UDC 615.45.473:661.122:616.2-008.331.1
DOI: 10.15587/2519-4852.2023.286303

SUBSTANTIATION OF CREATION OF TRANSDERMAL FORMS OF DRUG DELIVERY WITH ANTIHYPERTENSIVE ACTION

Tatyana Shyteyeva, Elena Bezchasnyuk, Oleg Kryskiv, Vasyl Grynenko

The article presents the theoretical justification for the choice of active pharmaceutical ingredients of antihypertensive action for the creation of new forms of delivery – transdermal therapeutic systems.
The aim: *monitoring of studies on the use of angiotensin-converting enzyme (ACE) inhibitors in the development of transdermal drugs for the treatment of hypertension.*
Materials: *open access electronic resources of scientific periodicals from around the world: Google Scholar (https://scholar.google.com/); PubMed (https://pubmed.ncbi.nlm.nih.gov/); Sciencedirect (https://www.sciencedirect.com/); Pubchem (https://pubchem.ncbi.nlm.nih.gov/); National Library of Ukraine named after V. I. Vernadskyi (http://www.nbuv.gov.ua/); Ukrainian Institute of Intellectual Property (Ukrpatent) (https://sis.ukrpatent.org/uk/); Industrial Property (https://base.uipv.org/searchBul/); USPTO. The United States Patent and Trademark Office (https://www.uspto.gov/patents/search); European Patent Office (EPO) (https://www.epo.org/).*
Methods of the research: *information search, theoretical analysis and systematization of data from scientific sources, logical analysis.*
Results: a review of scientific sources was carried out, and an analysis of ACE inhibitors as candidates for the creation of transdermal forms for the treatment of arterial hypertension was carried out. The pharmacological and physicochemical aspects of the possibility of their use for introduction through the skin are defined. It has been established that the search and development of the latest means of treatment of arterial hypertension, which would significantly increase the duration and quality of life of patients, are extremely relevant. Transdermal drug delivery systems are one of the pharmaceutical products being developed on the world market, and their use allows overcoming the associated disadvantages of other delivery routes.
Conclusions: *the review of domestic and foreign literature confirmed the relevance of biopharmaceutical research in the field of development of innovative dosage forms – transdermal therapeutic systems for the treatment of hypertension.*
The choice of promising antihypertensive active pharmaceutical ingredients of the ACE group (enalapril maleate, lisinopril dihydrate, and captopril) is substantiated, taking into account their specific physicochemical properties that are suitable for penetration through the skin.
The market for transdermal drug delivery is increasing, and there is a prospect of higher growth rates in this market in the coming years
Keywords: *arterial hypertension, transdermal therapeutic systems, ACE inhibitors, enalapril, lisinopril, captopril*

How to cite:
Shyteyeva, T., Bezchasnyuk, E., Kryskiv, O., Grynenko, V. (2023). Substantiation of creation of transdermal forms of drug delivery with antihypertensive action. ScienceRise: Pharmaceutical Science, 4 (44), 104–113. doi: http://doi.org/10.15587/2519-4852.2023.286303

1. Introduction

Hypertensive disease is one of the most frequent causes of disability and mortality in the population worldwide. Today, there is a significant increase in the incidence of this type of pathology [1, 2]. According to the WHO, more than 1 billion people, every fourth man and every fifth woman, suffer from hypertension today [3]. At the same time, in recent years, not only the quantitative increase of these diseases has been observed, but also the impact of these types of pathology on younger population groups [4]. It is noted that arterial hypertension (AH) is one of the most urgent problems in modern paediatrics. The prevalence of hypertension among children and adolescents, according to data from population studies, varies from 5 to 14 % in different countries. Moreover, among high school students, this indicator is 18 %, and among adolescent boys, it reaches 25.1 % [5, 6]. According to the results of the first stage of the implementation of the scientific and practical program "Study of the epidemiology of primary arterial hypertension and metabolic syndrome in children and adolescents", initiated by the Association of Pediatricians of Ukraine, elevated blood pressure (BP) is observed in 10–15 % of children [7]. According to STEPS data, a third of the population of Ukraine (34.8 % of those surveyed) had high blood pressure or hypertension or were taking antihypertensive drugs. The share of the population with elevated blood pressure increased sharply with age. In the age group of 18–29 years – approximately 12.7 %, in the age group of 60–69 years – 71.1 % [8].

Thus, the ageing of the population, the increase in the prevalence of chronic diseases, in particular, hypertension, and the need for effective, painless delivery of

drugs have led to the introduction of new technologies in their delivery systems [9, 10]. The search and development of the newest means of treatment of arterial hypertension, which would significantly increase the duration and quality of life of patients, are extremely relevant [11, 12]. Transdermal drug delivery systems have become an intriguing topic of research in the field of pharmaceutical technology and one of the most frequently developed pharmaceutical products on the world market [13, 14]. The use of these systems makes it possible to overcome the accompanying disadvantages of other delivery routes – oral and parenteral [15–17].

