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PREFORMULATION STUDIES ON THE DEVELOPMENT OF A TRANSDERMAL THERAPEUTIC SYSTEM WITH CAPTOPRIL

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The article presents the results of a study of the process of captopril penetration through a semipermeable membrane by in vitro dialysis to practically confirm the possibility of its use for creating new forms of delivery – transdermal therapeutic systems (TTS).

The aim: *Preformulation studies of pharmaceutical development of a transdermal dosage form of TTS with antihypertensive action with captopril, determination of the nature and kinetic parameters of the process of captopril permeability through a semipermeable membrane in vitro, as well as the influence of the initial concentration of the selected active pharmaceutical ingredient (API) on this process.*

Materials and methods: *At the initial stage of development of antihypertensive TTS, the in vitro process of captopril permeability through a semi-permeable membrane by dialysis was investigated at (37±0.5) °C. A phosphate buffer solution (pH 7.4) was used as a diffusion medium. The initial concentration of captopril in the donor solution was 30 mg/ml.*

Results: *Based on the analysis of the obtained experimental values of the amount of the studied substance in the sample of dialysate Xi and the specific flux gradient per unit of time ΔQ_t it was noted that the process of captopril permeability in model conditions is characterized by a uniform rate and corresponds to zero-order kinetics. The high value of the correlation coefficient R = 0.9996 for the obtained kinetic equation confirms the linear dependence of passage through the membrane of the studied substance on time.*

Conclusion: *Studies conducted to determine quantitative permeability characteristics have shown, first, the ability of molecules of the selected substances to overcome membrane barriers and allow a positive assessment of the acceptability of this active pharmaceutical ingredient as attractive for the creation of TTS*

Keywords: *hypertension, captopril, in vitro permeability, transdermal therapeutic system (TTS)*

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1. Introduction

Arterial hypertension (AH) or hypertension is one of the most common causes of disability and mortality in the population worldwide. To date, there has been a significant increase in the incidence of this type of pathology [1, 2]. According to the World Health Organization (WHO), today more than 1.5 billion people in the world suffer from hypertension [3]. Every year there is a numerical increase in cardiovascular diseases (CVD), the cause of which is AH. One of the global targets for noncommunicable diseases is to reduce the prevalence of hypertension by 33% between 2010 and 2030. The main objective of antihypertensive therapy is to achieve and stabilize the target blood pressure level of 140/90 mmHg recommended by the WHO (2021) [4].

Angiotensin-converting enzyme (ACE) inhibitors are one of the leading drugs in the treatment of cardiovascular pathology, which are included in the group of first-line drugs in the treatment of arterial hypertension and are recommended for patients with these diseases [5–7].

The first synthetic API of the ACE group that found application in medical practice was captopril [8]. It is used in the chronic treatment of hypertension, congestive heart failure, and left ventricular dysfunction after myocardial infarction as a first-line treatment due to the absence of side effects in most patients. Under the influence of captopril, peripheral vascular resistance and blood pressure decrease, and the load on the myocardium decreases [9]. Captopril provides a cardioprotective effect, has a vasodilatory effect, and reduces cardiac hypertrophy. With long-term use, captopril prevents the progression of heart failure. Captopril also has a nephroprotective effect on the kidneys, prevents the development of diabetic nephropathy. Captopril is rapidly absorbed after oral administration but has a short-term effect. The bioavailability of the drug when administered orally is about 75%. Simultaneous food intake reduces absorption by 30 to 55%. The maximum hypotensive effect is noted after 60–90 minutes. The duration of the hypotensive effect is dose-dependent and reaches optimal values within a few weeks [10].

Modern innovative developments of antihypertensive drugs are based on the use of an alternative oral route of delivery of active substances, in particular transdermal [11]. Dosed applied skin dosage form – transdermal therapeutic system (TTS) is intended for external use and ensures the entry of active substances

into the human body in the required therapeutic amount according to a given program [12, 13]. The use of TTS ensures the stability of the concentration of the active ingredient in the blood circulation and makes it possible to prolong the therapeutic effect of the drug [14]. The use of TTS significantly reduces or completely eliminates the risks and disadvantages of oral and parenteral administration. TTS are non-invasive, convenient to use and significantly increase patient compliance, especially in the long-term treatment of patients with chronic diseases, when a constant continuous supply of drug is required [15, 16].

Transdermal drug delivery systems have become a hot topic in contemporary research in the field of pharmaceutical technology and one of the most frequently developed pharmaceutical products on the global market [17–19]. Scientific reports from pharmaceutical laboratories have noted developments in transdermal delivery of captopril for many years [20–22]. However, commercial transdermal antihypertensive drugs containing captopril are not currently available on the global pharmaceutical market.

