Original article

TRANSDERMAL DELIVERY OF SOTALOL:  
IN VITRO AND EX VIVO STUDIES

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Abstract

The purpose of this study is to investigate in vitro release and ex vivo transdermal penetration of sotalol from monolithic films prepared by Eudragit E100 (E100) combined with Eudragit RS100 (RS100) or ethyl cellulose (EC) prepared onto a PVA backing membrane by solvent casting method. Film properties were evaluated by means of uniformity of the films, which was evidenced by the low standard deviations of thickness and drug amount studies as well as high sotalol contents. In vitro and ex vivo release studies were carried out by vertical Franz diffusion cells. Ex vivo skin penetration of drug was modified by either dimethyl sulphoxide (DMSO) or iontophoresis. Obtained results showed that films containing RS100 polymer gave higher degrees of swelling accompanied with higher in vitro release rates of drug that could attributed to the higher permeability of this polymer. In vitro release of drug from the films was found slower with E100 and EC combination, which best fitted to the Higuchi as well as Korsmeyer-Peppas kinetics. The skin penetration of sotalol from this film with application of 0.5 mA/cm² direct current for three hours was found two fold higher than pre-treatment for two hours of 5 % w/w DMSO in ethanol and best fitted to Higuchi kinetic.

Key words: Transdermal penetration, Sotalol, Eudragit, Iontophoresis, Dimethyl sulphoxide.

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Transdermal Yolla Sotalol Verilisi: In Vitro ve Ex Vivo Çalışmalar

Bu çalışmanın amacı Eudragit E100 (E100) ile Eudragit RS100 (RS100) veya etil selüloz (ES) kombine edilerek PVA sırt materyali üzerinde çözücü uçurma yöntemiyle hazırlanan tek tabakalı filmlerden sotalol in vitro salınımın ve ex vivo transdermal penetrasyonunun incelenmesidir. Film özelliklerini filmlerin homojenliği ile değerlendirmiştir, kalınlıklar ve etkin madde miktar tayin sonuçlarına ait standart sapma değerlerinin küçük ve miktar tayin sonuçlarının yüksek olduğu ile kantlanmıştır. In vitro ve ex vivo salın çalışmalarını dikey Franz hücreleri ile yapılmıştır. Etkin maddenin deriden penetrasyonunu dimetil sülfoksit (DMSO) veya iyontoforez ile modifiye edilmişdir. Edil aded sonucu, RS 100 polimeri içeren filmlerin daha yüksek şişme değerlerini ile birlikte bu polimerin daha yüksek geçirgenliğe sahip olması bağımlılıği daha hızlı salın verdiğini göstermiştir. E100 ve EC kombinasyonu ile filmlerden in vitro etkin madde salınımı yavaşlamış, Higuchi ve olduğu gibi Korsmeyer-Peppas kinetikine de yüksek uyumu bulmuştur. Bu filmden üç saatlik 0.5 mA/cm² doğrudan akım uygulamasını ile sotalolun deriden penetrasyonu 5 % a/a etanol içindeki DMSO’nun iki saatlik ön uygulamasına göre iki kat artış ve en iyi Higuchi kinetikine uyumu bulunmuştur.

Anahtar kelimeler: Transdermal penetrasyon, Sotalol, Eudragit, Iyonoforez, Dimetil sülfoksit.
INTRODUCTION

Transdermal delivery is an appealing method of introducing therapeutic agents that allows medication to bypass the gastrointestinal system (GIS). This reduces degradation by acid and proteolytic enzymes in the gastric environment, as well hepatic first-pass elimination and incomplete absorption due to gastrointestinal motility disorders (1,2). Transdermal patches are innovative drug delivery systems used for achieving systemic effect via transdermal route and increasing the fraction absorbed for therapeutic agents sensitive to GIS and hepatic elimination. This may be accompanied by reduced dosing frequency required for a chronic treatment that also provides steady-state drug levels and improves patient compliance because of its extended duration (3).

