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Research paper

Novel transdermal delivery of Timolol maleate using sugar esters: Preclinical and clinical studies

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ABSTRACT

The feasibility of matrix controlled transdermal patch based on sugar fatty acid ester (SE) as penetration and absorption enhancer containing Timolol maleate (TM) was investigated. The influence of fatty acid type, chain length and hydrophile–lipophile balance (HLB) on the in vitro drug release as well as its permeation across hairless rat skin were studied and compared aiming to select a patch formula for clinical performance. Skin irritation induced by SE patch was evaluated by visual scoring, color reflectance measurements and non-invasive transepidermal water loss (TEWL) technique. The results indicated that among different SEs tried, laurate SE with shorter fatty acid chain length and higher HLB value significantly increased the amount of TM liberated from the patch (99 ± 2.1%) and its permeation across rat skin (86 ± 4.3%). The total drug permeation and flux values were approximately 5-fold greater compared to SE free patch. The extent of absorption of TM–SE patch expressed by AUC was 64% larger as compared to the oral solution with steady plasma concentration over 18 h and relative bioavailability (F_{rel}) of 163%. The developed patch was well tolerated by all the subjects with only moderate skin irritation, which was recovered in 24 h after patch removal. The results are very encouraging and offer an alternative approach to maintain higher, prolonged and controlled blood level profile of the drug over 18–24 h.

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1. Introduction

Sugar esters (SEs) are non-ionic surfactants having a sugar substituent, sucrose, as the polar head group and fatty acids as non-polar groups. Properties of their hydrophilic and lipophilic balance (HLB) can be adjusted by varying fatty acid chain length (lauric, myristic, stearic, and oleic acid). They have HLB values from 1 to 16 depending on the type of fatty acid and the degree of esterification. Sucrose-based surfactants offer an attractive alternative to the generally more convenient ethylene oxide based non-ionic surfactant due to their low toxicity, biocompatibility, excellent biodegradability [1] and less dermatological damage [2]. The interest in using sugar ester in many areas is increased including pharmaceutical technology as emulsifiers, solubilizing agents, lubricants, penetrating enhancers and pore forming agents [1,3–8]. They can be applied in cosmetical applications [9] and as food additives as well [10].

Timolol maleate (TM) as a model drug (mol.wt. 332, log*p* 1.91, pK_a 9.2) is a non-selective beta-adrenergic blocking agent without membrane stabilizing or intrinsic sympathomimetic activities. TM is used in the management of hypertension, angina pectoris, myocardial infraction and glaucoma.

The main limitation of therapeutic effectiveness of TM is its short biological half-life, higher frequency of drug dosing, extensive first pass metabolism and poor bioavailability by oral route. It is rapidly absorbed from gastrointestinal tract with peak plasma concentration after 1–2 h., and metabolized up to 80% in liver with a half-life of 3–4 h. [11], thus necessitating frequent administration of larger doses (40–60 mg) daily to maintain therapeutic drug level. Therefore, the transdermal route is a better alternative to avoid hepatic first pass metabolism and to achieve constant plasma level over an extended period of time, which additionally warrants less frequent dose regime. Among different transdermal techniques investigated, iontophoretic delivery which is commonly used for the administration of ionic drugs through skin by the application of an electric current was extensively studied [12–16]. In the current work, a new transdermal matrix controlled strategy was adopted, in which TM and SEs as permeation and absorption enhancer were incorporated in a water insoluble but permeable polymer matrix without controlling the membrane. The TM liberation was controlled by diffusion through the matrix as the polymer cannot dissolve in the skin wrap. An example for an advanced transdermal system which is already on the market is Transtec® (35, 52.5 and 70 μg/h) transdermal patch containing 20, 30 and 40 mg buprenorphine incorporated into a polymer matrix which is able to control the drug delivery rate and produce stable plasma concentrations over a period of 96 h for the treatment of intermediate to severe pain [17].

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Thus, this study was designed to evaluate the suitability of different sugar fatty acid esters as permeation and absorption enhancer for transdermal matrix control delivery of TM. The influence of HLB of different SEs and their fatty acid type on the in vitro drug release and its permeation across hairless rat skin were also investigated. Skin irritation induced by SE patch was evaluated by visual scoring, color reflectance measurements and non-invasive transepidermal water loss (TEWL) technique. The second objective of this work was to select the best formulation for clinical study where in vivo TM plasma levels were measured after SE patch application.

2. Materials and methods

2.1. Materials

Timolol maleate was kindly provided by Epico Drug Company, Cairo, Egypt. Methacrylate ester copolymer (Eudragit® NE 30D) was purchased from Röhm Pharma GmbH, Germany. Different grades of sucrose esters; sucrose stearate S-1670 (HLB = 16), S-970 (HLB = 9), S-370 (HLB = 3), sucrose palmitate P-1670 (HLB = 15), sucrose myristate, M-1695 (HLB = 16), sucrose laurate L-1695 (HLB = 16) were purchased from Mitsubishi-Kagaku Foods Corporation, Japan. Disodium hydrogen phosphate and potassium dihydrogen phosphate were obtained from E. Merck, Darmstadt, Germany. All other reagents were of analytical reagent grade and were obtained from EL-Nasr Company, Cairo, Egypt.

