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Design and in vitro evaluation of adhesive matrix for transdermal delivery of propranolol

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Abstract

Propranolol hydrochloride, a water-soluble drug, was incorporated in three transdermal delivery systems using three polymers (hydroxypropylmethylcellulose, polyisobutylene and Ucecryl®MC808). The influence of different factors (polymeric material, matrix thickness, drug content, thickness of the adhesive layer and presence of a dissolution enhancer) was investigated. Microscopic observations and DSC thermograms have permitted to demonstrate that propranolol was essentially dissolved in the HPMC matrix and dispersed in the two other matrix types. In vitro dissolution study was carried out according to European Pharmacopoeia. Release from HPMC matrices without adhesive coating was fast. Release from these matrices became more regular (reduction of the burst effect) and slow when they are coated with a 12 μm thick Ucecryl layer. Release from different PIB matrices was too slow to be suitable as TDDS for propranolol. The best release modulation was obtained from Ucecryl matrices. In all matrices types, propylene glycol accelerated propranolol release rate. The kinetic of drug release from most matrix types was more closely described by the square-root model (Higuchi). © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Propranolol HCl; Transdermal therapeutic system; Hydroxypropylmethylcellulose; Polyisobutylene; Acrylic polymer; Propylene glycol

1. Introduction

The systemic treatment of disease via transdermal route is not a recent innovation. But, in the last two decades, transdermal drug delivery has gained increasing interest. So, transdermal controlled drug delivery systems have been investigated or developed in order either to avoid hepatic first-pass effect improving drugs bioavailability or to decrease the dosing frequency required for oral treatment. However, at present, marketed transdermal drug delivery patches are available only for a few drugs. Most investigated drugs don't cross the skin in adequate amount to produce the therapeutic effect.

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Propranolol (nonselective β-adrenoreceptor blocker) is widely used in the treatment of many cardiovascular diseases like hypertension, angina pectoralis, cardiac arrhythmia and myocardial infarction. But propranolol is subject to an extensive and highly variable hepatic first pass metabolism following oral administration. So, its oral bioavailability was reported to be between 15 and 23%. This would explain that many systems containing propranolol have been recently developed for oral and buccal (Ford et al., 1985; Taylan et al., 1996; Inoue et al., 1997; Sriwongjanya and Bodmeier, 1997; Remuñàn-Lopez et al., 1998) and transdermal (Kobayashi et al., 1996; Krishna and Pandit, 1996) administration. Local skin irritation due to propranolol-loaded transdermal patches was reported (de Mey et al., 1989; Krishna and Pandit, 1996).

Moreover, Kobayashi et al., (1996) have proved that skin irritation level was correlated with propranolol amount that penetrated through the skin. The weak intrinsic ability of propranolol to cross the skin has been successfully improved using prodrugs (Shamim et al., 1996), micellar solubilization (Ktistis and Niopas, 1998), chemical penetration enhancers (Hirvonen et al., 1993) and physical techniques as iontophoresis (Hirvonen et al., 1998; Chesnoy et al., 1999).

The aim of this work was to explore the propranolol interaction with matrix excipients of transdermal drug delivery systems. Three different patches were prepared and the influence of some characteristics of the matrix on the kinetic of propranolol release was also investigated.

Table 1
Main characteristics* of Ucercryl® MC 808[a]

Dry adhesive film	
Glass transition temperature by TBA	~ -50°C
Loop tack or peel adhesion	~8 N/2.5 cm
Cohesion by HBV	~125 min (cohesive failure)

[a] Classified non irritant in semi-occlusive application to intact rabbit skin.
* UCB informations.

2. Materials and methods

2.1. Materials

Propranolol hydrochloride (Propranolol HCl) was purchased from Sigma (France). Hydroxypropylmethylcellulose (HPMC: Methocel K4M Premium EP, viscosity 4000 cps) and Ucecryl® MC 808 (Ucecryl) were gifts from Colorcon (UK) and UCB (Belgium), respectively. Polyisobutylene (PIB; MW 400 000) and *n*-heptane were supplied by Aldrich (France). All other reagents were of pharmaceutical grade and supplied by Cooper (France). The backing layer (aluminium/polyethylene film) and the protective peel strip (Plastin®, polyethylene HD with one silicone side) were kindly supplied by Lawson–Mardon–Charmettes (France) and 4P Embalflex (Feucherolles, France), respectively.

Polymers used in this study (HPMC, PIB and acrylic polymer) are greatly cited for the preparation of TDDS (Bodmeir and Paeratakul, 1989; Krishna and Pandit, 1994; Costa et al., 1997; Dittgen et al., 1997; Chiang et al., 1998).