Especially, monolithic transdermal systems are favourable due to their ease of fabrication and lack of dose dumping (4-6). Several authors have reported the use of polymethacrylate kind of polymers (Eudragit) in matrix formulations for monolithic transdermal systems due to their high capacity for incorporating drugs and skin toleration (7-11). Eudragit polymers are nontoxic, non-absorbable and they do not lose their film forming properties when formulated with drugs and excipients (11). EC polymers are water-insoluble and can be used to modify the release of drugs in different dosage forms such as microspheres, tablets or transdermal films (11-13). Varying types and ratios of Eudragit polymers and EC polymer in the composition of films can provide modified release for therapeutic agents (8, 11).

In spite of several advantages offered by transdermal route, only a few drug molecules are administered transdermally because of the poor transport of others through the formidable barrier nature of stratum corneum. Two major approaches to increase transdermal permeation rate include physical techniques (iontophoresis, electroporation, sonophoresis, and microneedles) and use of chemical penetration enhancers such as solvents, surfactants, fatty acids, and terpenes. The use of chemical penetration enhancers decrease the integrity of skin barrier while the use of physical techniques such as iontophoresis increased the skin permeability from annexial pathways by applying a low-density electrical current (from 0.1 to 0.5 mA/cm²) that also utilized in extended delivery of drugs from transdermal patches. (3, 14, 15).

Sotalol is a non-selective beta-adrenergic receptor blocking agent with additional class III properties used for supraventricular and ventricular arrhythmias in adults and children. Medication with sotalol via oral route can probably cause proarrhythmic effects because of inadequate dosing and caused most important side effect namely torsades de pointes, especially seen for pediatric patients (16). As an alternative to oral route, transdermal delivery could provide reduced side effects and an adequate dosing of sotalol in a sustained manner rather than oral delivery (4, 7, 8).

The aim of this study is to investigate the in vitro-ex vivo release of sotalol from Eudragit based monolithic films which can be transdermally used and modified either by chemical (DMSO) or physical (iontophoresis) penetration enhancement methods.

EXPERIMENTAL

Materials

Sotalol (Adeka Drug Comp. Samsun/Turkey), Eudragit (E100 and RS100) polymers (Evonik Röhm GmbH, Darmstadt/Germany), ethyl cellulose 14cP (BDH), dibutyl sebacate (DBS) (Sigma), polyvinyl alcohol M_w 72000 (PVA) (Sigma), HEPES (Fluka), ketamine hydrochloride (Ketalar®, Pfizer, Turkey), cellulose acetate membrane (0.22 μm, Sartorius) were used in the study.
Preparation of the films
Films were prepared by solvent casting method with methanol:acetone (1:1, v/v) in glass moulds 22.89 cm$^2$ in area. The inside of the glass moulds were covered with 0.095 mm PVA as backing membrane by casting from 5 % w/w aqueous solution of PVA at 70 °C. Sotalol (3 % w/w of dry polymer weight) was dissolved in methanol and then polymer(s) and DBS (20 % w/w of dry polymer weight) were added to the beaker. The mixture was dissolved with acetone by stirring for 60 min at 500 rpm. Film solution was poured onto a PVA covered glass mould. The film solution cast on PVA membrane by evaporating at 50 % relative humidity and 25 °C conditions for 5 days before the experiments (6, 17). The drug amount in films was calculated according to the area of glass moulds. The contents of films were given in Table 1. Each formulation prepared as three parallels (batches).

Investigation of film properties
As a first stage, preparation method was validated by standardization of thickness and amount of drug homogeneity in the films, which were given in Table 2. These studies were carried out on three batches for each formulation and repeated three times from each batch. All experiments (thickness, swelling and \textit{in vitro} release) were performed by nine parallels for each formulation. Drug and excipient free films were set off from the method given in Röhm Pharma Catalogue (18) and were predicted as 0.300 mm in thickness. Sotalol contents of films were calculated as 0.9 mg/cm$^2$ theoretically.

Thicknesses and drug amounts of the films
Thickness of the films was determined by using a micrometer (NSK, Japan) on three batches. Three discs for each batch (n=9) were cut from different sides of the glass mould with a circular metallic die of 1.1 cm in diameter (17) and the thicknesses were given as mm ± SD in Table 2. In order to determine drug amounts and drug uniformity in the glass moulds, sotalol was quantitated from these discs by using spectrophotometer at 229 nm (Shimadzu 1404, Japan) after shaking continuously for 48 hours in 25 ml of HEPES buffer (pH 7.4) and then ultrasonicating for 1 hour (8). Sotalol content of films was calculated as mg/cm$^2$ ± SD for each disc (Table 2).

