely using IPM donors containing T12. In conclusion, butorphanol is a suitable candidate for transdermal administration and T12 is a very a suitable enhancer for it.

KEYWORDS Butorphanol, Transkarbam 12, Laurocapram, Transdermal delivery, Skin permeation enhancement

INTRODUCTION

The current interest in the improvement of pain management with opioid analgesics has led to investigations of alternatives to the parenteral and oral routes of administration. Transdermal administration is a possible approach to overcoming some of the problems associated with parenteral and oral administration of opioid analgesics, such as variable and incomplete bioavailability due to extensive first-pass metabolism and side-effects caused by high peak plasma levels. Furthermore, oral administration is inappropriate for patients suffering from nausea, vomiting or dysphagia, and parenteral administration might be difficult in some patients due to decreased venous access or coagulation defects (Payne, 1998). The advantages of transdermal drug administration are encouraging for possible extending of the range of transdermal delivery systems containing other drugs from the opioid analgesics group.

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Butorphanol (Fig. 1) is a synthetic agonist-antagonist analgesic drug from the 14-hydroxymorphinan series (Rosow, 1988). This drug was estimated to be 10 times more potent than morphine as an analgesic (Pachter & Evens, 1985). Butorphanol (0.1–0.4 mg kg^{-1}) is a mu-opioid antagonist that produces its analgesic actions through kappa agonist activity. It rapidly reaches a ceiling effect, is short-acting and is a weaker analgesic than pure mu-opioids. Animal studies display analgesia, antitussive effects, low gastrointestinal activity, limited respiratory depression, some cardiovascular and skeletal muscle actions, diuresis, slight miosis and opiate antagonism (Vogelsang & Hayes, 1991). Butorphanol is metabolized in the liver with renal excretion, yielding a half-life of 3 to 4 hr (Vachharajani et al., 1997). Pain relief is good to excellent after parenteral administration at 90% of patients with moderate to severe pain. Surgical anesthetic indications involve preoperative and preinduction supplementation, balanced anesthesia and postoperative pain. Butorphanol side effects are favourable and involve sedation, nausea, elevated pulmonary vascular pressures, and rarely CNS excitation; only limited respiratory depression exists (Homan, 1994). Butorphanol has not yet been tested for transdermal administration purposes, even though there is number of reasons making it suitable for this administration route.

The rate of passive transdermal drug absorption is dependent on the solubility of the drug within the vehicle and on the partition between the skin stratum corneum and the vehicle (Bunge & Cleek, 1995). The rate of a drug delivery through the skin using a simple vehicle is directly proportional to the concentration gradient of the diffusible drug between the vehicle and the membrane (Barry, 1987; Ritschel & Hussain, 1988). The maximum achievable rate and the rate used to determine a delivery feasibility are therefore set by the drug solubility in the vehicle, and, if the drug is an electrolyte, by the state of its ionization in an aqueous vehicle (Roy & Flynn, 1989). The main factors influencing passive transdermal permeation of a drug are polarity and pH of the vehicle, solubility and pKa of a substance, and an enhancer usage, respectively (Roy & Flynn, 1990). The pH of the vehicle can change the transdermal flux by changing drug solubility, by formation of charged moieties within a drug molecule and skin, and by changing skin hydration. It is generally accepted that, where possible, a free acid or free base should be used, however this premise could be questioned (Hadgraft, 1999; Hadgraft & Valenta, 2000). All these factors afford the possibilities to increase drug permeation; however all the presumptions must be quantified for a given drug during a preformulation process.

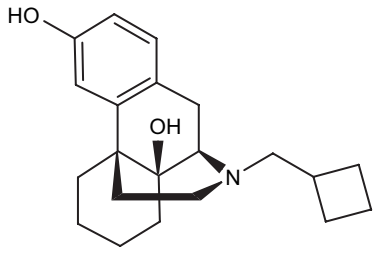

FIGURE 1 The Structure of Butorphanol.

Transkarbam 12 was formerly assessed to be a very potent member of two-chain amphiphile enhancers and was successfully used to improve transdermal absorption of several drugs (Hrabálek et al., 2001). The optimum concentrations of the enhancer in the preparations vehicle range between 0.1 and 5.0%, related to the total weight. When applied onto the skin at these concentrations, the enhancer is not an irritant in terms of the requirements imposed by the relevant pharmacopoeias (e.g., Ph Eur 5).