Aqueous colloidal dispersions (latexes) of water insoluble acrylic polymers can be used to circumvent the restrictions imposed on the use of organic solvents (skin irritation, environmental pollution, residual solvents and fire or explosion hazards). Supplied Ucecryl® MC 808 was an aqueous dispersion (pH 4.5) of a 100% acrylic copolymer (main monomer: 2-ethyl hexyl acrylate, C8 ramified). It contained $60.5 \pm 1\%$ of solids with a 350 nm average particle size. Its measured viscosity was about 500 m/Pa per s (Brookfield viscosity at 50 rpm). Latexes have a high solids content without encountering excessive viscosity. The main characteristics of dry Ucecryl adhesive film are resumed in Table 1.

2.2. Therapeutic drug delivery system (TDDS) preparation

The drug devices was set up on a backing foil (aluminium/polyethylene), on which were applied successively an adhesive layer (if necessary), a drug matrix, an adhesive/sustained release coating (if necessary) and finally a protective peel strip.

2.2.1. Preparation of polymeric mixtures

Three polymeric mixtures were prepared. Their compositions resulted from preliminary studies. The basic composition of the first matrix was as follows: propranolol HCl (2 g), HPMC 4000 cps (4.8 g), glycerol (3.2 g), polysorbate 80 (1.60 g) and de-ionised water (120 ml). It was prepared by mixing HPMC (particle size <250 μm) by mechanical agitation (Heidolph RZR 2101, Germany; 500 rpm, 20 min at 40°C) with propranolol aqueous solution containing glycerol and polysorbate 80.

In order to prepare the second type of mixture, propranolol HCl (1 or 2 g) was mixed with water (5 ml) by mechanical stirring at 25°C (200 rpm, 10 min). The obtained solution/suspension was then mixed with Ucecryl® MC 808 (6 g). Exception was done to U980 system in which the drug (1 g) was mixed with water (20 g) and Ucecryl® MC808 (30 g). Thus, propranolol HCl was partly dissolved in the latex prior to film casting and drying.

In the third matrix type, polyisobutylene (4 g) was dissolved in *n*-heptane (30 ml), then propranolol HCl (1 or 2 g; particle size <250 μm) was dispersed in *n*-heptane solution using a mechanical stirrer (500 rpm at 25°C) for 15 min.

All mixtures were used after 24 h rest in a darkroom.

2.2.2. Preparation of TDDS

Preparation of the propranolol patches was carried out in a discontinuous manner. The different matrices were obtained by spreading each mixture over the backing foil, at laboratory temperature and a constant rate of 25 cm/min using an automatic applicator (Control Coater K 101, Erichsen, France), and drying at 40°C over the applicator plate for 2 or 4 h according to the matrix thickness. Prepared matrices were of 80, 125, 980 or 1980 μm thick. Because adhesion of HPMC matrix to the backing foil was insufficient, a 12 μm thick layer of Ucecryl was previously applied to the surface of the backing foil and dried as described above. In the other hand, a 12 or 40 μm thick layer of PIB was applied to the surface of some PIB matrices.

After that, a 12, 40 or 80 μm thick layer of Ucecryl was poured on the external surface of most matrixes. Adhesive layer was used with HPMC and PIB patches in order to enhance their adhesiveness to the protective peel strip and to increase their contact with the skin (Minghetti et al., 1999). An Ucecryl layer was also applied to the matrix surface in order to study its influence on propranolol HCl release rate. In the other hand, a dissolution enhancer (propylene glycol) was incorporated in some adhesive coating. Finally, a protective peel strip (polyethylene HD with one silicone side) was applied to the surface of the last layer of Ucecryl.

Blank patches of HPMC, Ucecryl and PIB were prepared in the same way but omitting propranolol. The obtained sheets were used to die-cut circular patches of 6 cm diameter. Thirty-two different formulas listed in Table 2 were used to produce patches. Drug content of different systems is given in Table 3.

2.3. Physicochemical investigation of the interaction: DSC

In order to search possible interaction between propranolol HCl and polymeric materials of the patches, DSC analysis was carried out on pure substances, their physical mixtures and final transdermal drug delivery systems before and after dissolution studies. Moreover, for HPMC patch formulations, a second thermogram was recorded on the same samples after dehydration.

Thermograms were performed using a Mettler TA 4000 system with a differential scanning calorimeter equipped with a computerized data station (Mettler DSC 30, Mettler-Toledo AG, Switzerland). All samples were weighted and heated at scanning rate of 10°C/min between 30 and 250°C. Aluminium pans and lids were used and temperature calibrations were performed periodically using melting transition of indium as standard. The measurements were performed in triplicate.

