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RESEARCH PAPER

Acrylic Resins as Rate-Controlling Membranes in Novel Formulation of a Nine-Day 17β-Estradiol Transdermal Delivery System: In Vitro and Release Modifier Effect Evaluation

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ABSTRACT

The feasibility of transdermal controlled delivery system of 17β-estradiol was investigated by conducting in vitro release studies. Several new 17β-estradiol unilaminate adhesive devices capable of releasing 17β-estradiol in a controlled fashion over a 24-h, 36-h, 96-h, 104-h, 168-h, and 216-h period have been developed using acrylic resins (Eudragits E100, RSPO, and RLPO) as adhesive and rate-controlling polymers. The in vitro release profiles of 17β-estradiol from various TDS unilaminate devices were characterized in a new developed dissolution tester vessel (total volume 200 ml), using a new paddle. The release of drug from different formulations was measured by a sensitive high-performance liquid chromatographic (HPLC) method. The release of drug from all prepared adhesive devices seems to obey zero-order kinetics ($r > 0.98$). The effect of two different plasticizers (acetyltributyl citrate [ATBC] and triethyl citrate [TEC]) on the release patterns of 17β-estradiol from TDS formulations was studied, and they were almost identical. The effect of two different release modifiers, propylene glycol (PG) and myristic acid (MA), on the release pattern of 17β-estradiol from prepared unilaminate devices was evaluated. It was shown that the use of these release modifiers significantly increased

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the release of 17β-estradiol from a TDS unilaminate patch. Furthermore, these data clearly demonstrated that the acrylic resins are suitable polymers for the preparation of 17β-estradiol TDS adhesive devices.
Key Words: *Estradiol; In vitro dissolution testing; Polyacrylates; Release modifiers; Transdermal drug delivery.*

INTRODUCTION

Over more than two decades, rate-controlled transdermal drug delivery systems have been successfully developed and introduced for providing therapeutic action via skin into the systemic circulation (1,2). It also has been recognized that transdermal rate-controlled drug delivery offers many potential biomedical benefits (3). The 17β-estradiol transdermal therapeutic system is a cutaneous delivery device that delivers estradiol into the systemic circulation via the stratum corneum at a constant rate for up to a few days. This system is an effective alternative to oral administration for reduction of vasomotor menopausal symptoms (4,5) and prevention of postmenopausal osteoporosis (6,7). Furthermore, physiological levels of estradiol therefore can be maintained in postmenopausal women with almost low daily doses because first-pass hepatic metabolism is avoided (8).

There are now a number of different estradiol drug-in-adhesive patches on the market with various degrees of efficiency in vivo (9,10). In the past few years, many different in vitro release (dissolution) testing methods have been developed for quality control purposes (11). Each procedure requires a specific apparatus for the different products on the market (12). The use of penetration-enhancing agents is valuable and important for achieving therapeutic plasma levels of many drugs (13,14). These enhancers can be generally classified as polar (hydrophilic, like propylene glycol) or nonpolar (hydrophobic, like myristic acid) (15).

The purposes of this study were to develop an estradiol unilaminate transdermal delivery system (TDS) using acrylic resins as the rate-controlling matrix. Furthermore, the role of release modifiers and different plasticizers on alteration of the drug release from prepared TDS formulations was evaluated as well.

EXPERIMENTAL

Materials

The 17β-estradiol (Synopharm GmbH, Germany), propylene glycol (PG), and myristic acid (MA) were pharmaceutical grade. Triethyl citrate (TEC) and acetyltributyl citrate (ATBC) (Morflex, NC) and Eudragits® (methacrylate ester copolymers) E100, RSPO, and RLPO (Röhm, Darmstadt, Germany) were obtained as gifts. Acetonitrile was high-performance liquid chromatographic (HPLC) grade, and all chemicals were used as received.

Determination of Drug Solubility

An excess amount of 17β-estradiol was equilibrated with 5 ml of saline containing various concentrations of PG at 37°C for 24 h with constant shaking in a shaking incubator. The excess of 17β-estradiol was then filtered through a membrane filter (0.22 μm). The concentration of the various saturated solutions was determined by HPLC.