This study aims to estimate the factors influencing a suitable strategy for butorphanol transdermal delivery. The signal information on the topic was given by authors recently (Doležal et al., 2003). The influence of the vehicles of a relatively wide pH range and different drug concentrations using buffered aqueous vehicle was elucidated newly and the effect of transkarbam 12 (T12) and laurocapram (LC) using lipophilic isopropylmyristate (IPM) vehicle was assessed using much wider experimental support.

MATERIALS AND METHODS

Materials

Butorphanol base and butorphanol tartrate were gifted by Ivax-CR/Galena (Czech Republic). 2-dodecylazacycloheptan-2-one (laurocapram) was kindly provided by Teijin Co., (Japan). Transkarbam 12 was synthesized by the authors. HPLC grade acetonitrile and tromethamol (Aldrich-Sigma, USA), sodium phosphate, citric acid, propylene glycol (Pliva-Lachema, Czech Republic) and sodium azide (Merck, Germany) were obtained commercially. Water used for HPLC

was double-distilled and purified by a Milli-Q Plus water polishing system (Millipore).

Preparation of Skin Samples

Samples of the human skin were obtained from the Tissue Bank of the Faculty Hospital, Hradec Králové, Czech Rep.). Strips about 270–300 μm thick (i.e., the epidermis with the upper part of the *pars papillaris corii*) were dermatomed at the front side of the thigh of the cadaver (both of sex, 48 to 69 year of age) The grafts were subsequently adjusted into sterile hydrophilic gauze moistened with sterile 0.9% solution of sodium chloride and put in a sterilized Petri dish, capped and stored at 4°C for maximum 3 days, then replaced into a polyethylene package, evacuated, sealed, and kept frozen at –18°C until used in permeation experiments (maximum 9 months).

For the purpose of permeation experiments, the skin samples obtained from one individual donor were cut into sufficient number (at least 6) of smaller pieces (about 2 × 2 cm). These samples were consequently taken such as to use minimally four skin samples different by individual skin graft for each of the tested liquid donor sample.

Preparation of Donor Samples

The phosphate buffers used were prepared between pH 3.7 and 8 using sodium phosphate and citric acid; tromethamol buffer solution was of pH 8.63. The donor aqueous samples of butorphanol base were prepared as dispersions of 60 mg of the drug in 10 mL of aqueous buffered vehicles of six different pH's from pH 5.30 to 8.6 or the suspensions of 500 mg of the drug itself or with the contents of T12 (1.0% w/w) or LC (5.0% w/w), respectively, in 10 g of IPM by simple stirring at ca. 50°C (donor samples IPM, IPM+LC, IPM+T12); the samples were then stored (with 1 min intensive manual shaking for about four times daily) to equilibrate for 14 days (aqueous samples) or 2 days (IPM samples) at 32°C temperature.

The saturated solution samples of butorphanol tartrate were prepared as dispersions of 450 mg in 5 mL of aqueous buffered vehicles of six different pH's ranging from pH 3.7 to 5.3 by simple mixing (at ca. 50°C). The samples were then stored (with above mentioned shaking) for 14 days at a temperature of 32°C to equilibrate.

The equilibrated buffered samples of butorphanol tartrate were prepared as solutions of 87.5 mg of butorphanol tartrate in 10 mL of the buffered aqueous vehicle (equivalently to 60 mg of the base in 10 mL of the aqueous vehicle) of six different pH's ranging from pH 4.16 to 8.63 by mixing at ca. 50°C; the samples were then stored (with the above mentioned shaking) for 2 days at a temperature of 32°C.

Solubility Determination

For the purposes of the butorphanol base or butorphanol tartrate solubility testing in media of different pH at temperature of 32°C (used in permeation testing) the samples were prepared in a similar way as the pertinent donor samples (described above). After 14 days had elapsed, the pH level of the buffered donor samples was checked. 500 μL of liquid was withdrawn from the individual samples and filtered through a 0.20 μm filter. To prevent absorption affecting the efficiency of the filter membrane, the first 25% of the filtrate was removed. 100 μL of the filtrate was put into 250 mL volumetric flasks. All these steps were performed isothermically (at a temperature of 32°C) to avoid butorphanol precipitation caused by a drop in temperature. The content of the flasks was then diluted with a corresponding amount of the acceptor phase used for the permeation testing and well mixed. A sample from each of the flasks was then analyzed using HPLC. Based on the results of the HPLC determination of three replicates, the relation between solubility and pH was plotted.