2.4. Microscopic examination

The search for propranolol crystals in the patch

Table 2
Composition of different transdermal propranolol delivery systems and thickness of their spread coatings[a]

Drug delivery system name	Inner adhesive coating Ucecryl (μm)	Drug matrix (polymer + drug) (μm)			Outer adhesive/sustained release coating Ucecryl (μm)
		HPMC	PIB	Ucecryl	
HP 0.98	12	980	–	–	–
HP 0.98-U12	12	980	–	–	12
HP 0.98-U40	12	980	–	–	40
HP 0.98-U80	12	980	–	–	80
HP 1.98	12	1980	–	–	–
HP 1.98-U12	12	1980	–	–	12
HP 1.98-U40	12	1980	–	–	40
HP 1.98-U80	12	1980	–	–	80
HP 1.98-U12$^{(P)}$	12	1980	–	–	12$^{(P)}$
HP 1.98-U40$^{(P)}$	12	1980	–	–	40$^{(P)}$
PIB 0.98	–	–	980$^{(1)}$	–	–
PIB 0.98(2)	–	–	980$^{(2)}$	–	–
PIB 0.98-U12	–	–	980$^{(1)}$	–	12
PIB 0.98-U40	–	–	980$^{(1)}$	–	40
PIB 0.98-U80	–	–	980$^{(1)}$	–	80
PIB 0.98-PIB 12-U12	–	–	980$^{(1)}$/12	–	12
PIB 0.98-PIB 40-U12	–	–	980$^{(1)}$/40	–	12
PIB 0.98$^{(2)}$-PIB 12-U12	–	–	980$^{(2)}$/12	–	12
PIB 0.98$^{(2)}$-PIB 40-U12	–	–	980$^{(2)}$/40	–	12
U80	–	–	–	80$^{(1)}$	–
U80-U12	–	–	–	80$^{(1)}$	12
U80-U40	–	–	–	80$^{(1)}$	40
U80-U12$^{(P)}$	–	–	–	80$^{(1)}$	12$^{(P)}$
U80-U40$^{(P)}$	–	–	–	80$^{(1)}$	40$^{(P)}$
U125	–	–	–	125$^{(1)}$	–
U125-U12	–	–	–	125$^{(1)}$	12
U125-U40	–	–	–	125$^{(1)}$	40
U125-U80	–	–	–	125$^{(1)}$	80
U125$^{(2)}$	–	–	–	125$^{(2)}$	–
U125$^{(2)}$-U12	–	–	–	125$^{(2)}$	12
U125$^{(2)}$-U40	–	–	–	125$^{(2)}$	40
U980	–	–	–	980$^{(1)}$	–

[a] $^{(P)}$, Ucecryl® MC808 with 5% of propylene glycol. $^{(1)}$ or $^{(2)}$, TDDS prepared with 1 or 2 g propranolol HCl in 15 ml hexane (PIB patches) or in 5 ml water (Ucecryl patches).

matrices was performed with an optical microscope (Olympus BX40F with Sony SSM-171CE monitor, France). Films were applied to an object slide and linear polarization equipment was applied to distinguish propranolol crystals from the amorphous patch matrix.

2.5. In vitro release

The in vitro release kinetics of propranolol HCl from the drug device were performed using the dissolution test of transdermal delivery systems of the European Pharmacopoeia (third ed., adden-

dum 1999) (rotating paddle with complement cell method; dissolution apparatus Sotax model AT7, Switzerland).

The patch was centred into the extraction cell. The dissolution area was of 19.63 cm^2 (50 mm diameter). The cell was introduced horizontally in the dissolution medium (de-ionised water, 600 ml), cap at the top. The study was performed at 32 ± 0.5°C with a paddle stirring rate of 50 rpm. The dissolution medium was filtered through a 10 μm filter-fitted polypropylene tubing and continuously pumped (Watson Marlow 205U, UK) to flow cells (2 mm) in the UV double-beam spectrophotometer (Safas UV mc2, Safas Monaco), so that the absorbency was monitored automatically at 290 nm. Sink conditions were maintained during dissolution.

The dissolution tests were carried out over 24 (HPMC patches) or 48 h (other patch types). The results were computed with a standard calibration curve of the drug. The linearity interval established was 1–300 μg/ml (r: 0.9998) in the de-ionised water. At the end of each dissolution test, patches have been got back and carefully put to dry in a desiccator in order to determine unreleased propranolol amount and carry out DSC analysis. All experiments were carried out in triplicate and the relative results of standard deviation of data were always below 5%. Curves obtained with 'blank patches' were used as reference.

