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RESEARCH PAPER

Design and Evaluation of a Lorazepam Transdermal Delivery System

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ABSTRACT

The aim of this work was to study the release and the permeation rate of lorazepam, in order to develop a transdermal therapeutic system (TTS) containing that drug. Only a small number of drugs are by themselves able to permeate the skin at a useful rate in order to achieve a therapeutic effect. The lorazepam permeation rate did not reach that value and required a skin permeation enhancer to increase the skin's permeability. Three permeation enhancers (Tween 80, sodium lauryl sulfate, and benzalkonium chloride) were investigated in two different concentrations: 1% and 5% of the amount of lorazepam. The best permeation enhancement results were obtained using benzalkonium chloride in concentration of 5%.

INTRODUCTION

One of the advantages of transdermal therapeutic systems (TTS) is the maintenance of the blood concentration of a drug at a therapeutic level by means of controlled permeation of the drug throughout the skin (therefore avoiding the first-pass effect) during a long period of time and using only one administration.

The successful development of a TTS depends on a pondered choice of the drug, which must not be an irritant nor produce allergic diseases and, when applied in systems of this nature, should cross the skin in adequate amounts to produce the therapeutic effect. Drugs that produce their effect in small amounts (milligrams per day), such as benzodiazepines, are good candidates.

Benzodiazepines in general, and lorazepam in particular, are well absorbed when administered by the oral (1-3), intramuscular (4-7), rectal (8-11), sublingual (12), and intranasal (13) routes. Several problems arise in the parenteral administration of benzodiazepines. In addition, low water solubility limits its parenteral administration.

Transdermal delivery is comparable to continuous intravenous infusion for some cases of systemic medica-

tions. However, the transdermal route is limited because of the poor transport of many drugs through the human skin. To overcome this limitation, either chemical enhancers (14,15); physical methods such as iontophoresis, electroporation, and sonophoresis (16–24); or the utilization of novel drug delivery systems such as microspheres (25) or submicron emulsions (26,27), are being tested.

Lorazepam is a lipophilic drug with CNS activity, and in vivo studies have indicated that it is approximately 88–92% bound to plasma proteins (28), has an elimination half-life ranging from about 11 to 16 hr, and has no pharmacologically-active metabolites. The principal metabolic pathway is conjugation with glucoronic acid (28). Lorazepam is a benzodiazepine with actions similar to those of diazepam (a tranquilizer with anticonvulsant, sedative, muscle relaxant, and amnesic properties). Acrylic resin matrices have been used by several authors to control drug release, especially in the design of oral controlled-release systems. However, the addition of plasticizers enable the use of drug–polymer matrix films in transdermal drug delivery.

Transdermal therapeutic systems containing lorazepam were prepared, and the effects of the matrix (Eudragit RL PM, RS PM, and E-100) and of the plasticizer (dioctyl phthalate, glycerin, triethyl citrate, polyethylene glycol 400, and propylene glycol) in the release and skin permeation of lorazepam were studied (29,30). The effect of the temperature on the release and skin permeation of lorazepam was also studied (31). However, the permeation rate did not reach the previously established values and therefore some permeation enhancers were investigated.

To increase the permeation rate of lorazepam, three permeation enhancers, belonging to the group of the miscellaneous enhancers (32), were investigated: one nonionic (Tween 80 [T80]), one anionic (sodium lauryl sulfate [SLS]), and one cationic (benzalkonium chloride [BC]) surfactant.

MATERIALS AND METHODS

Lorazepam was supplied by Wyeth (Instituto Pasteur, Lisboa, Portugal). Eudragit RL PM was supplied by Röhm Pharma, Germany. Synthetic membrane type RS SM 16754 was supplied by Sartorius, Germany, and Scotchpak Film type 1009 and Co Tran Adhesive (PGTA) type 9871 were supplied by 3M Pharmaceuticals, Germany. Triethyl citrate (Aldrich), benzalkonium chloride (Sigma), sodium lauryl sulfate (Merck), Tween 80 (Merck), and 2-propanol (Merck) were pharmaceutical grade. All other chemicals were reagent grade.

Preparation of Lorazepam Transdermal Therapeutic Systems

The matrix (Eudragit RL PM) was dissolved in 2-propanol at 50°C. Lorazepam and other ingredients (Table 1) were added to the previous solution, which was agitated at room temperature for 30 min and homogenized for 10 min. The mixture was applied to the surface of Scotchpak Film (polyester film laminate, 9.5 cm diameter). 2-propanol was allowed to evaporate for 48-hr at room temperature.