Considering the promising prospects for the transdermal administration of known antihypertensive drugs of the ACE inhibitor group, we previously conducted preliminary studies on the development of a transdermal TTS pharmaceutical form with antihypertensive action using enalapril maleate [23] and lisinopril dihydrate [24]. This work is a continuation of these studies. We focused on the first-generation drug, captopril, which is the most studied in terms of clinical data [25]. Currently, only oral forms of captopril are available on the commercial pharmaceutical market.

The aim of the research. The aim of our work was to conduct preformulation studies of pharmaceutical development of a transdermal dosage form of TTS with captopril as antihypertensive action, determination of the nature and kinetic parameters of the process of captopril permeability through a semipermeable membrane in vitro, as well as the influence of the initial concentration of the selected active pharmaceutical ingredient (API) on this process.

2. Planning (methodology) of research

Effective development of new drugs is possible only with reasonable design of studies [26]. The initial stage in the development of TTS is the selection of a drug substance, assessment of the acceptability of its administration in this dosage form. The development of a specific TTC should be preceded by *in vitro* studies of API permeability through biological or synthetic membranes, which is one of the methods for developing TTS and controlling their quality. Carrying out the preformulation stage of the pharmaceutical development of TTS allows optimizing the methodology for creating this dosage form. In the course of conducting a wide range of *in vitro* studies of the permeability of the ACE class API – captopril – we determined the main algorithms for the methodology for the development of TTS with this substance. The quantitative parameters of the API permeability process were determined according to Fick's law (1), which describes the diffusion passive transport of substances along the concentration gradient *dC/dx*:

$$I_s = K_p \Delta C_s, \quad (1),$$

where I_s – the value of the steady-state flux of drug, mg×cm^{-2}×h^{-1}; ΔC_s – concentration gradient of the substance between the donor and acceptor solutions, mg/ml; K_p – permeability coefficient, cm/h.

The total amount of API diffused during the specified time of the experiment through a unit membrane area, or specific flux (Q_t, mg/cm^2) was calculated using equation (2):

$$Q_t = \Sigma C_i \times V \times S^{-1}, \quad (2),$$

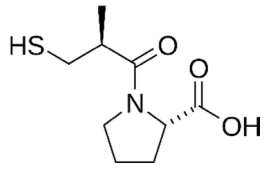
where C_i – the concentration of the API in the sample taken at time t, mg/ml; V – the volume of the diffusion cell, ml; S – the membrane area, cm^2.

3. Materials and methods

The research was conducted in 2023 at the State Research Laboratory for Quality State Research Laboratory for Quality Control of Medicinal Products of the National Pharmaceutical University.

The object of the study was captopril, manufactured by Changzhou Pharmaceutical Factory, China (series EC201003). The substance in this series of captopril meets all the requirements of the State Pharmacopoeia of Ukraine [27].

Captopril (Fig. 1) is a white or almost white, crystalline powder. Soluble in water, freely soluble in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides. The molecular formula $C_9H_{15}NO_3S$. The molecular weight M_r 217.3. The partition coefficient log$P_{o/w}$ 1.13 [27, 28].



(2*S*)-1-[(2*S*)-2-Methyl-3-sulfanylpropanoyl]pyrrolidine-2-carboxylic acid; 1-[(2S)-3-Mercapto-2-methylpropionyl]-L-proline; 1-[(2S)-3- mercapto-2-methyl-1-oxopropyl]-L-proline

Fig. 1. Chemical structure of captopril

Cellophane film produced by the Cherkasy Chemical Fiber Plant (cellophane grade B-8079, swollen film thickness 45 ± 0.4 μm, swelling degree 125 ± 2.2, porosity degree 6.25 g/ml) was used as the membrane.

In vitro studies of the permeability of the selected API through a semi-permeable hydrophilic membrane were performed by dialysis using the Valia-Chien diffu-

sion device (Station Horizontal Cell, Crown Glass, Germany). The experiment was performed at a temperature of (37 ± 0.5) °C. The volume of diffusion cells is 27 ml. The working area of the membrane is 4.15 cm^2. A phosphate buffer solution (pH 7.4) was used as a diffusion medium. The initial concentration of captopril in the donor solution was 30 mg/ml. Experimental solutions in the chambers of the device were stirred using magnetic stirrers (SES H3 Stirrer with Cell Clamps, SES GmbH – Analysesysteme, Germany). Every hour during the experiment, the sample of the acceptor solution was replaced with a new one, taking this factor into account in further calculations. The content of captopril in the dialysate sample was determined by the spectrophotometric method (Specord 200, Analytik Jena GmbH+Co. KG, Germany). Wavelength 206 ± 2 nm, cuvette with a layer thickness of 10 mm relative to phosphate buffer solution pH 7.4, as a compensation solution.