Table 3
Propranolol HCl concentration in different types of matrix devices (Key: see Table 2)

Drug devices	Propranolol HCl concentration (mg/cm^2)
All HP 0.98	1.05 ± 0.05
All HP 1.98	2.20 ± 0.20
All U80	0.85 ± 0.05
All U125	1.30 ± 0.10
All U125(2)	2.60 ± 0.20
U980	1.30 ± 0.10
All PIB 0.98	1.80 ± 0.20
All PIB 0.98(2)	4.10 ± 0.30

2.6. Drug content determination

Drug content of the patches before and after dissolution study was evaluated by dissolving an accurately weighted portion of the TDDS (equivalent to about 10 mg of drug before dissolution test) in a convenient solvent (4:1 v/v dichloromethane/methanol mixture, ethanol or *n*-heptane). The obtained solution was extracted with de-ionised water. The aqueous layer was centrifuged (4000 rpm, 15 min at 10°C; Jouan MR 18-22, St Herblain, France) and UV analysed (at 290 nm). The amount of released drug and the residual drug content in the films matched the original content closely, within 2.5–6%.

2.7. Data and statistical analysis

Statistical evaluations were performed by a one-way analysis of variance (ANOVA) using a statistical package Statview (Abacus Concepts, CA, USA).

Bonferroni test was employed after ANOVA to evaluate statistical differences between individual means, since it permitted a comparison of multiple results and isolation of the sources of significant differences. In all cases $P < 0.01$ was accepted to denote significance.

3. Results and discussion

3.1. Macroscopic and microscopic examination

Propranolol-loaded HPMC films were translucent while those obtained with Ucecryl and PIB were opaque. A similar observation was already reported by Bodmeir and Paeratakul (1989) from Eudragit-propranolol films study and attributed to the physical state of propranolol (dissolved or dispersed) in the dry films. So, the lower HPMC films opacity would be explained by the higher propranolol solubility in HPMC.

Microscopic examination of films showed a great number of needle crystals. However, as expected, crystals were fewer in the HPMC films than in Ucecryl and PIB films.

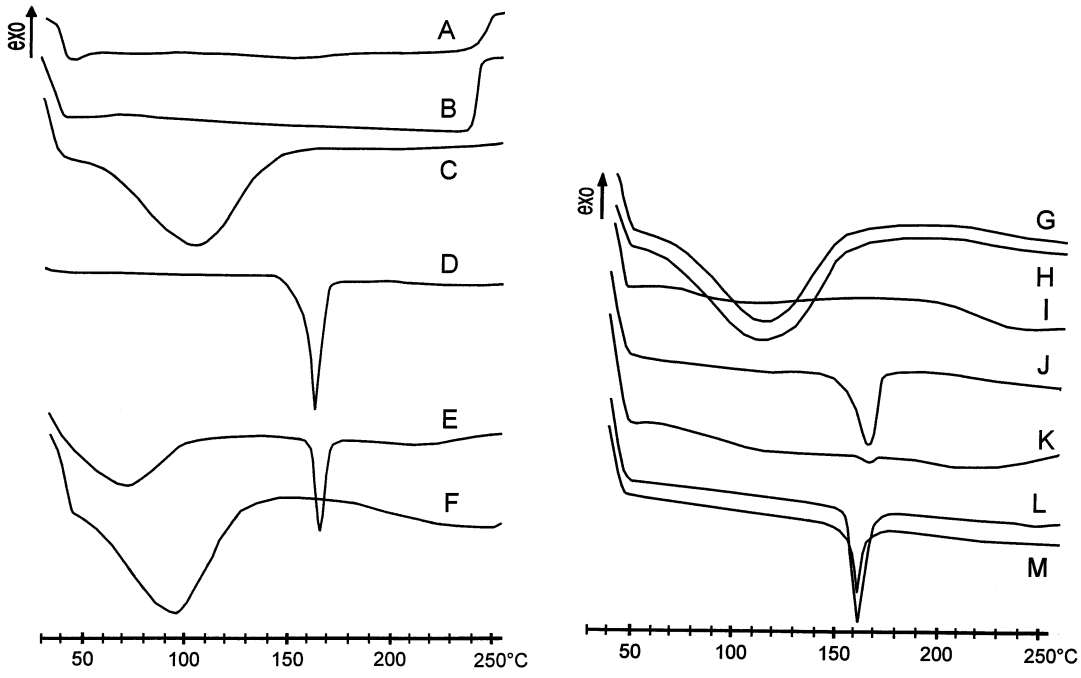

Fig. 1. DSC thermograms. A, Ucecryl® MC 808; B, Polyisobutylene (PIB); C, gel of blank hydroxypropylmethylcellulose (HPMC) matrix; D, propranolol HCl; E, HPMC-propranolol HCl physical mixture; and F, HPMC-glycerine-polysorbate 80-propranolol HCl physical mixture. (b) DSC thermograms of HPMC/TDDS (G, before; and H, after dissolution study; I, dehydrated HPMC/TDDS before dissolution), Ucecryl® MC808/TDDS (J, before; and K, after dissolution study) and PIB/TDDS (L, before; and M, after dissolution study).

