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Transdermal Desmopressin as an Alternative Dosage Form for the Treatment of Nocturia

Laura Andrade Junqueira[a], Arnaud A. Bezerra Júnior[a], Paulo José Lopes Cândido[a], Hudson Caetano Polonini[b;c], Anderson Oliveira Ferreira[b], Nádia Rezende Barbosa Raposo[a*], Marcos A. Fernandes Brandão[a]
[a] Núcleo de Pesquisa e Inovação em Ciências da Saúde (NUPICS), Universidade Federal de Juiz de Fora (UFJF), Juiz de Fora, MG, Brazil.
[b] Ortofarma, Quality Control Laboratory, Matias Barbosa, MG, Brazil;
[c] BFFOX, Juiz de Fora-MG, Brazil.
* nadiacritt@gmail.com

***Abstract* — Nocturia is a condition that affects the lower urinary tract and has a multifactorial etiology. It impacts negatively the patient quality of sleep and life. Therapy with desmopressin is effective in this condition. However, the routes of administration commonly practiced, oral and intranasal, have low bioavailability. Thus, the transdermal route is an alternative that could enables greater bioavailability and adherence to treatment when compared to existing routes. The main objective of the present study was to evaluate the *ex vivo* permeation of a transdermal formulation containing desmopressin, using Pentravan® as the transdermal vehicle. An excised human skin model was used to predict the drug permeation, using the Franz diffusion cells. The formulation developed was able to promote transdermal absorption of desmopressin, showing a permeation percentage of 21.5%. Thus, sufficient amounts of desmopressin were delivered to achieve a systemic effect. Finally, the results demonstrate the transdermal route as an alternative for the desmopressin administration.**

Keywords — Desmopressin; Transdermal route; Semisolid Vehicle.

I. INTRODUCTION

Nocturia is defined as wakening to void at least twice a night, preceded and followed by a period of major sleep, according to the International Continence Society (ICS) [1-2]. It has a higher prevalence in the male and elderly populations [3-4]. This condition may be associated with sleep loss, daytime fatigue and reduced quality of life [4-6]. Its etiology is multifactorial, including benign prostatic hyperplasia (BPH), diabetes, congestive heart failure, lower urinary tract obstruction and overactive bladder [7]. BPH is a common problem among older men that negatively impacts quality of life and results in considerable medical intervention and expense [8] and represents a condition associated with nocturia [9-10].

Desmopressin has been used to treat nocturia and other reported conditions included central diabetes insipidus, bleeding disorders such as von Willebrand disease and nocturnal enuresis [11]. This is a synthetic analog of vasopressin, which is secreted by the posterior pituitary, and act to increase water permeability on renal collecting ducts through V2 receptors, leading to water reabsorption and decreased urine volume [12]. Desmopressin is usually administered orally, but due to the low bioavailability of these formulations, high doses are necessary and could be associated with a greater onset of adverse effects [13]. Hyponatremia is the major risk associated with desmopressin administration, and occurred in 4.9% of all patients in high-dose desmopressin oral tablet studies [14-15]. Nasal spray formulation is an attractive non-invasive alternative route of drug delivery, however the most frequently reported adverse events in the patients included nasal discomfort or congestion, nasopharyngitis, epistaxis, or bronchitis [12] [16].

Transdermal administration of desmopressin is an alternative that could enables greater bioavailability and adherence to treatment when compared to existing routes [17]. Benefits of the transdermal route include targeted delivery of drugs with predetermined fixed rates and minimal inter- and intrapatient variability [18], low systemic exposure, noninvasiveness, self-administering [19-20], long plasma periods within the therapeutic window [21] and low toxicity [20][22]. Thus, the present work aimed to evaluate the percutaneous permeation of a desmopressin transdermal emulsion, in order to develop an alternative route of administration for this drug.

II. MATERIAL AND METHODS

A. Material

The acetonitrile, trifluoroacetic acid and ethanol used in the mobile phase and receptor medium were HPLC grade, and sodium chloride (NaCl), potassium chloride (KCl), sodium hydrogen phosphate (Na_2HPO_4), potassium dihydrogen phosphate (KH_2PO_4), magnesium sulfate ($MgSO_4$), magnesium chloride ($MgCl_2$), sodium bicarbonate ($NaHCO_3$) and hydroxypropyl-β-cyclodextrin were of analytical grade and were obtained from Sigma-Aldrich (USA). Desmopressin (raw material) was provided by Fagron (Brazil), and the standard used was United States Pharmacopeia (USP) grade.