2. Materials and methods

As materials in the research, open access electronic resources of scientific periodicals from around the world were used: Google Scholar (https://scholar.google.com/); PubMed (https://pubmed.ncbi.nlm.nih.gov/); Sciencedirect (https://www.sciencedirect.com/); Pubchem (https://pubchem.ncbi.nlm.nih.gov/); National Library of Ukraine named after V. I. Vernadskyi (http://www.nbuv.gov.ua/); Ukrainian Institute of Intellectual Property (Ukrpatent) (https://sis.ukrpatent.org/uk/); Industrial Property (https://base.uipv.org/searchBul/); USPTO. The United States Patent and Trademark Office (https://www.uspto.gov/patents/search); European Patent Office (EPO) (https://www.epo.org/).

Research methods: information search, theoretical analysis and data systematization of scientific sources, logical analysis.

3. Research results

Hypertensive disease or arterial hypertension is a chronic disease manifested by a persistent increase in blood pressure [18].

According to the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH), there is a constant relationship between the frequency of cardiovascular diseases and increased blood pressure. Arterial hypertension increases the risk of developing heart, cerebral and kidney diseases. In turn, uncontrolled hypertension can be associated with the development of cardiovascular (CV) complications, such as stroke and myocardial infarction, peripheral artery disease, atrial fibrillation [19, 20].

Pharmacotherapy of these pathological conditions is usually long-term, requires an individual approach and complex correction, considering all links of the pathological process [21, 22]. According to the conclusions of the WHO, non-compliance with the established regimen of therapy, namely the dose, frequency, and regularity of taking antihypertensive drugs, is an important cause of uncontrolled blood pressure (i.e., cases when it is not possible to reach the target level of blood pressure) [23, 24].

Angiotensin-converting enzyme (ACE) inhibitors are one of the leading drugs in the therapy 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 [25, 26]. Most of the beneficial effect of ACE inhibitors in clinical practice depends on their ability to inhibit the renin-angiotensin system [27, 28]. The mechanism of action of ACE inhibitors is implied in their name – blockade of the enzyme necessary for the conversion of angiotensin I (a biologically inactive substance) into angiotensin II (the effector hormone of the renin-angiotensin system) [29, 30]. In addition, when ACE inhibitors are prescribed, the content of bradykinin increases, the breakdown of which is catalyzed by ACE, which leads to vasodilation, improvement of endothelial function, and activation of blood thrombolytic activity [31, 32].

Today, ACE inhibitors are recognized as the "gold standard" in the treatment of patients with heart failure syndrome [33, 34]. Research results showed that the effectiveness of ACE inhibitors in reducing cardiovascular mortality and morbidity is equivalent to the effectiveness of "old" antihypertensive drugs – diuretics and β-blockers (CAPPP, STOP-2, ALLHAT) [35, 36]. ACE inhibitors have a proven renoprotective effect, which makes them drugs of choice in the presence of kidney damage. This especially applies to patients with diabetes. Under the influence of therapy with ACE inhibitors for a long time, the frequency of new cases of diabetes decreased (CAPPP, HOPE). There is information about slowing down the progression of atherosclerosis under the influence of long-term use of ACE inhibitors (including the results of the HOPE study) [25, 37]. Thus, today ACE inhibitors are recommended for all patients with systolic chronic heart failure (CHF), regardless of the presence of clinical symptoms. Long-term use of ACE inhibitors reduces mortality, reduces clinical symptoms, improves exercise tolerance, and reduces the risk of repeated hospitalizations [38, 39].

Among the group of ACE inhibitors, enalapril, lisinopril and captopril are widely used.

Enalapril is a compound that includes the amino acids L-alanine and L-proline. Enalapril is a prodrug; after oral administration, the drug is quickly absorbed and transformed (by hydrolysis) into an active metabolite – enalaprilat, which has the properties of a highly specific ACE inhibitor [40]. It was established that enalapril provides a statistically significant reduction in the risk of a fatal outcome in patients with CHF. Like other ACE inhibitors, enalapril is indicated for hypertension combined with other pathologies, including CHF, left ventricular dysfunction, diabetic and non-diabetic nephropathy, proteinuria (including microalbuminuria), metabolic syndrome, atherosclerosis of carotid arteries, and is also recommended for patients after a myocardium heart attack, with atrial fibrillation and left ventricular hypertrophy (LVH) [41].

Enalapril provides a stable decrease in blood pressure during the day when used 1–2 times a day. Characterized by a good tolerability profile. The drug is well absorbed when taken orally; food does not affect the rate of absorption. About 60 % of the drug is absorbed. Binding to blood proteins is 50–60 %. The therapeutic effect develops after 1 hour, the pronounced therapeutic effect – after 4–6 hours. The maximum concentration in blood plasma is reached after 1 hour [42]. Enalapril is the first represen-

tative of the group of long-acting ACE inhibitors. The duration of the effect of enalapril when taken orally is about 24 hours, and when it is administered intravenously – about 6 hours. The half-life of enalaprilat is 11–14 hours. When administered intravenously, 94 % of the total dose of enalaprilat is excreted unchanged in the urine [40].