Statistical analysis of data was performed using the linear regression method using the Microsoft Office Excel 2024.

4. Results

The in vitro assessment of captopril permeability through the hydrophilic membrane was carried out according to the determined values of the specific flux Q_t, the steady-state flux I_s, the permeability coefficient K_p and the diffusion lag time Θ. The results of the experiment are shown in Table 1.

Based on the analysis of the obtained values, it can be argued that the permeability of captopril through the semi-permeable membrane from the solution in the model conditions of the experiment (after the first hour) occurs at a constant rate corresponding to the zero-order kinetics, taking into account the concentration gradient of the donor and acceptor solutions.

The results of the study of the convergence of experimental values of the parameters of the process of captopril permeability through the membrane are shown in Table 2.

Table 1

Parameters of captopril permeability through a semi-permeable membrane *in vitro*

Number of a chosen sample, n	Sampling time, t, h	Quantity of API in a dialysis sample, $X_i \times 10^{-3}$, g	The concentration of API in the dialysate sample, C_t, mg/ml	Specific flux of API, Q_t, mg/cm^2
1	1	67.9850	2.5180	16.3822
2	2	49.7043	1.8409	28.3591
3	3	46.5075	1.7225	39.5657
4	4	49.3370	1.8273	51.4542
5	5	44.1234	1.6342	62.0863
6	6	44.9361	1.6643	72.9143

Table 2

Evaluation of the convergence of experimental values of kinetic parameters of captopril permeability *in vitro*

Evaluation parameters	Sampling of values in the dialysate sample		
	quantity of API, $X_i \times 10^{-3}$, g	concentration of API, C_t, mg/ml	steady-state flux of API, I_s, mg × cm^{-2} × h^{-1}
Variants of samples, x_i	44.1234	1.6342	10.6321
	44.9361	1.6643	10.8280
	46.5075	1.7225	11.2066
	49.3370	1.8273	11.8885
	49.7043	1.8409	11.9769
$\overline{x}$	46.9208	1.7378	11.3064
X_{low}	43.1671	1.5988	10.4019
X_{high}	50.6745	1.8768	12.2109

Fig. 2 presents a graphical representation of the kinetic process of *in vitro* captopril permeability through a semi-permeable membrane. The resulting kinetic equation has the form of general linear regression $Y = A + B \times X$.

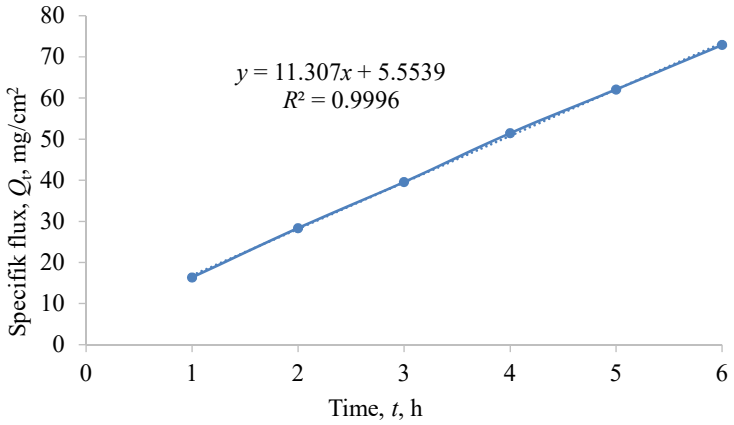


Fig. 2. Kinetics of the in vitro membrane permeability process of captopril (initial concentration 30 mg/ml)

The linear dependence of the passage of captopril is confirmed by the linear regression parameters determined by the calculated from the results of statistical analysis. It is noted that for the obtained kinetic equation, within the time of the experiment, the correlation coefficient R^2 is quite high and is 0.9996. The main quantitative characteristics of the in vitro process of captopril permeability, calculated from the results of statistical analysis, are shown in Table 3.

Table 3

Kinetic parameters of the in vitro process of captopril permeability through a semi-permeable membrane

Steady-state flux of drug, I_s, mg × cm^{-2} × h^{-1}	Diffusion lag time, Θ, min	Permeability coefficient, K_p, cm / h	Linear correlation coefficient, R^2
11.307	29.4	0.40	0.9996

The obtained results (Table 3) of the value of the steady-state flux I_s of captopril and the permeability coefficient K_p showed, first of all, the ability of the molecules of this compound to overcome membrane barriers, which practically confirms the choice of this API as attractive for the creation of TTS.

5. Discussion

The obtained data on the content of X_i and the concentration of C_i APIs in the dialysate sample (Table 1) show that the passage of captopril through the selected membrane after the first hour of the experiment is uniform. Higher values of these parameters for the first sample taken indicate that during the first hour of the experiment, the membrane is saturated and the stationary period of the process of the substance passing through the membrane is established.