Swelling studies
Swelling studies were carried out by drying the pieces of 1 cm$^2$ film in an oven at 50°C for 24 h and dried film was accurately weighed and subsequently immersed in a flask containing dissolution media (HEPES buffer, pH 7.4) at 37± 0.5°C. The swollen sample was withdrawn from the medium at the end of 1, 8 and 24 hours. Sample was weighed subsequently to removal of excess surface water with a filter paper. The percentage swelling, I$_s$ (%), was calculated as follows;

\[ I_s \(\%\) = \frac{(W_s - W_d)}{(W_d)} \times 100 \]

Where $W_d$ is weight of dried polymer film and $W_s$ denotes the weight after swelling (17, 19). Change in thickness (%) was also evaluated in same manner in order to explain swelling phenomenon. The results were given in Table 2 and Fig.1.

\textit{In vitro} release studies
\textit{In vitro} drug release studies were carried out in the jacketed vertical Franz diffusion cells with a surface area of 2.2 cm$^2$ and a receptor compartment capacity of 20 mL. Discs containing 0.9 mg sotalol were cut from formulated films and settled between the chambers of diffusion.
cells on a 0.22 μm cellulose acetate membrane as a donor phase. Then they were wetted with 0.1 mL of 100 mM, pH 7.4 HEPES buffer in order to ensure the humidity (20). The whole assembly was continuously stirred at 500 rpm and the temperature was maintained at 37± 0.5°C. The amount of sotalol released to the receptor compartment was determined by collecting 0.5 mL samples during 8 hours (0.5, 1.5, 2, 3, 4, 5, 6, 7 and 8 h) and receptor phase was replenished by adding 0.5 mL of buffer. Collected samples were filtered and analyzed spectrophotometrically (Shimadzu 1404, Japan) (21) at 229 nm. Drug release profiles and drug amounts obtained from monolithic films were given in Fig.2 and Fig.3 respectively. The release kinetics were evaluated by GraphPad Instat 3.0 programme and the results are given in Table 3.

Analytical validation of spectrophotometric analysis for quantitation of sotalol in HEPES buffer was done by performing linearity and range, precision, accuracy and specificity according to ICH Guidelines Q2R1 (22). Accuracy with the existence of minor components was found as 97.6 % with RSD of 1.7 %. Also indicated specificity and intermediate precision was obtained (P>0.05). Besides, low value for standard error of slope (0.039 ± 0.0003) and good correlation coefficient value (r²=0.9999) established the linearity of the method in concentration range of 1-28 μg/mL with a LOQ value of 0.115 μg/ml.

Ex vivo release studies

All animal care, procedures and studies were carried out in accordance with current guidelines for investigations and the experiments in animals were approved by the Animal Welfare and Ethics Committee of the University of Ankara. Adult male Wistar rats weighing 250-275 g were anesthetized by using 100 mg/kg ketamine hydrochloride intraperitoneally. The hair of test animals was carefully removed by using a hair clipper and the full thickness skin was removed from the abdominal region by a dissection scissor. Subsequent to subcutaneous fat was removed; skin pieces were washed with isopropyl alcohol and serum physiologic respectively. The skin pieces were covered with aluminium foils and stored in -20 °C for two weeks (23).