3.2. DSC

Interactions of polymers with propranolol were investigated by DSC. Thermograms corresponding to reference data from pure drug and polymers, and from TDDS before and after dissolution study are given in Fig. 1. A large endotherm peak, shown around 100°C for HPMC gel, was attributed to the evaporation of the absorbed water. Confirmation of this hypothesis arose from thermogram I (Fig. 1) obtained from dehydrated HPMC/TDDS. In the case of pure propranolol HCl, a sharp endotherm peak was observed at 163.6 ± 0.5°C.

The examination of HPMC/TDDS thermograms revealed the disappearance of the endothermic peak corresponding to the fusion of propranolol, whereas it was shown in the HPMC-propranolol physical mixture thermogram. In the other hand, thermograms from physical mixture (HPMC–propranolol HCl–glycerol–polysorbate) and from HPMC/TDDS patches were nearly the same. So, the absence of propranolol fusion peak in the HPMC/TDDS thermogram was likely due not only to matrix super-saturation after solvent evaporation as it was reported (Lipp, 1998), but also to the dissolution in glycerol of propranolol crystals before their fusion temperature was reached. This conclusion was confirmed by two other methods. On the one hand, HPMC-propranolol films, initially translucent at laboratory temperature, became perfectly clear when temperature was near 100°C after gradual oven heating. On the other hand, experiments carried out on propranolol solubility in glycerol proved that solubility and dissolution rate were dramatically increased when temperature was near 100°C. So, modifications showed in HPMC-propranolol matrix thermograms have likely occurred during DSC analysis. DSC thermograms of HPMC/

TDDS obtained after dissolution studies were identical to those obtained before the dissolution assays.

DSC analysis didn't reveal any interaction between propranolol and PIB or Ucecryl matrices. The presence of the propranolol fusion peak in the Ucecryl/TDDS thermograms suggested that drug was in part dispersed in the matrix. Interestingly, the melting transition for propranolol HCl was height decreased on DSC thermograms obtained from patches after dissolution studies. Thus, the drug amount remaining within the TDDS after the dissolution study was shortly detectable by DSC analysis and might correspond partly to the fraction of propranolol dissolved in the polymer.

In PIB patches, the sharp endotherm corresponding to melting point of propranolol was showed before and after dissolution tests. Thus, one can then conclude that propranolol HCl was dispersed in the rubber.

3.3. In vitro release study

In vitro release test is widely used because of its simplicity and reproducibility. It is acknowledged that usually in vitro drug release from transdermal systems do not correlate with in vivo release. Moreover, it has been showed that drug diffusion through matrix was influenced by the drug-polymer interaction (Kokubo et al., 1994). However, in vitro tests are very useful in the quality control of finished TDDS (Van Buskirk et al., 1997).

In Figs. 2–4 are shown the in vitro release profiles of propranolol HCl from the three transdermal drug delivery system types. Dissolution test on HPMC patches was carried out over 24 h only because HPMC films became very hydrated 26–30 h after the beginning of the test and then broken spontaneously. Solely TDDS prepared with HPMC films without Ucecryl coating showed a burst effect during the first hour of the assay and then plateaued. Thus, more than 70% of the initial propranolol TTDS content was released within the first hour. The explanation of this is likely the high hydrophilic character of the HPMC matrices due to its composition (glycerol, polysorbate 80 and HPMC). These hydrophilic components could help and accelerate matrices hydration and swelling leading to the burst effect.

The rate of release from HPMC Ucecryl-coated matrices was slow and decreased as the matrix thickness (HP 0.98-HP 1.98) and adhesive-coating thickness (U12/40/80) increased. However, differences were not statistically significant ($P < 0.01$). The cumulative released propranolol percentage

