The analysis of the permeability process of calcium antagonists in developing transdermal forms with a cardiovascular effect

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Abstract

Aim. The aim of the work was to evaluate the possibility of using calcium antagonists, namely, nifedipine and amlodipine besylate, while conducting transdermal delivery, that included the analysis of in vitro permeability process as a primary preformulation stage of pharmaceutical development of a transdermal dosage form, determination of qualitative and quantitative characteristics of a permeability process and the expediency analysis of development of a therapeutic transdermal system (TTS) with a cardiovascular effect.

Materials and methods. The active pharmaceutical ingredients (API) of nifedipine and amlodipine besylate. The study has been carried out in vitro by a dialysis method using a modified diffusion device of the Valia-Chien design.

Results. Character analysis, description of the mathematical model and definition of the kinetic parameters in the process of permeability of the studied medicinal products (MP) of nifedipine and amlodipine besylate allowed to evaluate their potential for creating TTS as being positive and appropriate. The implemented methodological approaches allow to substantiate the further algorithm for the development of cardiovascular TTS with the mentioned API.

Keywords

Nifedipine, amlodipine besylate, in vitro permeability, a transdermal therapeutic system

Introduction

Cardiovascular diseases, in particular, ischemic heart disease and arterial hypertension are the main causes of disability and mortality among the population. Nowadays, a numerical increase in the incidence of this type of pathology may be present. The pharmacotherapy of the mentioned pathological states usually requires a long time, an individual approach and a complex adjustment, taking into account all the parts of the pathological process.

The first line of the medicinal products in treating hypertensive disease includes calcium antagonists, which show antianginal and antihypertensive properties. Among the groups of the calcium channel blockers the medicinal products of 1,4-dihydropyridine type- nifedipine and amlodipine are widely spread.

Nifedipine is a short-acting calcium antagonist, widely known in the world of medical practice. Its main drawback is a short-duration half-life period, which takes only 2–4 hours. For these purposes, nifedipine requires
The study of the permeability of the chosen API medicinal products permeability in vitro through the membrane. The main advantage of such research is a possibility of a control over the experiment conditions and, therefore, the possibility to control changes in permeability due to the influence of different factors (Yasam et al. 2016; Shyteyeva et al. 2017; Shyteyeva et al. 2018).

In this context, the aim of our work is to study in vitro the process of calcium antagonist permeability, nifedipine and amlodipine besylate, and determining their application perceptiveness in the creation of transdermal patches with cardiovascular effect.

Materials and methods

The API of nifedipine (Suchem Laboratories company, India) and amlodipine besylate (Hetero Drugs Limited company, India) have been chosen as the objects of the study.

Nifedipine (Fig. 1) is a yellow crystal powder, which is practically insoluble in water, poorly soluble in ethanol. \( M_r = 346,34 Da \). \( \log P \) (octanol-water) = 2.20. Hydro solubility at 25 °C = 56.3 mg/l (Ukrainian compendium).

Figure 1. Nifedipine 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylic acid dimethyl ester.

Amlodipine (in the besylate form) (Fig. 2), is a yellow crystal powder, which is slightly soluble in water, sparingly soluble in ethanol. \( M_r = 408,89 Da \). \( \log P \) (octanol-water) = 3. Hydro solubility ~ 75.3 mg/l at 25 °C (Ukrainian compendium).

Figure 2. Amlodipine 3,5-Pyridinedicarboxylic acid, 2-[(2-aminophenyloxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3-ethyl 5-methyl ester.

The study of the permeability of the chosen API through a semipermeable membrane was carried out in vitro by a dialysis method using a modified diffusion de-
vice of the Valia-Chien design, which was earlier described in paper (Chien 1987). The initial saturated solutions of the test substances in a phosphate buffer solution were used as donor solutions. A phosphate buffer solution (pH 7.4) served as an acceptor solution. The experiment was conducted under the temperature of 37 ± 0.5 °C (the temperature of human subcutaneous layers). At certain intervals, 1 hour, that were corresponding to 1, 2, 3, 4, and 5 hours from the beginning of the experiment, the entire solution was removed from the acceptor compartment, replacing the sample acceptor solution with a new one, which was taken into account in the calculations. For every test sample the absorption spectra were recorded on the spectrophotometer Specord 200. The optical density of the obtained solutions was determined by the maximum absorption at the appropriate wavelength for each product.

The qualitative characteristics of the permeability process were determined with Fick’s law, which describes diffusion processes, including the active substance transfer through the skin or membrane.

**Results and discussion**

The assessment of the permeability process of the studied substances through a semipermeable membrane was conducted according to the determined values of the flux \( I_p \), permeability coefficient \( K_p \), and the diffusion delay time \( \Theta \). The experiment results have been presented in Table 1.