The statistical equivalence of the obtained results for the steady-state period was confirmed by the study of the convergence of experimental data in vitro of the process of permeability of captopril in the assessment of the change in variant x_i of the obtained samples, ordered in ascending order. Changes in variants x_i of the obtained samples can be considered insignificant if the values of their extreme variants do not exceed the limit values of the confidence interval X_{low} and X_{high}, calculated by the value of the maximum permissible half-width of the confidence interval ($\max\Delta_x$) [29, 30]. The maximum value calculated according to the requirements of the pharmacopoeia is 8%.

According to the results given in Table 2, it can be seen that the values of the variants of all samples x_i do not exceed the limit values of the confidence interval X_{low} and X_{high}, calculated from the value of the maximum permissible half-width of the confidence interval ($\max\Delta_x$). Consequently, the obtained experimental values of the studied parameters are within the confidence interval and change slightly.

Practical relevance. The application of basic concepts describing the transport of active substances across biological barriers allows the selection of appropriate experimental models and data analysis for a specific problem related to the determination of the flow and permeability of a drug substance.

The permeability data of the substance under study could be used for several purposes. The permeability constant and the substance flow rate obtained in an in vitro model could be used to predict the design of a transdermal form (membrane or matrix) of a specific drug substance. The parameters of the quantitative characteristics of the degree and rate of drug permeability and the time to reach a steady state are the basis for determining the initial concentration of the drug in the transdermal therapeutic system. The main advantage of these studies is the ability to control the conditions of the experiment and, therefore, the ability to control changes in permeability due to the influence of drug concentration, excipient composition, etc.

The permeability obtained could be compared with the permeability values obtained in a similar experimental setup for comparing the permeability of a number of related medicinal substances to select a candidate medicinal product with high permeability. Based on previous experience, the active substances under study could be evaluated in terms of their permeability. Thus, quantitative permeability parameters can be compared between series of related compounds in order to select drug candidates during the screening process.

The determined qualitative and quantitative characteristics of the captopril penetration process in vitro indicate the acceptability of this API for use in a transdermal form and the creation of a TTS. The results obtained could be used to create a captopril preparation in the form of a TTS with a specified delivery rate depending on the required biopharmaceutical properties, which contributes to the safety and effectiveness of drug therapy.

The methodological approach we use for primary (basic) research and the algorithm developed on its basis for designing transdermal forms of ACE inhibitors based on captopril allows us to optimize research, shorten the time required for pharmaceutical development, and reduce the risk of negative results in the final stages of drug development.

Research limitations. The analysis of the results presented in this article is limited by the conditions of conducting in vitro permeability studies, which require temperature control within the given range. This study is limited by the fact that only one composition of the diffusion medium (water) was used in the study and the model solutions had only one value of captopril content (30 mg/ml).

Prospects for further research. The development of a TTS for captopril is promising and relevant. The creation of a TTS with captopril requires further physical, chemical, technological, and biopharmaceutical research aimed at selecting the optimal composition and technology and achieving a balance between the release of the specified amount of drug and the time interval required for this. The implementation of the next stages of the pharmaceutical development of TTS with captopril will allow the introduction of a new transdermal therapeutic system with antihypertensive action into medical practice in the future.

The expansion of the scientific search for the development of transdermal antihypertensive drugs of other groups will allow us to analyse even greater future prospects for the introduction of transdermal technologies in the treatment of arterial hypertension.

6. Conclusions

Thus, as a result of the preformulation studies, the qualitative and quantitative characteristics of the process of permeability of captopril (the value of the specific flux of the active substance, the time of diffusion delay, the permeability coefficient) were determined. Based on the statistical analysis of the obtained experimental data, the linear dependence of the process of passage of the selected API through the semiperme-

able membrane was confirmed. It was noted that the process of captopril permeability under model conditions is characterized by a uniform rate. The algorithm of preformulation studies for the development of TTS developed in this study can be considered as promising. The next stages of pharmaceutical development of TTS with captopril will allow further introduction into medical practice of an alternative transdermal form of the drug for the treatment of arterial hypertension. This is especially true for significantly improving the lives of patients in this group who need long-term treatment. Taking into account the absence of transdermal preparations with this API on the pharmaceutical market, the relevance of such developments remains high.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this study, including financial, personal, authorship, or any other, that could affect the study and its results presented in this article.

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Data availability

The manuscript has no associated data.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies in creating the submitted work.

Authors' contributions

Tatyana Shyteyeva: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition; **Elena Bezchasnyuk:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition; **Oleg Kryskiv:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

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