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COMMUNICATION

In Vitro Release Study of Transdermal Delivery Systems of Progesterone

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ABSTRACT

A potential transdermal application of progesterone was investigated. In vitro diffusion studies of the drug were performed. Investigations were carried out in order to examine if the addition of urea, pantothenol, or laurocapram can enhance the release rates from Eud (Eudragit NE 30 D) matrices. Pantothenol and urea increased the release 1.4- to 1.6-fold. The transdermal therapeutic system (TTS) containing 10% laurocapram delivered the highest release rates with a 2.8-fold enhancement.

INTRODUCTION

The results of new studies suggest treatment with progesterone lessens the distressing symptoms of premenstrual syndrome (PMS) patients (1). PMS may be defined as a combination of physical and behavioral symptoms which occur during the luteal phase of the menstrual cycle and are absent during follicular phase. A topically applied progesterone-hydrogel (Progestogel, Besins Pharma, Germany) is suggested for treatment of premenstrual mastodynia. A formulation study deals with an adhesive dispersion type transdermal delivery system with progesterone and other steroids such as hydrocortisone or testosterone (2).

In the present study the influence of incorporated penetration enhancers of matrix type transdermal therapeutic system (TTS) to the in vitro release was investigated.

MATERIALS AND METHODS

Chemicals

Materials

Progesterone (Sigma, St. Louis, MO), Eudragit NE 30 D® Eud, (Röhm, Darmstadt, Germany) according to polyacrylate dispersion 30% Ph.Eur., Plastoid E 35 L (Röhm), and hydroxypropylmethylcellulose (HPMC), according to Metolose SH-4000 USP/NF were used. laurocapram (Azone) was synthesized according to the method from Bodde (3). D-Pantothenol (ICN Biomedicals, Germany), urea, Tween 80 (Merck,

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Darmstadt, Germany), back foil (3M/1109 Scotchpak) polyester film laminate, and supporting foils (Scotchpak polyester film liners, fluoropolymer coated) 3M/9743 or 3M/1022 (3M Medica, Borken, Germany) were used.

Preparation of Transdermal Patches

The variable ingredients of the compositions are listed in Table 1. The preparation was altered as follows: progesterone was suspended in Eud and then the HPMC-gel thickener was added. Urea was pulverized to progesterone and the polymer-dispersion and HPMC-gel were added. Because of its high viscosity pantothenol was warmed on a water bath, then an equivalent of ethanol was added. After the progesterone was suspended in this mixture, the polymer-dispersion and HPMC-gel were added. Because of the formation of air bubbles the manufacturing of laurocapram required addition of the surfactant Tween 80. The polymer-dispersion and Tween-80 were mixed together and the corresponding amount of progesterone was suspended in half of this mixture, to the other half of the mixture laurocapram was added and then both parts were assembled. The HPMC-gel was added to the resulting suspension. The TTS formulations were obtained by casting a corresponding amount for 200 cm^2 of the drug/polymer dispersion onto a supporting foil, which was fixed on a glass plate, and drying at 40°C for up to 24 hr. The glass plate was adjusted to water level. Afterward, the adhesive layer (Plastoid E 35 L®) was applied by using a stainless steel applicator and dried at 60°C for 30 min. Then the back foil was rolled on the top of the polymer-adhesive layer. The TTSs were blanked out in a suitable size (r = 2.2 cm). Matrix and adhesive thickness of all TTSs were 100 μm.

Analytical Procedure

The amount of progesterone released from the matrix systems was determined specrophotometrically at 248 nm with a Lambda 16 UV/VIS (Perkin-Elmer). Each liberation process was carried out in four runs. Patches prepared in the same way without drug were checked photometrically. The linearity interval established was 0.998–49.99 μg/ml (r = 0.9956) in the acceptor phase propyleneglycol/water (40/60; w/w).

Release Rate Testing

Release studies were perfqrmed with the Stricker cell (5). Originally this apparatus was developed to study the diffusion of drugs through lipid membranes. Instead of the lipid membrane, the TTS was applied and there was only one direction of flow for the acceptor medium. The area of TTS amounted to 15.2 cm^2.

RESULTS AND DISCUSSION

Drug release kinetics are described by an exponential curve, which is typical for all matrix TTS (5). The influence of the drug loading (mg/cm^2) is expressed in Fig. 1. A two-fold loading with progesterone leads to a 1.5-fold increase of liberation. With a matrix thickness of 100 μm, an unlimited increase of drug loading is impossible from the view of the preparation technique. Therefore, other possibilities of increasing the release rates, such as the incorporation of suitable penetration enhancers, should be considered. The effect of inclusion of various enhancers on the liberation of progesterone

Table 1

Compositions (mg/cm^2) of TTS Formulations

Code	Progesterone	Eud	Urea	Panto	Laurocapram	HPMC	Tween 80
1A	4.5	34.5	-	-	-	2.0	-
1B	9.0	34.5	-	-	-	2.0	-
1C	4.5	34.5	7.2	-	-	1.9	-
1D	4.5	34.5		9	-	1.75	-
1E	4.5	34.5	-	29	-	1.0	-
1F	4.5	34.5	-	-	7.25	1.9	2.5
1G	4.5	34.5	-	-	14.5	1.72	5.0

Eud: polyacrylate dispersion 30%; HPMC: hydroxypropylmethylcellulose; panto: pantothenol.