CoTran Adhesive was applied to the surface of one formula to study its influence on lorazepam release and permeation. In the formulas containing the permeation enhancers, this adhesive was not applied.

Drug Content Study

Drug content of the transdermal system was evaluated by dissolving an accurately weighted portion of the system (about 25 mg) in about 25 ml of 2-propanol. This solution was quantitatively transferred to volumetric flasks and appropriate dilutions were made with phosphate buffer solution (pH 7.0). The resulting solutions were filtered and analyzed by UV spectrophotometry (at 230 nm).

Release Study

The in vitro release kinetics of lorazepam from the transdermal systems were evaluated using the Keshary-Chien diffusion cell.

The transdermal system with 1 cm^2 of surface area was put in contact with the receptor fluid. This fluid consisted of a phosphate buffer solution (pH 7.0) and was maintained at 37 ± 0.5°C throughout the study. Uniform mixing of the drug in the receiver phase was

Table 1

General Formula for the Preparation of the TTS

Lorazepam	100 mg
Eudragit RL PM	900 mg
2-Propanol	50.0 ml
Triethyl citrate	300 mg
Permeation enhancer	1 or 5%

achieved by a small magnetic stirring star driven by an external 100 rpm motor. At predetermined time intervals, the receptor fluid was totally removed for analysis and was replaced with an equal volume of fresh receptor fluid. The concentration of lorazepam in the receptor fluid was determined by UV spectrophotometry.

Permeation Study

The in vitro permeation kinetics of lorazepam from the transdermal systems were evaluated using the Keshary-Chien diffusion cell with rat skin and synthetic membranes. These synthetic membranes were prepared according to the manufacturer's instructions. The transdermal system with 1 cm^2 of surface area was applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with the lipophilic side in contact with the receptor fluid. Full-thickness abdominal skin was excised from rat (Wistar). The transdermal system with 1 cm^2 of surface area was applied to the stratum corneum side of the hairless skin and then mounted in the diffusion cell with the dermal side in contact with the receptor fluid.

This fluid consisted of a phosphate buffer solution (pH 7.0) and was maintained at 37 ± 0.5°C throughout the study. Uniform mixing of the drug in the receiver phase was achieved by a small magnetic stirring star driven by an external 100 rpm motor. At predetermined time intervals, the receptor fluid was totally removed for analysis and replaced with an equal volume of fresh receptor fluid. The concentration of lorazepam in the receptor fluid was determined by UV spectrophotometry (in the case of synthetic membranes) and high-performance liquid chromatography (HPLC) (in the case of rat skin).

HPLC Analysis

The HPLC system consisted of a pump (Varian model 9012), a 200-µl loop, and a variable-wavelength detector (Varian model 9050). A C18 column (Spherisorb ODS 1 10U 250 × 4.6 mm) was used. The mobile phase was methanol/water (70/30), at a flow rate of 1.0 ml/min, and the detector was set at 230 nm.

DISCUSSION

To analyze the mechanism of drug release from this TTS product, the following equation can be used (33,34):

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

where M_t/M_∞ is the fractional release of drug, M_t is the release amount at release time t, M_∞ is the total amount of drug contained in the dosage form, K is a kinetic constant, and n is the diffusional release exponent indicative of the mechanism of drug release.

The values of n for different modes of drug transport are indicated in Table 2.

The lorazepam release rate from the TTS (RL PM) at 37°C is 0.326 $mg \cdot cm^{-2} \cdot h^{-1/2}$ (Fig. 1). There is a linear relation between the amount of released lorazepam from TTS and the square root of time, according to the Higuchi equation (35,36), as can be seen in Table 3. The lorazepam permeation rate through biological membranes is 0.6 $\mu g \cdot cm^{-2} \cdot hr^{-1}$, a value quite inferior to the lorazpeam permeation rate through synthetic membranes (12.3 $\mu g \cdot cm^{-2} \cdot hr^{-1}$). Both of these values are lower than the lorazepam release rate. This shows that the limiting step in the overall process is the permeation of lorazepam through the membranes.