2.2. Methods

2.2.1. Preparation of matrix controlled patches

TM matrix controlled patches were prepared using different SEs. Thirty micrograms of TM was dissolved in 5.0 ml distilled water. One hundred and fifty micrograms of different SEs was added and continuously mixed using magnetic stirrer (OFI Testing Equipment, Inc., model 152-45, Texas, USA) for 30 min at room temperature. Five percent of w/w aqueous polymeric dispersion (5.0 ml) diluted from Eudragit® NE 30D was added to the previous solution and the resulting dispersion was poured into a non-stick round container with a standard diameter of 55 mm to produce a thickness of about 0.15 ± 0.02 mm. Samples were dried at 25 °C, 50% RH for 48 h. Six patches, P1–P6, were prepared using L-1695, M-1695, P-1670, S-370, S-970 and S-1670, respectively. Drug-free patches (Pc_1) as well as SEs-free ones (Pc_2) were prepared as described above except that no drug or SEs were added, respectively, as control patches for comparative purposes in the release and skin permeation studies.

2.2.2. Dissolution studies

A USP dissolution tester (Hanson SR6, California, USA) was used to attain the dissolution profiles of TM-SEs different patches. The paddle over disk method was performed according to USP 29 apparatus 5. Five hundred milliliters of phosphate buffer (pH 5.5) was used as the dissolution medium. The release study was carried out at 32 ± 0.1 °C and the paddle rotation speed was adjusted to 50 rpm. Five milliliter samples were withdrawn periodically at predetermined time intervals of 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, and 5 h. Every withdrawal was followed by replacement with fresh medium to maintain a constant volume. The samples were analyzed spectrophotometrically (Shimadzu UV-1601 PC Double Beam, Kyoto, Japan) at 295 nm against the samples withdrawn at respective time interval from drug-free patches treated in a similar manner. The method was validated, the accuracy, repeatability (intra day and intermediate precision (inter day) and reliability were ensured. The recovery % was >98%. The dilution of the release medium due to replenishment following each aliquot withdrawal was taken into account in the calculation of the amount of TM released from the patch. The results were the mean values of three runs. The obtained release data were subjected to kinetic treatment according to zero, first and Higuchi diffusion models [18]. The correlation coefficient (r) and the order of release pattern were determined in each case.

2.2.3. In vitro skin permeation studies

Newly born Wistar albino rats (National Research Center, Dokki, Giza, Egypt) weighing between 80 ± 20 g were sacrificed and the full thickness skin, free of bites and scratches were excised. The study performed in this section was approved by the University Protection for Animal Care and Use Committee and the protocol was compliant with the "Principles of Laboratory Animal Care" [NIH Publication # 85-23, revised 1985]. The dermal surface was carefully cleaned to remove subcutaneous tissues without damaging the epidermal surface. When not used immediately, the skin was kept refrigerated (2–5 °C) and was used within 3 days. A Franz diffusion cell was first filled with 5 ml of phosphate buffer, pH 7.4, and the skin with a surface area of 3.14 cm^2 was placed across the ground glass joint with the stratum corneum facing the donor compartment. TM patch was mounted over the skin membrane and the Franz cell clamped together. The temperature of the receptor compartment was maintained at 37 ± 0.5 °C with an external constant temperature circulator water bath and the receiver medium was continuously stirred with a small magnetic bar in order to prevent any boundary layer effects. Control experiments (without patch) were carried out simultaneously to ensure the non-interference of skin leaching. At predetermined time intervals, samples (0.5 ml) were taken from the receptor compartment and the cell was refilled with an equivalent amount of fresh buffer solution. The samples were analyzed by HPLC method mentioned by Kubota et al. [19] and are described in Section 2.2.4. Each permeation experiment was replicated three times and from the concentration of TM in the receiving solution the amount permeated through the skin membrane was calculated. The cumulative amount of TM permeated into the receptor compartment was plotted against time to obtain a percentage permeation profile. The steady state flux, J_{ss} (μg/cm^2/h) was calculated from the linear portion of the plot of the cumulative amount permeated vs. time and expressed as

$$J_{ss} = Q/t = K_p C_{donor}$$

where Q is the amount of TM permeated through membrane in (μg/cm^2) in experimental time t in (h), C_{donor} is the concentration of TM in the donor chamber in (μg/cm^3) and K_p in (cm h^{-1}) is the permeability coefficient of TM through the membrane [20].

2.2.4. HPLC analysis of TM

The concentrations of TM were determined by HPLC assay. The system consisted of a solvent delivery system comprised a pump 600 E multi, C-18 reverse-phase micro-particulate μBondapack column, particle size 10 μm, 25 cm × 4.6 mm (Waters Corp., Milford, MA, USA). The mobile phase was acetonitrile–water–triethylamine (18:81:1, v/v/v) adjusted to pH 3.0 with phosphoric acid. The flow rate was 2 ml/min. Effluents were monitored at 295 nm using UV detector (Waters Model 2487, Milford, MA, USA).

2.2.5. Measurement of transepidermal water loss (TEWL)

TEWL as non-invasive technique has been used in relation to the assessment of either the irritation [21–23] or the effect of penetration enhancers [24,25]. Four healthy volunteers without visible skin abnormalities participated (2 women aged 22, 25 years and 2 men aged 23–28 years). All gave an informed consent. They were not allowed to use soap, moisturizers or any other cosmetics and creams on the lower mid volar arms 48 h prior to and during the

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