Permeation Studies

Infinite dose in vitro permeation experiments were designed to imitate occlusive conditions. The squared pieces of skin were placed between two plexi-glass slides with a central hole of 1.0 cm^2 area and mounted in modified Franz diffusion cells.

The pre-tempered acceptor liquid consisting of phosphate buffer of pH 3.6 and propylene glycol (7:3) with an addition of 0.02% of sodium azide was then filled into the acceptor compartment (volume of about 20 mL). The air bubbles from the dermal

side were carefully removed by slightly tilting the cell.

Prior to applying the donor samples, each piece of skin was equilibrated for half an hour with the acceptor medium of the required temperature (32°C). A blank sample of the acceptor medium was withdrawn before the application of the donor on the skin surface. 400°μL of the donor sample was placed on the surface of the skin and subsequently covered with a piece of glass. The permeation cells were then placed back in a tempered water bath.

Samples (0.7 mL) of the stirred acceptor phase were withdrawn at predetermined time intervals up to 48 hr and replaced with a fresh pre-tempered acceptor buffer. The number of replicates at the permeation experiments was $n \leq 6$ for aqueous donor samples and $n = 12$ for isopropylmyristate donors. The samples withdrawn were immediately analyzed using the method described below.

Determination of Butorphanol

Determination of the permeant was performed using HPLC method. The analytical system consisted of an autosampler AS 54 with a 100 μL loop, a LCP 4000 pump and a thermostated column compartment LCO 101 (ECOM, Czech Republic), a UV/VIS detector V4 (ISCO) and the chromatographic CSV 1.7 software (Data Appex, Czech Republic). HPLC was performed under the following conditions: acetonitrile/phosphate buffer (pH 2.3) (34:66) as the mobile phase; 1.5 mL/min flow rate; 221 nm wavelength; LiChroCART® 125-4 HPLC column with LiChrospher® 100 RP Select-B (5 μm), and LiChroCART® guard column with LiChrospher® 100 RP-18 (5 μm) (Merck, Germany).

Data Treatment

The primary data of concentrations of butorphanol moiety in the acceptor phase quantified with the use of HPLC were treated with a usual procedure. Briefly, the corrected concentration values of butorphanol taken into account the continuous sampling and adding of the pure acceptor phase into a receiver. The amounts of the drug passed through the skin membrane of 1 cm^2 size into the acceptor phase were obtained. The cumulative time dependence of the drug was always used to calculate the pertinent slope values of the first linear segment of the concerned dependence with linear regression. The values obtained were understood as the individual flux values J ($\mu g\ cm^{-2}\ hr^{-1}$) of the pseudosteady state permeation.

The pertinent flux values means and standard deviations of these arithmetic means were calculated and the data were used in further calculations of the permeability coefficients. The lag time values, T_{lag}, were calculated from extrapolation of the pseudosteady state portion of the permeation profile to the intercept on the time axis.

The enhancement ratio, ER, as the rate of the butorphanol flux using an enhancer to the flux of the butorphanol blank sample without the content of enhancer, was also expressed for the purposes of the evaluation of butorphanol permeation using the lipophilic IPM vehicle and both the enhancer effects. The mean ERs reported were obtained using skin samples from at least six donors. Statistical analysis was done using the Student's *t*-test.

RESULTS AND DISCUSSION

The mean values of the absolute butorphanol fluxes obtained using the saturated aqueous donor samples of the drug base are summarized in Table 1. As the pH

TABLE 1 **The lag time (T_{lag}) and fluxes of butorphanol (n = 4, mean ± SD) using saturated buffered donor samples of different pH, the mean saturated concentration of the butorphanol base (n = 3, mean ± SD), and the calculated mean (±SD) of coefficients of butorphanol permeability**