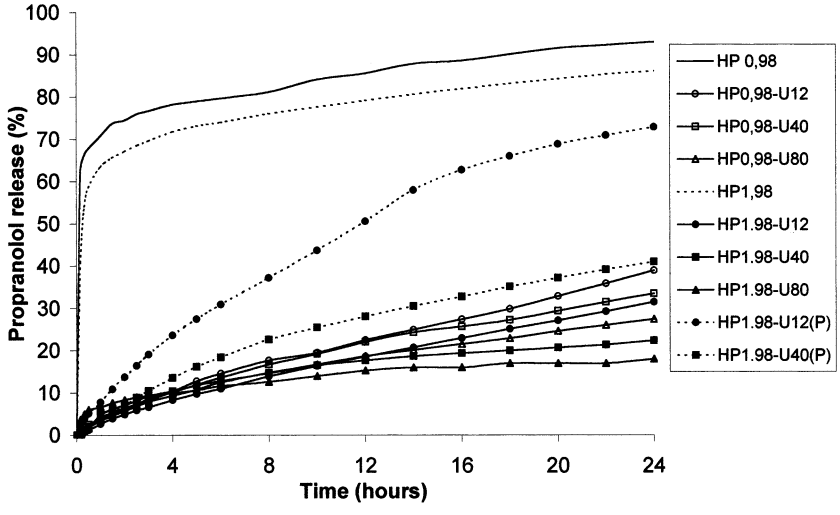

Fig. 2. Cumulative percentage of in vitro propranolol HCl release from different types of hydroxypropylmethylcellulose devices. Key: see Table 2.

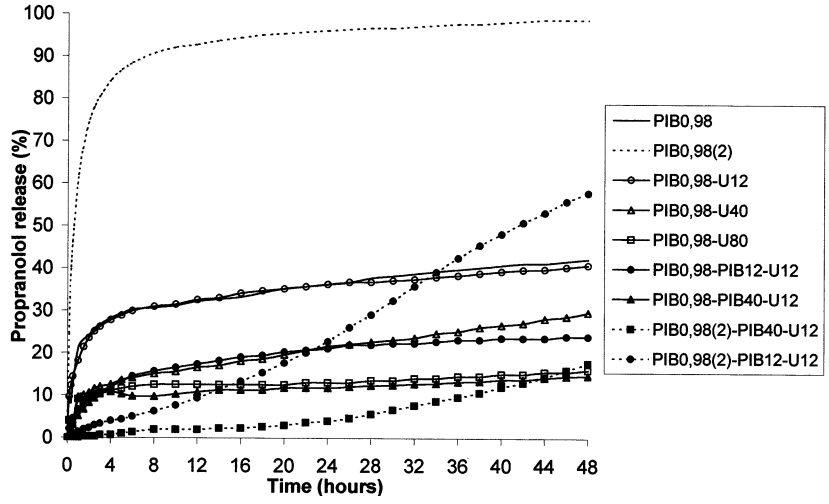

Fig. 3. Cumulative percentage of in vitro propranolol HCl release from different types of polyisobutylene devices. Key: see Table 2.

over 24 h varied between 18 and 39% of the initial drug content of the propylene glycol free patches. This result suggested that adhesive film thickness was a release-limiting factor more effective than HPMC matrix thickness, which had only a secondary role in the release rate control. The incorporation of propylene glycol in the HPMC patch formulations (HP 1.98-U12$^{(P)}$ and HP 1.98-U40$^{(P)}$) led to a more rapid drug release (51.33 and 27.62 μg/cm^2 per h, respectively) than from corresponding propylene glycol free patches HP 1.98-U12 and HP 1.98-U40 (25.06–11.73 μg/cm^2 per h, respectively). The presence of propylene glycol in the adhesive film accelerated the propranolol diffusion rate through it probably by formation of hydrophilic micropores in the adhesive film.

The regular release of propranolol from all HPMC-Ucecryl coated TDDS led to prove that Ucecryl films had homogeneous physical structure.

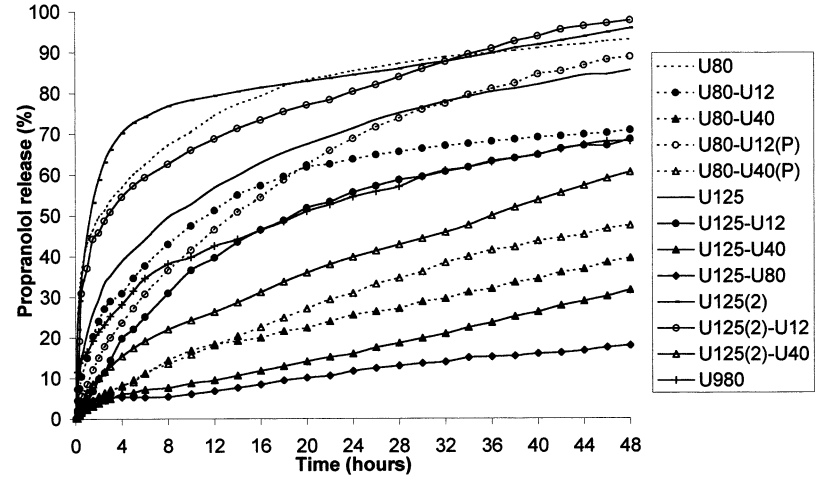

Fig. 4. Cumulative percentage of in vitro propranolol HCl release from different types of acrylic polymer (Ucecryl® MC808) devices. Key: see Table 2.

