Preformulation studies on the development of a transdermal therapeutic system with Captopril

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Introduction. Every year there is a numerical increase in cardiovascular diseases (CVD), the cause of which is arterial hypertension (AH). Controlling blood pressure (BP) within target values is the main task of treating patients with hypertension. Modern innovative developments of antihypertensive drug are based on the use of an alternative oral route of delivery of active substances, in particular transdermal. The algorithm for designing transdermal therapeutic systems (TTS) predetermines the preformulation studies of the biopharmaceutical properties of the active substance as a candidate for transdermal delivery.

Materials and Methods. At the initial stage of development of antihypertensive TTS, the in vitro process of captopril permeability through a semipermeable membrane by dialysis was investigated. The experiment was performed at a temperature of (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.

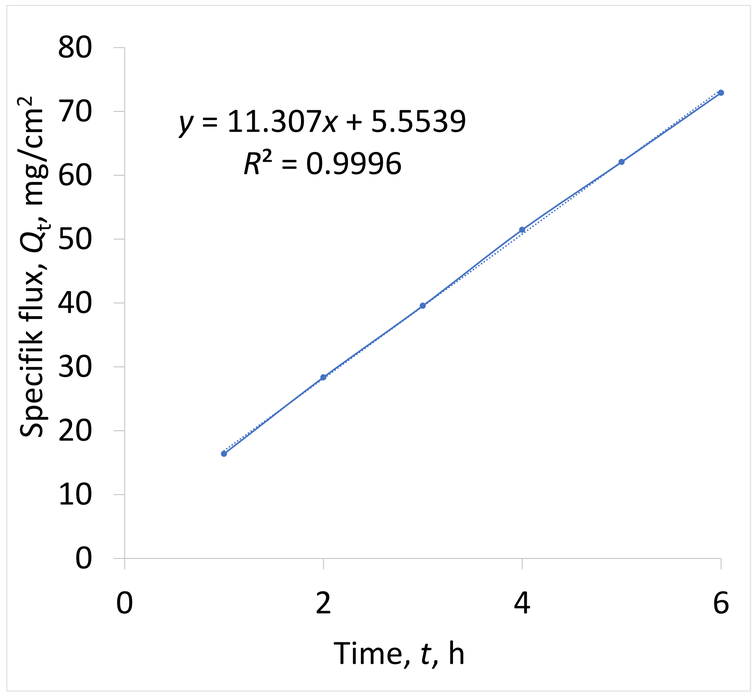

Fig 1. Kinetics of the in vitro membrane permeability process of captopril (initial concentration 30 mg/ml)

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_i, mg/ml	Specific flux of API, Q_t, mg/cm²
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_i, 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
$\bar{x}$	46.9208	1.7378	11.3064
X_{low}	43,1671	1.5988	10.4019
X_{high}	50,6745	1.8768	12.2109

Results. Based on the analysis of the obtained experimental values of the amount of the studied substance in the sample of dialysate X_i and the specific flux gradient per unit of time ΔQ_t it was noted that the process of captopril permeability in model conditions is characterised 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.

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

Conclusions. The obtained results of the steady-state flow velocity I_s = 11.307 mg·cm^{-2}·h^{-1} and the permeability coefficient K_p = 0.40 cm/h indicate a high potential of this substance in overcoming membrane barriers, which practically confirms the choice of this API as an attractive one for the creation of TTS.