pH of donor samples	T_{lag} (hr)	Flux ($\mu g\ cm^{-2}\ hr^{-1}$)	Saturated concentration ($mg\ mL^{-1}$)	Coefficient of permeability ($cm\ hr^{-1}$)
5.30	1.3 ± 0.5	13.4 ± 2.4	23.41 ± 0.11	$(5.74 \pm 1.02) \times 10^{-04}$
5.64	6.9 ± 4.5	4.9 ± 1.7	12.03 ± 0.20	$(4.09 \pm 1.45) \times 10^{-04}$
6.30	18.6 ± 5.5	1.9 ± 0.8	2.84 ± 0.12	$(6.62 \pm 2.67) \times 10^{-04}$
7.50	19.3 ± 2.6	2.4 ± 1.9	2.16 ± 0.12	$(1.12 \pm 0.90) \times 10^{-03}$
8.26	20.3 ± 5.5	0.9 ± 0.4	0.74 ± 0.06	$(1.18 \pm 0.49) \times 10^{-03}$

value reaches pKa of the examined substance (8.34), butorphanol base becomes less soluble in the donor buffer. The increase in butorphanol fluxes using the donors of pH below 6.0 can be also related to permeation of its ions through intercellular spaces, intercellular canals, and sweat glands. The influence of the formation of new ion pairs of the drug base with a citric acid anion may also be speculated. This factor may contribute to the increase of the dermal absorption of a drug such as butorphanol (Roy & Flynn, 1989).

Considering very low solubility of the butorphanol base in an aqueous vehicle at pH above 8, a possible influence of the butorphanol precipitate that sediments and forms a continuous layer on the skin surface may be speculated; however, the skin fluxes remained always relatively very low. Even though stratum corneum represents the major barrier influencing transdermal transport, it is very likely that even deeper parts of the epidermis with their mostly hydrophilic properties cause a considerable diffusion resistance for substances which are poorly soluble in water (Roy et al., 1994a,b).

It is possible to note that data brought at preliminary testing of drug stability under condition used at the described permeation experiment did not signal any problems and so they were not specified further. The data documented a reaching of an equilibrium state of the samples and used for the solubility values determination and calculation of the permeation coefficients were also without a problem.

The T_{lag} values obtained tends to increase proportionally with the rising butorphanol fluxes (see Tables 1–3) regardless of the differences between the T_{lag} values observed when using identical donors on skin grafts of various donors. The T_{lag} values so seems to decrease with an increasing concentration diffusible form of a drug, however, the data as are not so homogeneous to possess a sufficiently strong interpretation (at the level of 95% significance), so are not comment further.

The permeability coefficients for individual pH values of the saturated donor samples of butorphanol base were calculated from the pertinent flux and the values of the concentration of the dissolved butorphanol. Solubility of butorphanol base decreases with increasing pH of the vehicle and the observed values of the permeability coefficient rise at the same time as could be expected due to a slightly basic nature of this substance (Table 1). For comparison, an examination of transdermal buprenorphine permeation brought

TABLE 2 The lag time (T_{lag}) and fluxes of butorphanol (n = 6, mean ± SD) using saturated buffered donor samples of different pH prepared using butorphanol tartrate. Mean saturated concentration of butorphanol (n = 3, mean ± SD) and calculated mean (±SD) of coefficients of butorphanol permeability

pH of donor samples	T_{lag} (hr)	Flux (μg cm^{-2} hr^{-1})	Saturated concentration (mg mL^{-1})	Coefficients of permeability (cm hr^{-1})
3.75	0.1 ± 0.1	32.6 ± 6.7	39.87 ± 0.26	(8.18 ± 1.65) × 10^{-04}
4.00	2.0 ± 1.7	28.0 ± 4.4	40.82 ± 0.27	(6.86 ± 1.07) × 10^{-04}
4.35	2.3 ± 1.7	24.8 ± 5.8	51.94 ± 0.32	(4.78 ± 1.12) × 10^{-04}
4.45	4.1 ± 1.2	15.7 ± 7.3	34.60 ± 0.48	(4.53 ± 2.12) × 10^{-04}
5.20	4.1 ± 1.9	8.1 ± 4.0	9.20 ± 0.26	(8.76 ± 4.36) × 10^{-04}
5.25	4.3 ± 5.0	4.3 ± 1.8	4.14 ± 0.22	(1.04 ± 0.44) × 10^{-03}