The ex vivo skin permeation studies from selected film (F3) was modified by either iontophoresis or DMSO were carried out using Franz diffusion cells with a diffusional area of 2.27 cm². Rat abdominal skin was mounted between the compartments of the diffusion cell with stratum corneum facing the donor compartment and it was waited for 1 hour before the experiments. Later on, the films (2.27 cm²) were placed onto these membranes as donor phase and wetted with 1mL of 100 mM, HEPES buffer pH 7.4 (20). The receptor phase volume of 20 mL HEPES buffer pH 7.4 was stirred at 500 rpm with a magnetic stirrer. The stratum corneum side of the skin was kept in intimate contact with the film and over it placed a backing membrane. The whole assembly was kept in a water bath at 37 ± 0.5°C. Samples (0.5 mL) were collected at predetermined time points and replaced with fresh buffer. The concentration of drug was determined by spectrophotometricaly (Shimadzu 1404, Japan) (21) at 229 nm. Blank was consisting of drug free solution that was kept in the receptor compartment for 1 hour before the experiments. Spectrophotometrical analysis was validated before the experiments, as given in section 2.3. Specificity of the method was studied with the existence of polymers and chemical enhancer used in the study.

In order to show the effect of iontophoresis on sotalol release, direct current density of 0.5 mA/cm² was applied on film continuously for 3 hours in comparison with control group. Ag/AgCl electrodes attached to a constant current source were placed to vertical Franz-type cells in order to ensure the current. HEPES buffer (100 mM, pH 7.4) was used as medium and no extraneous ions were used with the buffer.

In order to investigate the effect of chemical enhancer, alcoholic solution of DMSO (5 % w/w, 600 μl) was pre-treated for two hours onto abdominal skin pieces after fixing between the
compartments. Afterwards the treatment region was washed five times with HEPES buffer and film was placed onto the skin (24).

Amount of sotalol penetrated from rat abdominal skin was studied on F3 film and the results were given in Fig. 4, Fig. 5 and Fig. 6.

RESULTS AND DISCUSSION

Each individual film formulation given in Table 1 was evaluated for their thickness, drug homogeneity and swelling characteristics are presented in Table 2.

Table 1. Contents of film the formulations given in mg.

<table>
<thead>
<tr>
<th>Codes</th>
<th>Sotalol</th>
<th>E100</th>
<th>RS100</th>
<th>EC</th>
<th>DBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>20.6</td>
<td>686</td>
<td>-</td>
<td>-</td>
<td>140</td>
</tr>
<tr>
<td>F2</td>
<td>20.6</td>
<td>343</td>
<td>343</td>
<td>-</td>
<td>140</td>
</tr>
<tr>
<td>F3</td>
<td>20.6</td>
<td>343</td>
<td>-</td>
<td>343</td>
<td>140</td>
</tr>
</tbody>
</table>

Film properties were evaluated by means of thickness, drug content and swelling percentage of the polymeric films. When the thickness of individual films was compared, variation was observed among the films, which took its source from the raw materials; mainly from the polymers (Table 2). However, the essential point of these results was the low standard deviation (SD) values, which was interpreted as the reproducibility of the preparation method for each individual film formulation.

Table 2. Characterization of the films.

<table>
<thead>
<tr>
<th>Film code</th>
<th><em>a</em> Thickness (mm) ± SD</th>
<th><em>a</em> Drug content (mg/cm²) ± SD</th>
<th><em>b</em> Change in thickness % ± RSD</th>
<th><em>b</em> Percentage Swelling Is % ± RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.377 ± 0.021</td>
<td>0.880 ± 0.041</td>
<td>7.33 ± 0.29</td>
<td>17.21 ± 3.69</td>
</tr>
<tr>
<td>F2</td>
<td>0.324 ± 0.013</td>
<td>0.797 ± 0.110</td>
<td>18.0 ± 4.28</td>
<td>33.25 ± 1.24</td>
</tr>
<tr>
<td>F3</td>
<td>0.313 ± 0.015</td>
<td>0.889 ± 0.051</td>
<td>18.8 ± 2.71</td>
<td>18.33 ± 2.49</td>
</tr>
</tbody>
</table>

*a* n=9,  
*b* n=3, for uniformity in thickness and drug contents 3 different discs were studied from each batch and 3 batches were investigated for each formulation.

When the uniformity of drug amounts in films was evaluated, generally, high drug amounts were determined with low SD values (Table 2). Difference between drug content of the films could be attributed to the batch difference explained by separate preparation, also reported by Siepmann et al. (25).