Table 2

Interpretation of Diffusional Release Mechanisms from Drug Release Data

Diffusional Release Exponent (n)	Drug Transport Mechanism	Rate as Function of Time
0.5	Fickian diffusion	$t^{-0.5}$
0.5–1.0	Anomalous (non-Fickian) transport	t^{n-1}
1.0	Case-II transport	zero order
$n > 1.0$	Super Case-II transport	t^{n-1}

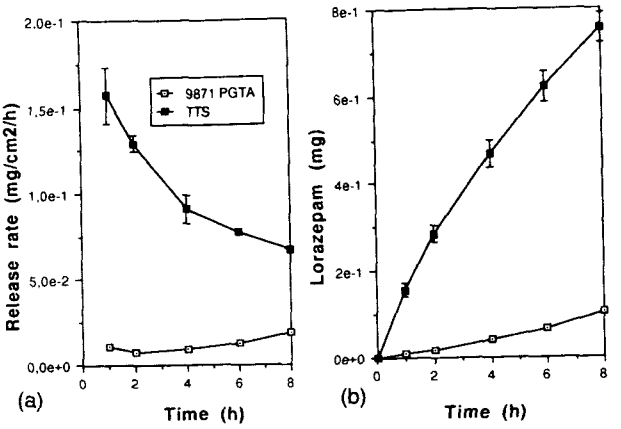

Figure 1. Comparison between release rate (a) and cumulative amount (b) of lorazepam with and without the adhesive layer 9871 PGTA.

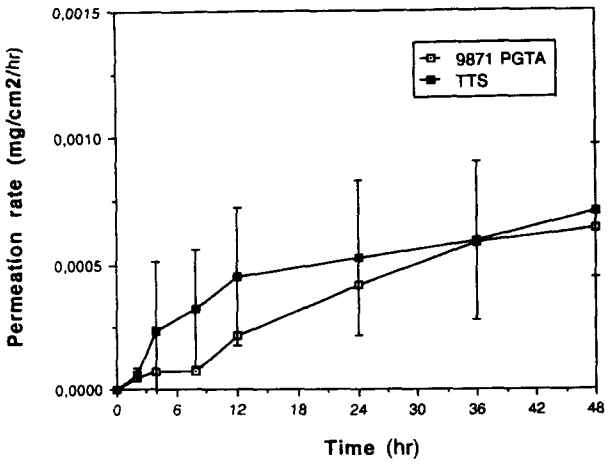

Figure 2. Comparison between lorazepam permeation rate with and without the adhesive layer 9871 PGTA.

One adhesive layer from 3M, no. 9871 Cotran™ pharmaceutical-grade transfer adhesive (PGTA), was evaluated in order to increase the contact between the transdermal system and the skin. This adhesive layer interfered with the release of lorazpeam, but did not interfere with its permeation (Figs. 1 and 2).

The lorazepam release rate from the TTS (9871 PGTA) follows a zero-order kinetic (the drug release rate is independent of time) as can be seen in Table 3. The results of the skin permeation study in the presence of the enhancers at different concentrations are shown in Figs. 3 and 4.

CONCLUSIONS

Currently, a great number of chemical substances enhancing the penetration of compounds across biological membranes are being studied. Benzodiazepines have a very low water solubility, which makes parenteral administration difficult. The inclusion of a benzodiazepine in a TTS that could release the drug during a long time period at a constant rate through the skin is our objective, but the use of some kind of permeation enhancer is required.

T80 (nonionic) acted on the skin to produce small increases in the penetration of lorazepam, changing its permeability. Nonionic compounds are comparatively lipophilic and could be expected to penetrate skin readily and to interact with the lipid matrix of the stratum corneum. In contrast, BC (cationic) and SLS (anionic) are ionic and can be expected to penetrate the stratum corneum slowly.

These surfactants, especially BC, appear to penetrate the stratum corneum, thus decreasing its barrier func-

Table 3

Values of Kinetic Constant (K), Release Exponent (n), and Relation Coefficient (R^2) Following Linear Regression of Dissolution Data by $M_t/M_\infty = k\,t^n$ Equation

Product	K	*n*	R^2
RL PM	0.1683	0.501	0.9926
9871 PGTA	0.0070	0.956	0.9884

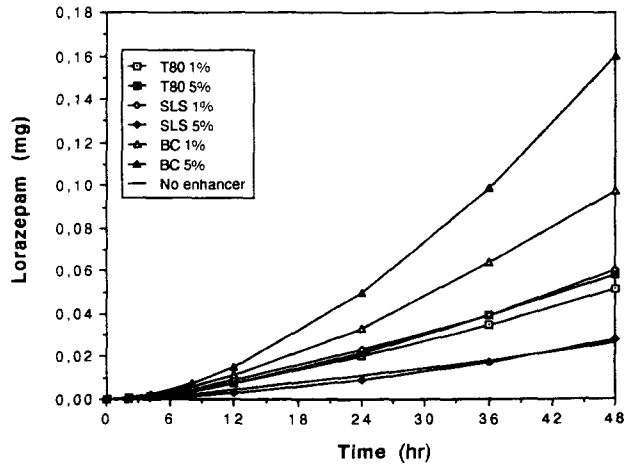

Figure 3. Cumulative amount of lorazepam permeated through the skin in the presence of the permeation enhancers.