TABLE 3 The lag time (T_{lag}) and fluxes of butorphanol (n = 6, mean ± SD) and Napierian logarithms of the fluxes using equilibrated buffered donor samples of different pH and butorphanol tartrate. The mean concentrations of butorphanol (n = 3, mean ± SD) and the calculated mean (±SD) of coefficients of butorphanol permeability

pH of donor samples	T_{lag} (hr)	Flux (μg cm^{-2} h^{-1})	Equilibrated concentration (mg mL^{-1})	Coefficients of permeability (cm hr^{-1})	Napierian logarithms of fluxes J (μg cm^{-2} hr^{-1})
4.16	8.1 ± 2.4	9.9 ± 3.0	5.91 ± 0.06	(1.68 ± 0.49) × 10^{-03}	2.549
5.00	10.6 ± 5.6	5.4 ± 4.0	5.92 ± 0.05	(9.12 ± 6.62) × 10^{-04}	1.985
5.97	15.1 ± 5.5	2.7 ± 2.6	3.69 ± 0.06	(7.32 ± 6.82) × 10^{-04}	1.228
6.94	10.3 ± 6.8	1.4 ± 0.4	0.44 ± 0.02	(3.18 ± 0.73) × 10^{-03}	0.751
7.61	11.6 ± 3.6	1.0 ± 0.2	0.22 ± 0.01	(4.55 ± 0.67) × 10^{-03}	0.146
8.63	15.9 ± 5.1	0.5 ± 0.1	0.05 ± 0.01	(10.21 ± 0.03) × 10^{-03}	–0.437

the same results (Roy et al., 1994b). It is probable that the main factor producing the increasing permeability coefficient values is related to a decrease in butorphanol solubility while the pH values of the donor vehicles rise.

The permeability coefficients found using the donors containing the butorphanol base at the donor sample of pH of 7.5 ($(1.12 \pm 0.9) \times 10^{-3}$ cm^{-1} hr^{-1}) are similar to those found with fentanyl ($(5.6 \pm 0.9) \times 10^{-3}$ cm^{-1} hr^{-1}) and meperidine ($(3.7 \pm 0.9) \times 10^{-3}$ cm^{-1} hr^{-1}) (at the donor pH of 7.4; Roy et al., 1994a). The obtained permeability coefficients at this situation are higher by two orders of magnitude than with codeine and hydromorphone and by as much as three orders of magnitude than with morphine. Moreover, higher butorphanol flux values were achieved at pH level of 7.5 comparing fentanyl and meperidine (Roy & Flynn, 1989). When transdermal permeation of buprenorphine was examined, the permeability coefficient of $(8.3 \pm 2.3) \times 10^{-2}$ cm h^{-1} was detected at the pH of 7.9; however, this data were measured at the fluxes of 0.05 $\pm$ 0.02 μg cm^{-2} hr^{-1} (Roy et al., 1994b), i.e., at a relatively low level.

The drug permeability coefficients and flux values obtained in our permeation testing using saturated aqueous donors prepared with butorphanol tartrate are restricted by a narrow pH range of the donor samples (between 3.6 and 5.25) as a result of the buffer components and tartrate anion interaction. The arithmetic means of butorphanol fluxes as well as the influence of the pH of the donor solutions of butorphanol tartrate on solubility and the permeability coefficients are shown in Table 2. Despite a decrease in butorphanol tartrate solubility in the pH range from 4.35 to 3.75, the means of butorphanol fluxes are not statistically different at the level of 90% significance. The permeability coefficients calculated for using donor vehicles having pH 4.45 to 5.25 and the butorphanol tartrate content also correlate with an increase in the dissolved (e.g., thermodynamically active) form of the examined substance (Flynn, 1989). Thus, an opposite dependence of solubility and the permeability coefficient against pH of the donor vehicles was observed.

Among all the opioid substances mentioned considering the permeability coefficient values measured using saturated butorphanol donors appear to be a very convenient drug for transdermal delivery.

As mentioned above, a significant pH decrease in saturated donors prepared with butorphanol tartrate resulted in the absence of data of the fluxes using vehicles above pH about 8.6. Based on this knowledge, an additional experiment was conducted, which purpose was to provide results of permeation of donor samples of as wide a pH range as possible. Using 87.5 mg butorphanol as tartrate salt form in 10 mL of the donor was sufficient for these purposes because such drug concentration ensured an almost infinite dose condition and at the same time such concentration will not restrict the pH range of the donor samples. The flux values (as usually well interpretable data) from that part of permeation experiment and other data are shown in Table 3. Flux values obtained could be simply evaluated (Fig. 2), even if directly compared for all the permeation sets (Fig. 3).