Dissolution efficiency (D.E.) was determined from dissolution curves for all transdermal drug delivery system types (Table 4). It can be noted that D.E. values from coated systems remained very low as compared with patches coating free.

In the HPMC or HPMC-Ucecryl coated devices, propranolol was partly in dispersed state, sandwiched between the backing layer and the rate control membrane (adhesive layer). After a little burst effect (around 0–4 h) and as long as propranolol crystals remained in the matrix, the rate of drug release was constant. Similar result has been already reported from investigation of HPMC/TDDS containing propranolol with an EVA rate control membrane (Krishna and Pandit, 1994).

Even if in vitro drug release was slow, in vivo drug release could be sufficient for a therapeutic effect. Thus, it has been shown that permeability of rabbit skin to propranolol was higher in vivo than in vitro, because in vivo permeability was correlated with the associated skin irritation (Hirvonen et al., 1993).

The description of dissolution profiles by a model function has been attempted using different kinetics (zero order, first order and Higuchi square-root model) and using the following equation derived by Korsmeyer et al. (1983):

$$M_t/M_\infty = K \cdot t^n$$

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 TDDS, t is the release time, K is a kinetic constant and n is the diffusional release exponent indicative of the operating release mechanism. Higuchi square root seemed to be the most appropriate model describing release kinetics from all HPMC patches (correlation coefficients between 0.992 and 1). On the other hand, n values ($0.414 \leq n \geq 0.702$; coefficient of determination R^2: 0.992–1) indicated that amount of released drug by Fickian diffusion predominated with Ucecryl coated HPMC patches. This result is in agreement with that reported by Verma and Murthy (1997) from transdermal flurbiprofen delivery investigation using HPMC matrices.

Results from HPMC patch coated with Ucecryl/propylene glycol were promising but skin irritation due to propranolol itself could be unavoidable. Such reaction has been already reported when HPMC patch containing propranolol HCl was applied to the skin (Krishna and Pandit, 1994).

Dissolution study of Ucecryl and PIB devices has been carried out during 48 h time periods. The film remained intact during the dissolution study. Propranolol release rate from PIB/TDDS was rather slow (Fig. 3) except for patches prepared with propranolol (2 g) dispersed in an organic solvent (PIB $0.98^{(2)}$). In this case, more than 80% is released over the first 4 h. All propranolol in vitro release curves from PIB 0.98 and PIB 0.98-U12 showed the same burst effect and were practically stackable. This result suggested that Ucecryl coating had no effect on drug release rate when its thickness was equal or less than 12 μm. The rate of release from other patches decreased as Ucecryl and PIB coating thickness increased.

Propranolol release profiles from PIB patches suggested that various diffusion kinetics did exist depending on PIB and/or Ucecryl coating (n values and R^2 varied from patch to other).

During the last 24 h, propranolol release from PIB/PIB coated matrices was slow and varied with initial drug content. So, the drug release rate varied between 2.25 and 6.0 μg/cm^2 per h and between 23.6 and 60.0 μg/cm^2 per h for patches containing 1.8 and 4.1 mg/cm^2 of propranolol, respectively. In the other hand, as expected, DE values calculated from propranolol dissolution profiles of PIB patches were lower than those obtained from HPMC patches. All these results led to prove that propranolol diffusion through the PIB matrix structure was slow. A possible explanation of this could be the weak solubility of propranolol in the PIB matrix and the slow diffusion rate of the drug through the different patch layers. Owing to the high hydrophobic properties of PIB, water couldn't freely and deeply penetrate the patch. So, only the fraction of propranolol that reached the external surface of the adhesive layer was released in the dissolution medium.

Table 4
Dissolution efficiency (D.E.)(*) corresponding to different types of propranolol HCl TDDS[a] (Key: see Table 2)

	HP 0.98	HP 0.98-U12	HP 0.98-U40	HP 0.98-U80	HP 1.98	HP 1.98-U12	HP 1.98-U40	HP 1.9-U80		HP 1.9-U12$^{(P)}$		HP 1.9-U40$^{(P)}$	
D.E. % (24 h)	84.30	21.81	20.31	17.26	74.79	17.85	15.91	13.83		47.03		25.92	
	U80	U80-U12	U80-U40	U80-U12$^{(P)}$	U80-U40$^{(P)}$	U125	U125–U12	U125-U40	U125-U80	U980	U125$^{(2)}$	U125$^{(2)}$-U12	U125$^{(2)}$-U40
D.E. (48 h)	79.91	57.50	24.25	62.04	29.09	66.42	49.49	16.75	11.14	51.27	82.63	77.74	37.76
D.E. (24 h)	70.32	47.25	16.24	43.55	17.75	53.21	36.12	9.69	7.27	40.15	75.37	65.31	25.54
	PIB 0.98	PIB 0.98$^{(2)}$	PIB 0.98-U12	PIB 0.98-U40	PIB 0.98-U80	PIB 0.98-PIB12-U12		PIB 0.98-PIB40-U12		PIB 0.98$^{(2)}$-PIB12-U12		PIB 0.98$^{(2)}$-PIB40-U12	
D.E. % (48 h)	35.31	93.22	34.79	20.67	13.18	19.62		11.82		26.00		6.04	
D.E. % (24 h)	30.99	88.79	31.09	15.98	11.87	16.29		10.37		10.37		2.04	