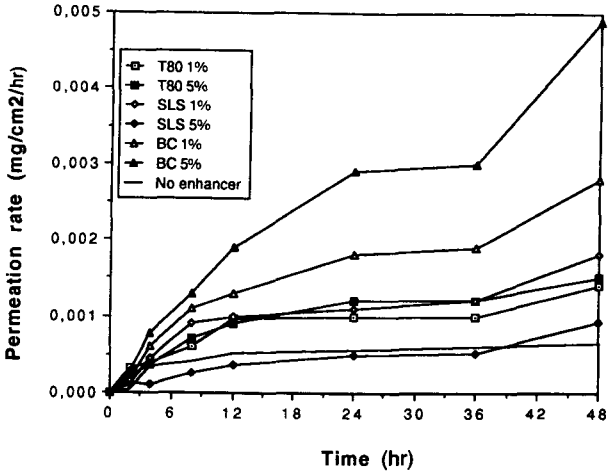

Figure 4. Lorazepam permeation rate in the presence of the permeation enhancers.

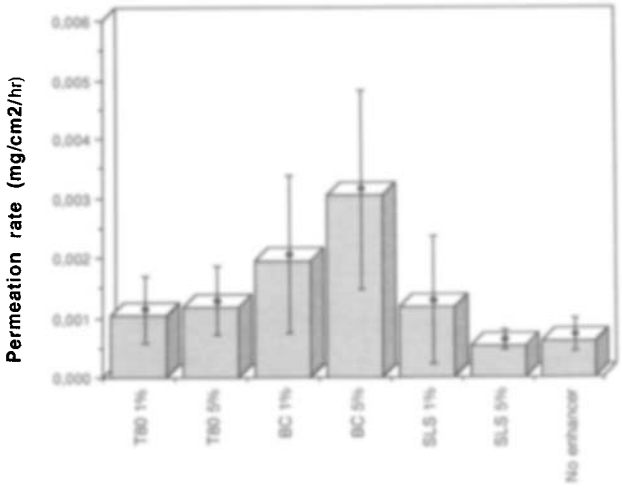

Figure 6. Lorazepam permeation rate, determined at 36 hr of the assay.

tion and increasing the penetration of lorazepam. The permeability of the skin therefore markedly increases over time. In general, cationic surfactants are more damaging and cause a greater increase in flux than anionic surfactants, and these cause greater enhancement, as can be seen in Figs. 4 and 5, and damage than nonionic surfactants (37–39).

The best results of the permeation enhancers were obtained using benzalkonium chloride in a concentration of 5% (Figs. 5 and 6). The enhancement factor obtained was approximately 5 (Fig. 5). The lorazepam permeation rate through biological membranes using benzalkonium chloride (in a concentration of 5%) as the permeation enhancer is about 3.0 $\mu g \cdot cm^{-2} \cdot hr^{-1}$.

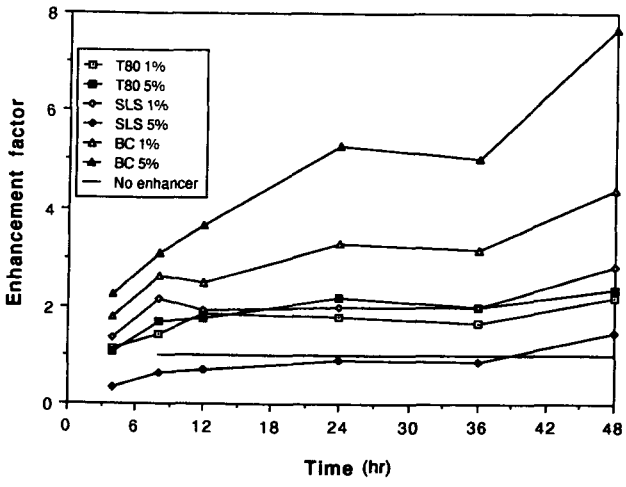

Figure 5. Enhancement effect of the surfactants in different concentrations in the permeation of lorazepam across hairless rat skin.

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