The dependence of Napierian logarithms of the butorphanol flux from the donor samples mentioned may be regarded as linear (Fig. 2), considering the favorable correlation coefficient of regression ($r = 0.997$), in the pH range of the donor vehicles used. For the theoretical flux values "J" Eq. (1) may be given as:

$$J = e^{-0,66x+5} \tag{1}$$

It is interesting that a similar correlation could not be proved for the saturated butorphanol donors, so the speculations from the first part of the discussion linked to the permeation coefficients could be realized again.

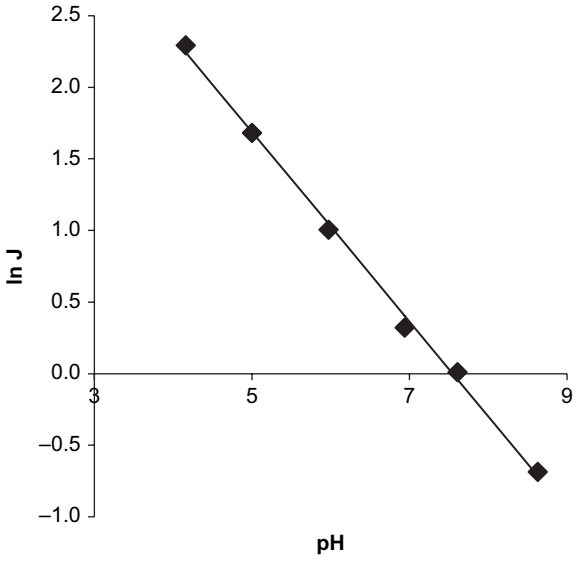

FIGURE 2 **Dependence of Napierian Logarithms of Mean of Butorphanol Fluxes Using Donor Samples Containing Butorphanol Tartrate (87,5 mg/10 mL) on the Donor Samples pH.**

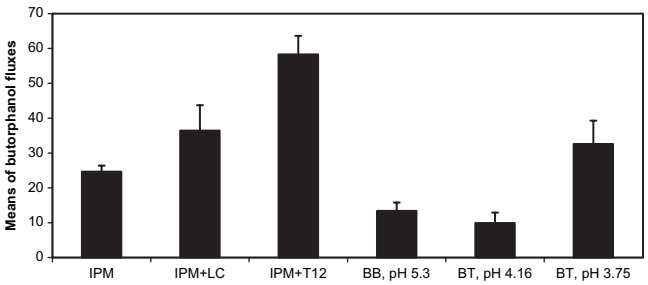

FIGURE 3 **The Mean (±SD) of the Butorphanol Fluxes Using an Isopropylmyristate (IPM) Donor Samples With the Content of Laurocapram (5% w/w) (LC) or Transkarbam 12 (1% w/w) (T12), Respectively), the Mean (±SD) of the Butorphanol Fluxes Using Saturated Buffered Donor Samples of pH 5.3 of the Butorphanol Base (BB) and Donor Samples of pH 4.16 and pH 3.75 of Butorphanol Tartrate (BT).**

As an opioid agonist-antagonist it offers a lower capacity for tolerance, and developing physical or psychological addiction, than pure agonists of the morphine type. Its euphoriant potential is insignificant, which considerably reduces the reasons for its abuse. A lot of other advantages of the use of butorphanol for transdermal administration correlate with its physicochemical properties (Homan, 1994).

For the purpose of testing the butorphanol transdermal permeation potential a lipophilic vehicle was also used and an estimation of possible enhancement effects of transkarbam 12 and laurocapram was performed. The butorphanol base was tested in an IPM vehicle containing 5% of w/w LC, or 1% of w/w T12 as transdermal permeation enhancers of the choice. The concentrations of both enhancers were chosen with respect to the preliminary tests (unpublished results). The transkarbam 12 activity partly stems from its interaction with skin ceramides (Hrabálek et al., 2006). Interference of the enhancer and the hydrophobic chains in the lipid bilayer makes the fluidity of the chain arisen, which results in an easier diffusion of the lipophilic permeants. A change in the structure of the lipids may even cause altering their polar domains with a consequent enhancing influence on the flux of the penetrated substance of polar nature as for laurocapram was discussed previously (Barry, 1987; Bouwstra et al., 1999).

Final data from that part of our permeation experiments are also indicated in Fig. 3 and compared to chosen fluxes measured with the use of the buffered aqueous donor samples.