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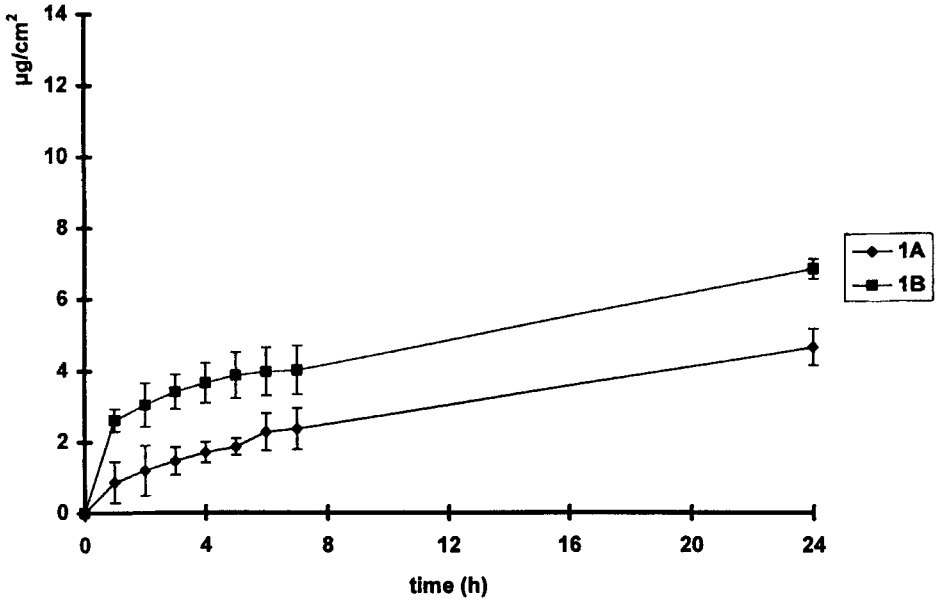

Figure 1. Liberation of progesterone from a matrix polymer system. Dependence between delivery rate (µg/cm²) and drug concentration in the matrix. Data incorporate the SD of four experiments.

from Eud matrices over a period of 24-hr is shown in Figs. 2, 3, and 4. Addition of 5% urea caused a 1.6-fold increase of liberation rates compared to the pure matrix (Fig. 2). From the technical point of production and from the appearance of the final product it is not possible to incorporate more urea than 5%.

It is known that pantothenol can act as penetration enhancer for several drugs; there would be also the

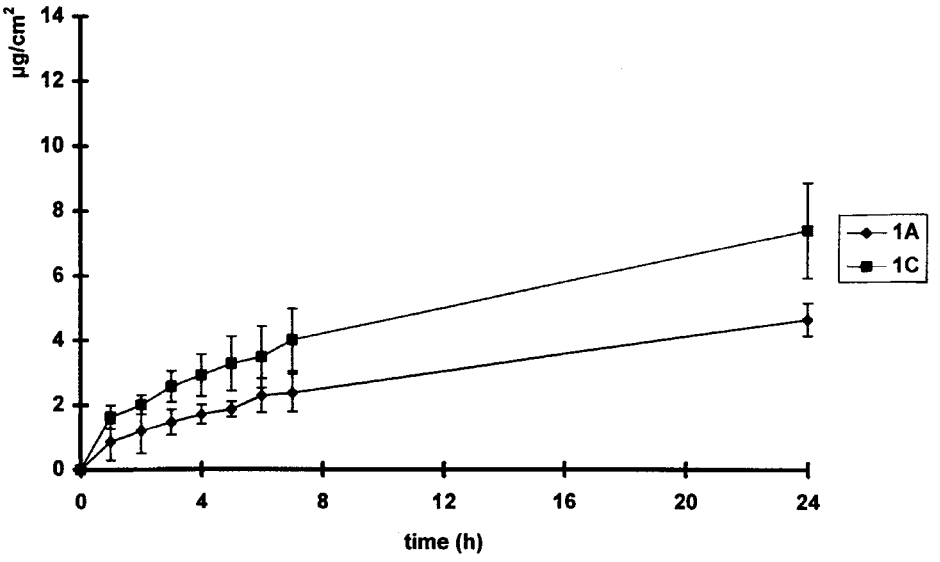

Figure 2. Influence from urea on the release of progesterone (µg/cm²). Data incorporate the SD of four experiments.