Preparation of Estradiol Unilaminate Transdermal Delivery System

The transdermal estradiol unilaminate device was fabricated by a casting process. First, 17β-estradiol was homogeneously dissolved in acetone, mixed well, and then an appropriate amount of the mixture of Eudragits E100, RLPO, and RSPO (in the ratios of 4:1:2, 4:2:2, 4:1:3, 4:1:3.1, 4:2:3, and 3.8:2:3.5 for 24 h, 36 h, 96 h, 104 h, 168 h, and 216 h patches, respectively) during gently rotating was added. Next, suitable amounts of TEC (as a plasticizer) and succinic acid were added and mixed well; isopropyl alcohol and absolute ethanol were added, followed by gentle mixing on a magnetic stirrer for 3 h to form a film solution. Finally, by pouring the drug/adhesive combination on the backing layer prepared earlier, the solvent was allowed to evaporate at room temperature overnight to form the dry reservoir compartment.

In Vitro Release Studies

To conduct the in vitro drug release from the TDS patches, a modified USP 24 paddle-over-disk method was designed. The vessel volume was 200 ml, and a new

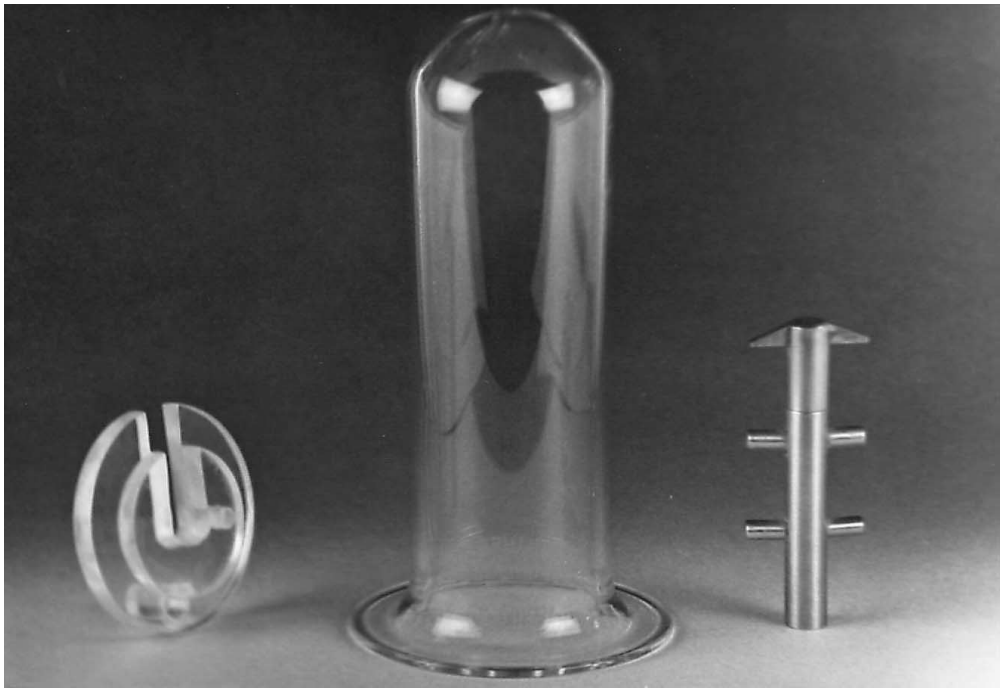

Figure 1. Photograph of developed vessel, paddle, and lid (adaptable to Erweka system) for in vitro release studies.

paddle (Fig. 1) was prepared and used (this system is adaptable to the Erweka dissolution tester, Erweka, Heusenstamm, Germany). The USP 24 screen mesh size was used for drug release measurement . The receptor solution consisted of isotonic saline (NaCl 0.9%) and PG (40:60 v/v). The receptor solution volume was 200 ml, and it was maintained at 32°C ± 0.5 under constant stirring at 75 rpm.

The TDS patch was positioned at the bottom of the dissolution vessel. At 1-h intervals, 2-ml samples were removed and replaced with the same volume of dissolution medium. The amount of estradiol release was measured by HPLC using a modified (different flow rate and mobile phase) method developed in our research laboratory (16,17).