Investigated main polymer E 100 has cationic property while combining polymers RS100 and EC have zwitter ionic or non-ionic properties respectively in their nature. All these polymers have different swelling properties related with type and amount of their functional groups (26). In our study, 1:1 combination of RS100 with E100 in the films (F2) caused high swelling degrees of approximately two folds compared to E100 containing films (F1), while 1:1 combination of EC with E100 in films (F3) resulted as a negligible swelling compared to films...
containing RS100 (Table 2, Fig. 1). Higher swelling degrees of F2 could be attributed to the quaternary ammonium groups (QAGs) of RS100 increased water permeability and thus swelling capacity of the film. Lack of QAGs in EC resulted as a poor swelling capacity of F3 film (11,26). According to Yasuda’s “free volume theory”, a higher degree of swelling of membrane would result in longer free volume available for diffusion of water soluble drug and thus higher permeability and also higher release of drug could be obtained in consequence (27). When the release of sotalol was evaluated by means of combined polymers in films, it was observed that in vitro drug release from the film including RS100 polymer (F2) was higher than the film containing EC (F3) because of the existence of QAGs (Fig. 2 and Fig. 3). The QAGs of polymers had effect on swelling of film and release of cationic sotalol which was determined as higher swelling degrees and release of drug. This could be attributed to repulsive forces between the cationic or zwitter ionic polymers and cationic sotalol (27).

Drug release kinetics was evaluated by Higuchi and Korsmeyer-Peppas kinetic models. As shown in Table 3, closer values of determination coefficient ($r^2$) and residual mean squares (RMS) were obtained from F1, F2 and F3 films for both kinetic models. The $n$ values calculated from the Korsmayer Peppas kinetic indicated that the amount of drug released by Fickian diffusion ($n<0.500$) predominated from the films. The results obtained of Fickian mechanism and Higuchi equation indicates the similar transport of drug (7, 8, 28).

### Table 3. Kinetic evaluation of drug release from F1, F2 and F3 films.

<table>
<thead>
<tr>
<th>Kinetic Parameter</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higuchi $r^2$</td>
<td>0.9424</td>
<td>0.9795</td>
<td>0.9899</td>
</tr>
<tr>
<td>$k_{H}$</td>
<td>0.9008</td>
<td>0.9809</td>
<td>0.4055</td>
</tr>
<tr>
<td>RMS</td>
<td>1.844</td>
<td>0.5559</td>
<td>0.0460</td>
</tr>
<tr>
<td>Korsmeyer-Peppas $r^2$</td>
<td>0.9443</td>
<td>0.9510</td>
<td>0.9911</td>
</tr>
<tr>
<td>$n$</td>
<td>0.4320</td>
<td>0.2992</td>
<td>0.3598</td>
</tr>
<tr>
<td>RMS</td>
<td>0.0021</td>
<td>0.0005</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

$r^2$ indicates determination coefficient; $k_H$ is kinetic constant; $n$ is diffusional exponent indicative of the mechanism of drug release; RMS is residual mean squares.
Figure 2. *In vitro* drug release profiles of F1, F2 and F3 films.

Between the films, F3 containing E100 and EC gave the slowest release of drug and it was selected for investigation of the effects of DMSO as chemical penetration enhancer and iontophoresis as physical technique on the release of drug with *ex vivo* studies. Compared with control group, DMSO caused a similar drug penetration profile during 5 h, however following amount was increased at the end of 6 h. Application of direct current (0.5 mA/cm²) for 3 h, significantly increased the penetration amount of drug compared to control group as presented in Fig. 4. Cumulative amount of drug penetrated from rat skin because of either DMSO or direct current is presented in Fig. 5.
Due to hydrophilic and positive charge properties, permeation of sotalol across the skin is expected to be poor. As skin has a negative charge on physiological pH, it is permselective and behaves like a negatively charged membrane (29). In that point of view cationic drug sotalol could easily be transported from skin with the help of anodal iontophoresis or chemical enhancers. Studies have shown that iontophoresis, at current densities greater than 0.3 mA/cm² can electroporate the skin to a certain degree. Iontophoresis was reported to cause the formation of transient aqueous pores by electroporating the skin, and that these pores constituted a significant transport route during iontophoresis (30). On the other hand, DMSO an aprotic solvent can denature proteins and change the intercellular keratin confirmation. DMSO can also interact with the intercellular lipid domains of human stratum corneum. Furthermore, DMSO within skin membranes may facilitate drug partitioning from the formulation to the tissues (31). Although DMSO is an excellent accelerator, it creates problems. The effects of enhancers are dependent on the concentration and generally co-solvent like alcohol is needed for optimum efficacy. However, at high concentrations DMSO can cause erythema and may denature proteins (31).