[a] (*), D.E. is defined as the area under the dissolution curve up to a certain time (here 24 and 48 h) expressed as a percentage of the area of the rectangle described by 100% in the same time (Khan and Rhodes, 1972).

By comparison with all other patches adhesive coating-free, Ucecryl TDDS (0.980 mm thickness) showed a relatively slow release following Higuchi model kinetic ($R^2 = 0.997$). In order to improve dissolution characteristics of Ucecryl device, thinner matrices (80 and 125 μm) were prepared. Release kinetics from these patches showed that the thinner was the matrix thikness the higher was the drug release, but results were not statistically different (Bonferroni test, $P > 0.01$).

As expected, the rate of propranolol release increased as the Ucecryl matrix drug loading increased and differences were statistically significant ($P < 0.01$). This result is in agreement with that already reported by Bodmeir and Paeratakul (1989) from investigation of Eudragit® films containing propranolol. Moreover, the propranolol release decreased significantly ($P < 0.01$) when the adhesive layer thickness increased.

Propylene glycol incorporation in the drug free Ucecryl layer (-U12$^{(P)}$ and -U40$^{(P)}$) was less effective than in HPMC patches and results were not significantly different ($P > 0.01$) from those obtained from propylene glycol free patches. The coating of Ucecryl matrices with propranolol-free Ucecryl layer permitted at once to reduce the drug release rate and the burst effect. However, the effect of the coating became more effective when it was thicker than 12 μm. Thus, the cumulative percentage of propranolol released from TDDS having an Ucecryl coating of 40 or 80 μm thick, was always less than 40% over the first 24 h and less than 60% over 48 h. In all other Ucecryl patches, where coating was of 12 μm thick or absent, the cumulative released percentage of drug over 24 and 48 h was higher than 70 and 90%, respectively.

Ucecryl patches D.E. (0–48 h) were found to be between 66.42 and 82.63%. These values are higher than those obtained with HPMC and PIB patches. Devices showed an initial high dissolution rate, but after 24 h it fell down. Thus, the release rate varied respectively between 2.5 and 7 μg/cm^2 per h for U80/U80-U12/U80-U12$^{(P)}$, between 8 and 10 μg/cm^2 per h for U125 and U125-U12 and between 12 and 20 μg/cm^2 for U125$^{(2)}$ and U125$^{(2)}$-U12.

As regards the propranolol release kinetic, it seems to be rather described by a matrix diffusion model (square root, Higuchi; correlation coefficients between 0.973 and 0.998) practically over the entire dissolution curve (Higuchi, 1963). The n values extracted from Korsmeyer et al. (1983) equation varied between 0.318 and 0.728. Thus, the drug free Ucecryl coating can be seen as a second matrix laminated on the first drug-loaded Ucecryl matrix. Such Higuchi kinetic has been already showed with Eudragit patches containing cephalexin (Shin and Cho, 1996) and lorazepam (Costa et al., 1997). However, a zero order kinetic was found when matrix was coated with CoTran® adhesive (Costa et al., 1997).

Initial drug release from most of prepared TDDS was rapid, then 'linearized' and the drug was never completely released. The initial rapid release of propranolol HCl can be explained by the dissolution of the dispersed drug crystals located at the external surface of the device. The slow drug release phase could be then attributed to its low diffusion rate through polymeric matrices. On the other hand, propranolol HCl release was depending on the drug loading: at low and intermediate loadings, drug (in dissolved and/or dispersed state) was released by diffusion through the polymer and/or through liquid-filled cavities left behind by the released drug. At higher loadings, the drug was released rapidly and primarily by diffusion through interconnected water-filled pores and channels as found by Bodmeir and Paeratakul (1989).

In conclusion, PIB devices give lower release rate and make these formulations unsuitable as TDDS for propranolol HCl. In return, promising results were obtained with HPMC matrix coated with thin Ucecryl film containing dissolution enhancer (propylene glycol) (73% of dissolved drug after 24 h and a D.E. of 47%). The best release modulation was obtained with Ucecryl TDDS. This device avoided the pronounced burst effect and, whatever its formulation, results were increased as compared with other polymeric TDDS.

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