High-Performance Liquid Chromatographic Determination of Estradiol in Transdermal Delivery Systems

The HPLC (Waters 510 Millipore, Bedford, MA) consisted of a pump set at a constant flow rate of 0.8 ml min^{-1}, a variable ultraviolet detector (Waters 490E programmable multiwavelength, Millipore) set at 205 nm, a μBondapak C_{18} 3.9 × 150 mm reversed-phase 10 μm column, and an automatic integration system (Waters 746 data module, Millipore). The mobile phase was a combination of acetonitrile and water (40:60 v/v) (16,17).

RESULTS AND DISCUSSION

Effect of Propylene Glycol on the Solubility of 17β-Estradiol in Aqueous Solution

The aqueous solubility of estradiol is extremely low and could be improved by addition of a water-miscible hydrophilic polymer like polyethylene glycol (PEG) 400 to an aqueous solution as a solubilizer for estradiol (18). In this study, the PG was used for the first time as a solubilizer and was added to the saline solution to increase the solubility of estradiol in the dissolution medium. Different ratios of PG to estradiol were studied. It was observed that the aqueous solubility of estradiol increases logarithmically with increasing volume fraction of PG in normal saline (Fig. 2).

17β-Estradiol Release from Transdermal Delivery System Adhesive Patch

The release rate of estradiol across the mesh from various unilaminate TDS adhesive formulations contain-

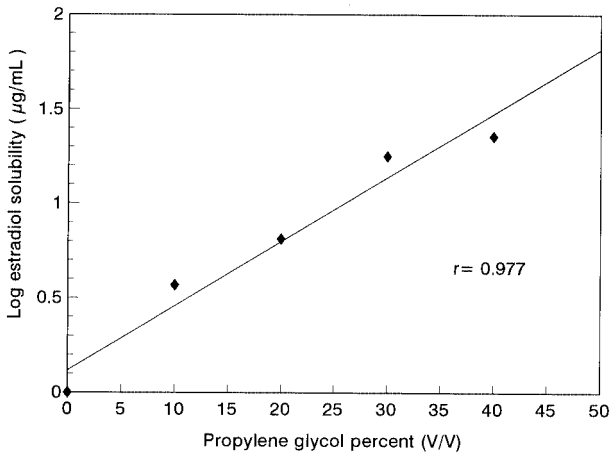

Figure 2. Effect of propylene glycol (PG) volume fraction on the aqueous solubility of 17β-estradiol.

ing Eudragits E100, RLPO, and RSPO (in the ratios of 4:1:2, 4:2:2, 4:1:3, 4:1:3.1, 4:2:3, and 3.8:2:3.5 for 24 h, 36 h, 96 h, 104 h, 168 h, and 216 h, respectively) as release-controlling and adhesive polymers, as well as TEC as a plasticizer, were observed to follow zero-order release kinetics ($r > 0.98$) over 24 h, 36 h, 96 h, 104 h, 168 h, and 216 h (Fig. 3). The release data were obtained by plotting the amount of estradiol released per square centimeter against time. These data clearly demonstrate that an increasing amount of methacrylate ester copolymers (Eudragits RLPO and RSPO) in prepared formulations decreased the release of estradiol from the unilaminate patch. These polymers are neutral polymers that are insoluble in the entire physiological pH range. However, they possess a defined swelling capacity and permeability with respect to water and dissolved drugs that is independent of pH (19). The predominant mechanism of drug release from these polymers is believed to be diffusion (20). In addition to diffusion, however, osmotic and convective forces are believed to play a critical role in the rate and the extent of drug release (21). Therefore, the amount of drug released per unit of time is a composite function of drug solubility in the receiver medium and the osmotic activity of the components of the patch.

The effect of ATBC as a plasticizer on the release profile of estradiol from a TDS adhesive patch was studied and compared to the release pattern of this drug from a TDS formulation containing TEC as the plasticizer (Fig. 4). The release of drug from a 216-h estradiol formulation containing ATBC was not significantly different from the release pattern of estradiol from a 216-h formulation containing TEC ($P < .05$). These results clearly demonstrate that the effect of different plasticizers on the release behavior of estradiol from TDS formulations prepared by acrylic resins is almost identical. A comparison of the estradiol release profile from a 168-h formulation containing TEC (as a plasticizer) with an available brand sample is depicted in Fig. 5. Although the release pattern of drug from the brand sample obeyed zero-order release kinetics, the amount released was not identical with the release profile of the 168-h fabricated sample.