B. HPLC quantification

Desmopressin quantification was performed through standard curves prepared immediately before each sample analysis using our previously validated method. The HPLC runs were carried out in a qualified and calibrated Young Lin (Korea) chromatography system composed of the following: quaternary pump (YL 9110), photodiode array detector (YL 9160), automatic injector (YL 9150), column compartment (YL 9130), and software controller (Clarity). Chromatographic separation was achieved using a C18, 3.9 × 150 mm, 5 µm particle size column, the mobile phase (trifluoroacetic acid and acetonitrile 75:25, v/v) was pumped at a flow rate of 1 mL min^{-1}, and detection was performed at 220 nm.

C. Transdermal emulsion

Desmopressin transdermal emulsion was produced using the Pentravan® vehicle. The desmopressin powder was accurately weighed and thoroughly triturated, then it was combined with etoxydiglycol, next the vehicle was added and mixed thoroughly with the drug. The final concentration was 0.4 mg g^{-1}.

D. Selection of the receptor medium for the permeation studies

The desmopressin solubility in different receptor solutions was evaluated in order to select the most suitable for the experiments. The biorelevant media were prepared as described by Baert et al. (2010) [23], and the following compositions were used: 0.01 M phosphate buffered saline (PBS) pH 7.4 (NaCl–138.0 mM; KCl–2.7 mM; KH_2PO_4–1.43 mM; Na_2HPO_4–8.57 mM); artificial human sweat (SS) (NaCl–49.96 mM; $CaCl_2$–0.15 mM; $MgSO_4$–1.0 mM; KH_2PO_4–7.5 mM); simulated body fluid (SBF) (NaCl–136.8 mM; KCl–3.0 mM; $CaCl_2$–2.5 mM; $MgCl_2$–1.5 mM; Na_2SO_4–0.5 mM; $NaHCO_3$–4.2 mM; KH_2PO_4–1.0 mM). Moreover, we also evaluate these media plus ethanol (20%) and hydroxypropyl-β-cyclodextrin (5%), with a total of 10 different receptor solutions. Aliquots of 10 mg of desmopressin were weighed in 10 individual glass tubes, and each receptor solution was added to volume (10 mL) in its respective tube. Subsequently, the tubes were shaken (10 min), sonicated (30 min), and left in a water bath (32 °C) overnight (12 h). Finally, the tubes were centrifuged (20,000 x g) and the supernatant was transferred into glass HPLC vials for quantification.

E. Excised human skin for the permeation studies

The abdominal human excised skin was obtained from 1 patient that underwent abdominoplasty (38 years, woman, with no previous skin disease). The skin was collected immediately after the surgery and checked visually to ensure that it was healthy and unaltered by clinical removal conditions. For transportation (less than 30 min), the skin was kept in an isothermal container at 4 °C. At the laboratory, it immediately had its subcutaneous fat and connective tissue removed with a bistoury, then it was cleaned with water and saline, finally it was cut into small round discs that fit the vertical diffusion cells. The skin was used at full thickness. This protocol followed The Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the Ethics Committee of the Universidade Federal de Juiz de Fora (Approbation no. 2.698.850).

F. Permeation studies

The experiments were performed in 7-mL static vertical diffusion cells with automatic sampling (Microette Plus; Hanson Research Systems, Seal Beach, California). The donor compartment contained the transdermal formulation (n=6) and the receptor compartment was filled with the select receptor medium (to maintain *sink* conditions), making sure all air under the skin was removed. The skin discs were positioned between both cell compartments, and a finite dose (60 mg) of the formulation was applied by using a calibrated positive displacement pipette Pos-D MR-110 (Mettler-Toledo Rainin, Oakland, California) at the surface of the membrane. The emulsions were then carefully and evenly spread to achieve complete coverage. The available diffusion area was 1.86 cm^2, and a clamp was used to hold the compartments together. The receptor medium was constantly mixed with a magnetic stirring bar (600 rpm), except during the period of sample collecting, and maintained at 32 °C ± 2 °C during the whole experiment. Aliquots (1 mL) were withdrawn at regular time intervals (1 h, 2 h, 4 h, 8 h, 16 h, and 24 h), collected in HPLC vials, and immediately replaced with receptor medium at the same temperature. The drug concentrations were correspondingly corrected for the replenishments. The diffused quantity of the drug (Qreal,t), in the time t, was calculated using Equation 1:

$$Q_{real,t} = C_{measured,t} \times V_r \times V_a \times \sum^{n-1} C_a \quad (1)$$

where $C_{measured,t}$ is the concentration measured at sampling time t, V_r is the volume of the diffusion cell, V_a is the aliquot volume, and C_a is the concentration of the aliquot.