At the permeation sets using isopropylmyristate-based donors, much lower variability of the skin flux values was observed than in the case of aqueous vehicles. This finding is entirely consistent with the results of testing of transdermal permeation of various structural substance types from hydrophilic and lipophilic donor vehicles, when much lower variability of skin fluxes was observed (Bunge & Cleek, 1995).

The butorphanol flux values obtained using IPM as the donor vehicles were comparable with the highest skin flux values achieved using aqueous vehicles. Generally, the high skin flux values achieved using isopropylmyristate donor vehicles correlate with the high solubility of the examined drug base in a lipophilic environment. The presence of transkarbam 12 in the donor vehicle made the transdermal absorption of butorphanol nearly 2.5 times higher (58.1 ± 5.7 μg cm^{-2} hr^{-1}) compared to the pertinent blanks. The recent information on a very favorable permeation enhancing effect of transkarbam 12 was confirmed and extended. As Fig. 3 shows, it was also clear that ER values of transkarbam 12 were more than about 50% higher than ER's observed using laurocapram (36.4 ± 7.0 μg cm^{-2} hr^{-1}). The ER's of laurocapram found in this study for butorphanol are generally smaller (while its concentration is the same) than the ER′s observed when examining the dermal absorption of methadone and pethidine dispersed in a propylene glycol vehicle (Fullerton & Christup, 1991), or calculated using the skin flux values from methadone (Ghosh & Bagherian, 1996). A probable interpretation of this fact can be simply linked with high fluxes of butorphanol.

When a dose needed to produce an analgesic effect is administered (0.5–2 mg intravenously, 1–2 mg intranasally or 1–4 mg intramuscularly), the butorphanol plasma concentration ranges between 1 ng/mL and 3 ng/mL (Homan, 1994). These data together with the pharmacokinetic parameters of butorphanol can be used at for the calculation of the rate of transdermal delivery needed to maintain the target steady-state drug concentration in blood using Eq. (2). For the purposes of this calculation, the effective butorphanol plasma concentration observed may be considered the drug plasma concentration in the steady state.

$$R = c_{ss}CI \tag{2}$$

where R rate of transdermal delivery, Cl body clearance, and c_{ss} steady state concentration.

When the values of butorphanol clearence (102.20 ± 34.50 L/hr), distribution volume (9.02 ± 2.40 L/kg) and $t_{1/2}$ (3.67 ± 0.52 hr; Pachter & Evens, 1985) are putted in Eq. (2), the transdermal flow rate values necessary to maintain effective butorphanol concentration in the blood are between 102.2 μg/hr and 306.6 μg/hr provided that butorphanol is not significantly metabolized in the skin. Even though the dermal metabolism of butorphanol has not been investigated, it may be regarded as insignificant due to low monooxygenase content (Roy et al., 1994b).

Thus, to achieve an effective butorphanol concentration in the blood when using the transdermal therapeutic system in the form of a patch sized 20 cm^2, the skin flux values ranging between 5.1 and 15.3 μg cm^{-2} hr^{-1} should be sufficient. It is true that these values exceed the analogical values observed with fentanyl (the minimum flux needed is 5 μg cm^{-2} hr^{-1}; Roy & Flynn, 1989) and buprenorphine (1.9–2.7 μg cm^{-2} hr^{-1}; roy et al., 1994b), considering the higher value of the total butorphanol clearance. Comparing some other analgesics of the opioid type which have been successfully tested in vitro such as buprenorphine (Budd, 2003), fentanyl, sufentanyl (Roy & Flynn, 1989), oxymorphone (Aungst et al., 1990), naloxone (Jolicoeur et al., 1992; Panchagnula et al., 2001), and etorphine (Jaiswal et al., 1999), the results obtained with butorphanol are promising. Regarding the permeation profile of butorphanol found out in this study, the practical obtaining them using a passive transdermal preparation seems to be realistic.

CONCLUSION

The sufficiently high butorphanol skin fluxes in vitro using human skin and buffered aqueous vehicle (preferred pH of about 4) or lipophilic IPM vehicle were obtained comparing some other analgesics of the opioid type which have been successfully tested in vitro. Therefore, butorphanol can be classified as a substance suitable for transdermal delivery. A very favourable permeation enhancing effect of transkarbam 12 was estimated and can be exploited at this context.

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