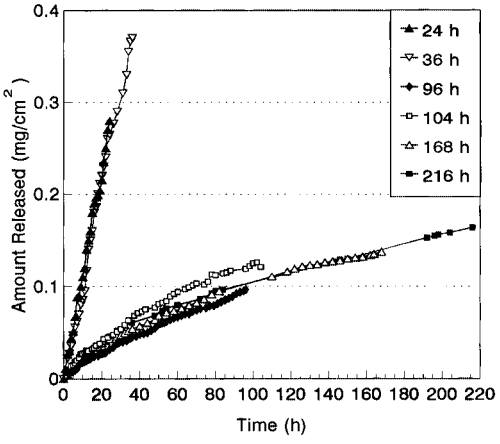

Figure 3. Drug release profile of estradiol from 24-h, 36-h, 96-h, 104-h, 168-h, and 216-h unilaminate adhesive patches using acrylic resins as controlling polymers and TEC as a plasticizer ($N = 3$); standard deviation $< 10\%$.

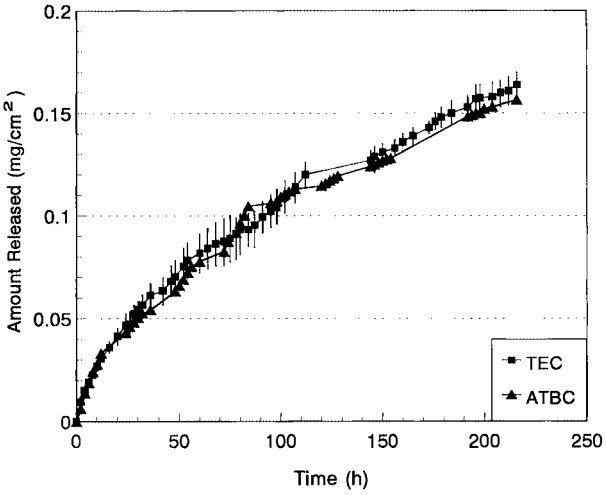

Figure 4. Comparative release profiles of estradiol from 216-h TDS patches consisting of acrylic resins as controlling polymers and TEC and ATBC as plasticizers ($N = 3$).

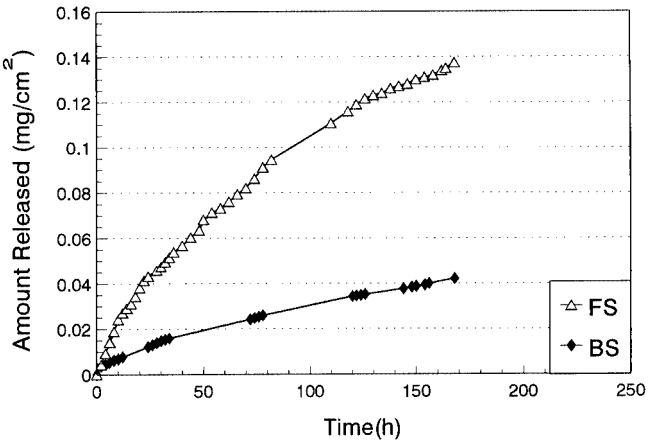

Figure 5. Comparative release profiles of estradiol from 168-h TDS fabricated sample (FS) and one available brand sample (BS) ($N = 3$).

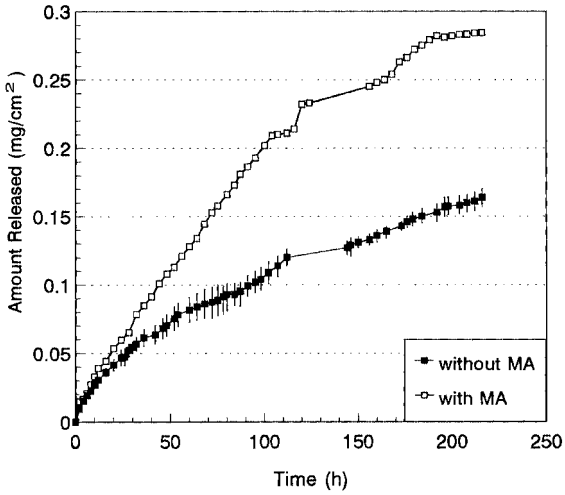

Figure 7. Effect of myristic acid (MA) as a release modifier on estradiol release profile from 216-h TDS patch using TEC as a plasticizer ($N = 3$).