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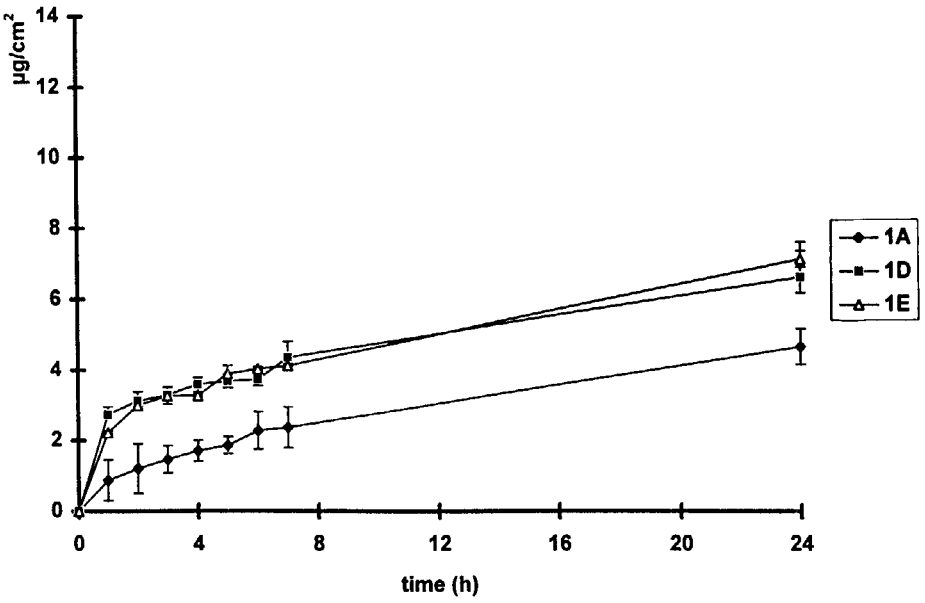

Figure 3. Influence from pantothenol on the release of progesterone (µg/cm²). Data incorporate the SD of four experiments.

advantage of less skin irritations. The incorporation of 1–20% pantothenol is suggested (6). Addition of 6% pantothenol caused 1.4-fold higher release rates. No further increase of release rates could be detected if 20% pantothenol was added (Fig. 3).

The highest release rates could be achieved by incorporating laurocapram. Addition of 5% caused a two-fold increase. The incorporation of 10% laurocapram (composition 1G) gave the highest increase in the drug release rates, which amounted to 12.81 µg/cm² (Fig. 4),

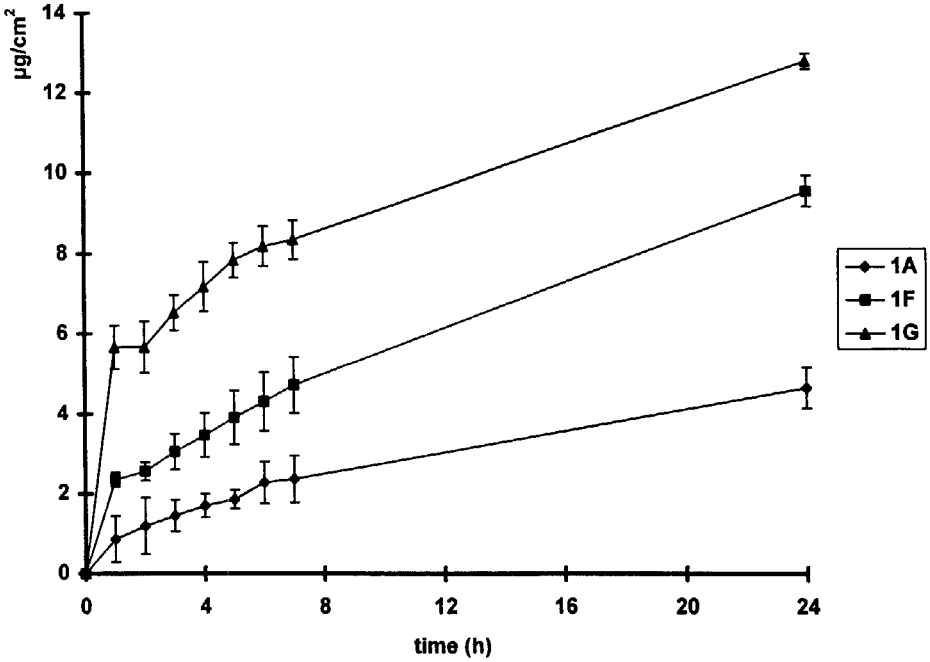

Figure 4. Influence from laurocapram on the release of progesterone (µg/cm²). Data incorporate the SD of four experiments.

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which corresponds to a 2.8-fold increase. This positive effect is not only caused by laurocapram, but may be intensified by the addition of Tween 80. It was impracticable to form homogenous laurocapram-containing films without Tween 80. Drug release or dissolution testing helps to ensure product quality but may not predict in vivo performance. A test which can be used to predict in vivo drug delivery is the investigation of drug penetration through human cadaver or animal skin. The significant effect of laurocapram incorporation on the release of progesterone should be the basis for further investigations using human or animal skin. Testing other polymer matrices in connection with penetration enhancers would also be of interest.

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