It was obtained that application of a 0.5 mA/cm² direct electric current for 3 h resulted in approximately 2 fold increase in the amount of drug penetrated from the skin (from 169.07 mcg to 315.08 mcg) and this was found more effective than the 2 h pre-treatment of 5% w/w DMSO in ethanol (Fig. 4, Fig. 5) as it was expected. At the end of the study, the amount of drug retained in the skin was extracted by shaking the skin during 24 h with 20 ml HEPES buffer pH 7.4 (24). The results showed that, the amount of drug retained in the skin was highest with DMSO as it was expected (Fig. 6). The differences in the penetration enhancement mechanisms of these two methods could be interpreted as the reason of this difference in obtained amounts, which could be attributed to lipid pool forming effect of DMSO in the skin that resulted as a lag time of drug transport due to accumulation of drug in mentioned pools.

Figure 4. Amount of sotalol penetrated through rat skin, following release from F3 film (n=3).
Figure 5. Cumulative amount of sotatol (mcg/cm$^2$) penetrated from rat skin at the end of 6 h (n=3).

Table 4. Kinetic data for the release of sotalol from F3 film ex vivo through rat skin.

<table>
<thead>
<tr>
<th>Kinetic Parameter</th>
<th>Control group</th>
<th>DMSO pretreatment</th>
<th>Iontophoresis application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higuchi</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$r^2$</td>
<td>0.9166</td>
<td>0.9441</td>
<td>0.9934</td>
</tr>
<tr>
<td>$k_{H}$</td>
<td>1.119</td>
<td>1.448</td>
<td>1.978</td>
</tr>
<tr>
<td>RMS</td>
<td>1.312</td>
<td>1.015</td>
<td>0.6759</td>
</tr>
<tr>
<td>Korsmeyer-Peppas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$r^2$</td>
<td>0.8618</td>
<td>0.9254</td>
<td>0.9919</td>
</tr>
<tr>
<td>$n$</td>
<td>0.7096</td>
<td>0.8662</td>
<td>0.5591</td>
</tr>
<tr>
<td>RMS</td>
<td>0.8650</td>
<td>0.5006</td>
<td>0.0438</td>
</tr>
</tbody>
</table>

Figure 6. Amount of sotatol determined (mcg) in film, skin and receptor phase at the end of 8 h.
Release kinetics showed that the release of sotalol from F3 film through Wistar rat skin was best fitted to Higuchi release kinetics with $r^2$ of 0.9166, 0.9441 and 0.9934, for control group, DMSO pre-treatment and iontophoresis application respectively (Table 4). However closer $r^2$ of 0.9919 was obtained for Korsmeyer-Peppas kinetic model from iontophoresis application and obtained $n=0.5591$ value indicated that drug release by non-Fickian mechanism was predominated (0.5<n<1.00) defining a drug transport with a combination of drug diffusion and polymer relaxation proces (28).

CONCLUSION

Sustained release transdermal films of sotalol were prepared by using solvent casting method in laboratory scale. Eudragit type polymers were chosen because of their ease of handling and manufacture process. It is observed that type of polymer and drug by means of containing a functional group as if QAGs have a great influence on the release of drug from Eudragit based monolithic films. Sotalol release from Eudragit films mostly fitted to Higuchi kinetic model. Films formulated with E100:EC gave more uniform release profile, thus ex vivo studies on rat skin was done on it and results showed that sotalol release could effectively be modified by using transdermal iontophoresis.

ACKNOWLEDGEMENT

The authors wish to thank ADEKA, Samsun-Turkey and Karadeniz Pharmaceutical Warehouse, Samsun-Turkey for their kind contributions.

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Received: 10.09.2009
Accepted: 08.10.2009