Effect of Release Modifiers on the Release Behavior of Estradiol from Transdermal Delivery Systems

The effects of PG and MA as release modifiers on the release behavior of estradiol from a 216-h TDS patch containing TEC as the plasticizer are depicted in Figs. 6 and 7. A comparison of PG and MA effects on the release behavior of estradiol from a 216-h TDS patch is given in Fig. 8. It has been observed that the release of estradiol from a 216-h TDS patch (Fig. 6) was significantly increased ($P < .05$) when PG was used in this formulation as the release modifier. The effect of PG content on in vitro release behaviors of two topical steroids from a Carbopol 934 gel formulation containing PG was reported by Poulsen et al. (22). This work showed the action of PG as a cosolvent. Extrapolating from our results, it is assumed that the major effect of PG arises from a solvent drag effect for estradiol. Furthermore, the release of estradiol from a TDS adhesive patch containing MA (Fig. 7)

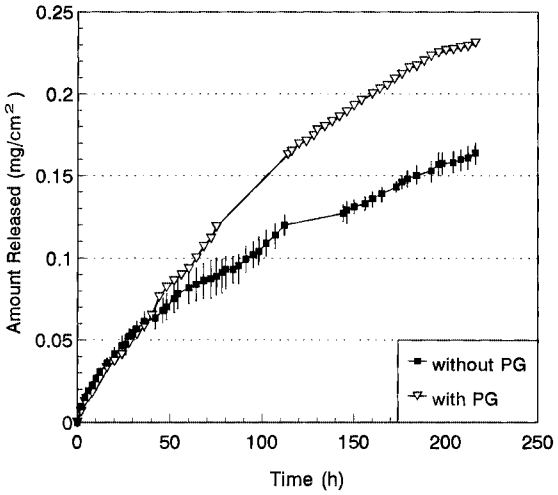

Figure 6. Effect of propylene glycol (PG) as release modifier on estradiol release profile from 216-h TDS device using TEC as a plasticizer ($N = 3$).

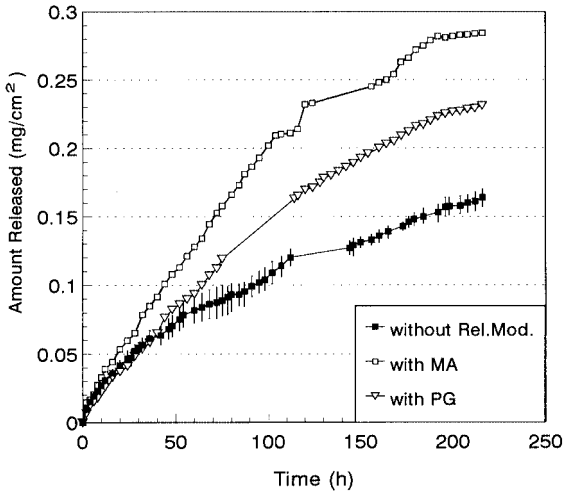

Figure 8. Comparative release profiles of estradiol from 216-h TDS devices consisting of propylene glycol (PG) and myristic acid (MA) as release modifiers (Rel. Mod.) ($N = 3$).

as the release modifier was tremendously increased. Fatty acids were most effective as enhancers when PG was used as the vehicle (23,24). The large increment in estradiol release from the 216-h TDS adhesive patch formulation containing MA in comparison with the formulation containing PG could be due to the presence of PG in the receptor solution, which increased the effectiveness of MA as the release modifier.

CONCLUSIONS

These data clearly demonstrated that the acrylic resins are suitable polymers for the preparation of estradiol TDS adhesive devices. No significant difference between release patterns of the drug from TDS formulations containing TEC and ATBC (as plasticizers) was observed.

Furthermore, the use of PG increased the release amount of this drug from TDS patches in receptor solution. It also is concluded that the use of MA and PG as release modifiers exhibited a pronounced and significant effect on the release behavior of estradiol from the TDS.

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