<table>
<thead>
<tr>
<th>API</th>
<th>Number of a chosen sample, n</th>
<th>Sampling time, t, h</th>
<th>API quantity in a dialysis sample, ( X \cdot 10^{-4} ), g</th>
<th>API concentration in a dialysis sample, ( C \cdot 10^{-4} ), mg/ml</th>
<th>Specific flux of API, ( Q \cdot 10^{-3} ), mg/cm²·h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>1</td>
<td>1</td>
<td>30,771</td>
<td>113,9666</td>
<td>74,1470</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>28,539</td>
<td>105,7000</td>
<td>142,9157</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>31,751</td>
<td>117,5062</td>
<td>219,4241</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>4</td>
<td>28,727</td>
<td>106,3962</td>
<td>288,6458</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>5</td>
<td>27,725</td>
<td>102,6851</td>
<td>355,452</td>
</tr>
<tr>
<td>Amlodipine besylate</td>
<td>1</td>
<td>1</td>
<td>45,890</td>
<td>167,0000</td>
<td>108,6507</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>45,839</td>
<td>169,7740</td>
<td>219,1060</td>
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<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>46,897</td>
<td>170,7286</td>
<td>330,1831</td>
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<td>4</td>
<td>4</td>
<td>47,584</td>
<td>176,2370</td>
<td>444,8434</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>5</td>
<td>48,010</td>
<td>177,8148</td>
<td>560,5301</td>
</tr>
</tbody>
</table>

According to the obtained results of the API quantity, \( X \) and its concentration \( C \) in a dialysis sample (Table 1), it can be noted that these indices practically do not change within the duration of the experiment, that the passage of all the tested substances through the selected membrane has been carried out uniformly that corresponds to the zero-order kinetics with respect to the concentration gradient of donor and acceptor solutions.

The statistical equivalence of the obtained data was evaluated on the basis of a study of samples with experimental values, organized in ascending order. Changes in the variant \( X \) of the received samples can be considered insignificant if the values of their extreme variants do not exceed the limit values of the confidence interval, calculated by the maximum permissible half-width of the confidence interval (max \( \Delta_x \)). The value max \( \Delta_x \) was defined on the basis of the relative uncertainty of quantitative analysis of the given API (\( \Delta_{x,y} \)) (equation 1) based on the relative tolerance of API quantitative content in TTS B = 25 % according to the State Pharmacopoeia of Ukraine (SPhU) requirements (State Pharmacopoeia of Ukraine).

\[
\text{max } \Delta_x = 0.32 \cdot B = 0.32 \cdot 25 = 8.0\% \quad (1)
\]

The limit values of the confidence interval were determined by equations 2 and 3:

- the upper limit

\[
X_{\text{high}} = \bar{X} \cdot \left(1 + \frac{\text{max } \Delta_x}{100}\right) \quad (2)
\]

- the lower limit

\[
X_{\text{low}} = \bar{X} \cdot \left(1 - \frac{\text{max } \Delta_x}{100}\right) \quad (3)
\]

The convergence estimation results of experimental values of process parameters of the examined API permeability through a membrane have been presented in Table 2.

According to the results, presented in Table 2, it can be seen that the variant values of all the selections \( X \) do not exceed the limit values of the confidence interval \( X_{\text{low}} \) and \( X_{\text{high}} \). Thus, all the obtained experimental values of the studied parameters are within the limits of the confidence interval.
tions, within the time of the experiment, the correlation coefficient ($R^2$) was not less than 0.999.

The main quantitative characteristics of the permeability process of the studied API in vitro, calculated on the basis of a statistical analysis, have been presented in Table 4.

Table 4. The kinetic parameters of the permeability process of API with cardiovascular effect in vitro through a semipermeable membrane.

<table>
<thead>
<tr>
<th>API</th>
<th>API steady-state flux, $I_s$, mg/cm²h</th>
<th>Time of diffusion delay, $\Theta$, min</th>
<th>Permeability coefficient, $K_p$, cm/h</th>
<th>Linear correlation coefficient, $r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>0.7083</td>
<td>-3.06</td>
<td>0.075</td>
<td>0.9997</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>1.1295</td>
<td>3.28</td>
<td>0.124</td>
<td>0.9999</td>
</tr>
</tbody>
</table>

According to the obtained results (Table 4), the kinetic parameters of the amlodipine besylate permeability process are 1.6 times higher than the same indices for nifedipine. Thus, the value of the steady-state flux rate $I_s$, obtained for nifedipine, is 0.7083 mg/cm²h, and for amlodipine besylate is 1.1295 mg/cm²h. In the same ratio for these substances the values of the permeability coefficient $K_p$ were defined, that is 0.075 cm/h for nifedipine and 0.124 cm/h for amlodipine besylate. The diffusion delay time determines the duration of the non-stationary period of the process. In the frame of the experiment, the non-stationary period for the permeability process of both nifedipine and amlodipine besylate is defined within 3 minutes but at that point, the negative significance of this indicator for nifedipine indicates a lack of the membrane saturation.

Conclusions

In the result of the carried out research it was defined that nifedipine and amlodipine besylate permeability process in the simulated conditions is characterized by uniform velocity. Based on the statistical analysis, the linear dependence of this process was confirmed. The obtained quantitative values of the steady-state flux velocity and the coefficient of permeability indicate the potential of the selected substances in overcoming membrane barriers, and allow to predict a positive assessment of the acceptability of the selected API for the use in the design of TTS.
References