G. Drug retention

After the permeation experiments, each skin disc was withdrawn from the cells for analysis of drug retention in the skin layers. A tape-stripping technique was used to separate the stratum corneum (SC) from the viable epidermis + dermis (EV): 10 stripes (3M, USA) were used for each skin disc. The SC and EV were placed separately into 10-mL conical polypropylene tubes (Eppendorf, Hamburg, Germany) containing 5 mL of receptor medium. All tubes were shaken mechanically, sonicated for 1 h, filtered using 0.45-µm filters, and then transferred to HPLC vials. They were all quantified via HPLC, and the drug concentrations were corrected for the dilutions used.

III. Results And Discussion

Prior to permeation studies, it is essential to verify which receptor medium is most appropriate. It should

enable the solubilization of the drug, not limiting its diffusion across the membrane [24]. The results obtained are shown in the Table 1.

Desmopressin solubility was high in all receptor media tested. Thus, artificial human sweat + 20% EtOH was chosen as receptor medium because it presented the best chromatogram (without any interference).

The results obtained for the permeation studies are expressed in Table 2. In the experiment, no measurable amounts of desmopressin were detected in the receptor medium. However, the amount of desmopressin permeated is the sum of the drug in the receptor medium and also the amount detected in the dermis. What explains this is the fact that *in vivo* the dermis is a vascularized layer, thus the amount of drug that can reach this layer, will be able to get into the bloodstream [25]. Moreover, the skin used in the experiments has its microcirculation obliterated, thus, the dermis could retain drug amounts that would penetrate *in vivo* [26].

Typically, the amount of transdermal emulsion used is 1 g [27]. Taking into account the permeation percentage found, applying 1 g of the emulsion containing 400 µg of desmopressin, we estimate it will release 86.5 µg of the drug into the bloodstream for 24h. Desmopressin injectable formulations have a dose of 1 to 20 µg [28], thus our transdermal formulation would be able to provide enough amount of desmopressin. In addition, the amount of transdermal formulation could be reduced to 233 mg, this would be sufficient to promote the permeation of 20 µg desmopressin.

The routes of administration that are commonly used for the treatments with desmopressin are oral and intranasal. However, this routes presents low bioavailability. When the desmopressin is administered by the intranasal route, the bioavailability is between 3.3% and 4.1%, whereas for oral administration

TABLE I. RESULTS OF THE RECEPTOR MEDIUN SELECTION

Receptor medium	Solubility ($\mu g.mL^{-1}$)
PBS	959.84
PBS + HPBCD	957.67
PBS + EtOH (20%)	971.34
SS	993.40
SS + HPBCD	933.90
SS + EtOH (20%)	999.76
SBF	980.26
SBF + HPBCD	993.12
SBF + EtOH (20%)	989.90

PBS: 0.01 M phosphate buffered saline, pH 7.4. SS: artificial human sweat. SBF: simulated body fluid. HPBCD: hydroxypropyl- β-cyclodextrin. EtOH: ethanol

TABLE II. RESULTS OF THE PERMEATION STUDIES

Parameter	Results
Desmopressin applied (mg)	24.0
Desmopressin quantified into the receptor medium + VE + dermis (µg)	5.15
Desmopressin retained into the SC (µg)	6.17
Permeation percentage (%)	21.5

VE: Viable epidermis; SC: Stratum corneum.

typically ranges from 0.08% to 0.16% [16]. In this context, transdermal desmopressin seems to be a promising therapeutic option in improving nocturia, since it has a permeation percentage of 21.5%. However, further studies are needed to demonstrate the effectiveness of the transdermal route.

The vehicle used for the production of transdermal desmopressin was Pentravan®, which is a ready to use transdermal vehicle. This is a colloidal system with a hydrophilic external phase composed of synthetic lecithin and isopropyl palmitate, and an aqueous phase [29]. It has been shown to promote transdermal permeation of several drugs, including: metformin [30], human female sexual steroids [31], testosterone, ketoprofen [32] and oxandrolone [33].

Getie et al. (2005) evaluated the permeation of desmopressin from two different formulations: a colloidal system (water-in-oil microemulsion) and an amphiphilic cream [28]. They found that about 6% of the applied dose reached the receptor medium from the microemulsion instead of 2% from the cream within 300 min. The total percentages of dose obtained from different skin layers (stratum corneum to subcutaneous tissue) were 15.54 and 14.4 for the microemulsion and cream, respectively. These values are slightly lower than those found in our study, but they also demonstrate the feasibility of the transdermal route for desmopressin administration.

IV. CONCLUSION

The desmopressin emulsion showed an ability to promote permeation of the drug (21.5%) through the layers of the skin. This formulation could delivery desmopressin in amounts necessary to exert the therapeutic effect. Thus, the transdermal route appears to be a promising alternative for desmopressin administration in the treatment of nocturia.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

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