Lisinopril is the active hydrophilic metabolite of enalapril. Reduces blood pressure and total peripheral vascular resistance without affecting heart rate. In addition to a direct decrease in blood pressure, lisinopril reduces albuminuria due to changes in the histology and hemodynamics of the glomerular apparatus of the kidneys [43]. Lisinopril is a long-acting ACE inhibitor. The hypotensive effect develops approximately 1 hour after oral administration, reaches a maximum after 6 hours and persists for 24 hours. The duration of the effect depends on the dose. When taken internally, it is absorbed unchanged; the simultaneous intake of food does not affect the absorption of the drug. It is not metabolized in the body; it is excreted in the urine. Slightly binds to blood plasma proteins. The hypotensive effect of lisinopril persists with long-term use [44, 45].

Captopril is a highly specific competitive ACE inhibitor. Under the influence of captopril, as a result of a decrease in the active concentration of angiotensin-II in the blood, the peripheral resistance of blood vessels and blood pressure decrease, and the pre- and afterload on the myocardium decreases [46]. Captopril also reduces the level of vasoconstrictor substances (endothelin-I, norepinephrine) and increases the level of vasodilator substances (bradykinin, nitric oxide, prostacyclin). Due to the presence of SH-rpyp in the chemical structure, the drug not only quickly binds to the zinc atom in the angiotensin-converting enzyme molecule but also provides a cardioprotective effect. The drug reduces heart hypertrophy. It has a nephroprotective effect on the kidneys, normalizes intraglomerular hemodynamics, and reduces proteinuria in glomerulonephritis [47]. Captopril is quickly absorbed after oral administration, has a short-term effect, and is biotransformed into inactive metabolites. The bioavailability of the drug is about 75 %. Simultaneous food intake reduces absorption by 30–55 %. The maximum hypotensive effect is observed after 60–90 minutes; the duration of action is dose-dependent and is 6–12 hours [48].

The main task of treating patients with hypertension is to reduce blood pressure (BP) to target values and maintain it at an optimal level for a long time [49, 50]. However, according to statistics, only 20 % of patients effectively control blood pressure, and only half of the patients with this pathological condition receive drug therapy, and the main reason, in this case, is considered to be non-compliance of the patient's behaviour with the recommendations given to him [51, 52]. Taking into account this fact, as well as the fact that even those patients who follow all the recommendations often do not have the desired result in relation to the target blood pressure values, that is why to date, the unwavering work on clarifying the mechanisms of development, principles of diagnosis and treatment of this disease continues [53, 54].

Modern therapeutic strategies are aimed at increasing adherence to therapy in hypertension and are focused both on simplifying medication regimens and on new methods of their delivery [15]. Creation of innovative medicines in the form of transdermal therapeutic systems (TSS) is one of the most promising scientific directions of modern pharmaceutical technology [55, 56].

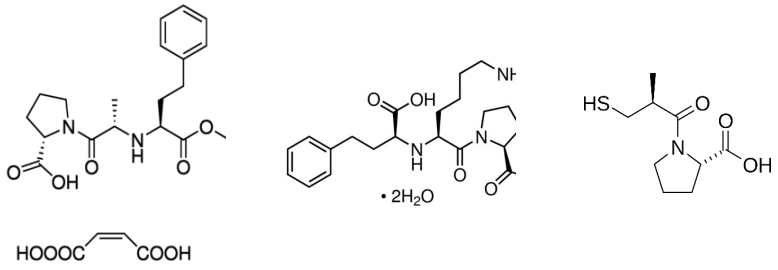
The use of TTS ensures the stability of the concentration and long-term therapeutic level of the substance in the bloodstream, which contributes to the prolongation of the therapeutic effect [56, 57]. TTS, compared to oral drug forms (DF), eliminate the risks of developing gastrointestinal adverse reactions, which increases their safety profile. When using transdermal patches, a reduction in dosing frequency is achieved, and high systemic bioavailability of substance is ensured. TTS are convenient to use and significantly increase compliance with the treatment regimen [58, 59].

Many APIs, including antihypertensive agents, are being investigated by pharmaceutical companies for systemic transdermal use [60, 61]. Advances in formulation development continue to make transdermal patches capable of delivering more complex drugs. Transdermal patches can be tailored and designed according to the physicochemical properties of the active and inactive ingredients, as well as suitability for long-term use. Therefore, a number of chemical approaches and physical methods are currently being investigated for the development of transdermal patches [62, 63].

Successful delivery of the drug through the skin depends on the physicochemical properties of the drug: molecular weight (<500 Da), partition coefficient (log-P_{ow}≤5), melting temperature (<200 °C) and the potency of the drug, which is recommended in small daily doses [64–66]. But, in the case of developing a drug with an API that falls outside these ranges, the key to obtaining a successful TTS depends on a highly efficient drug delivery device. Effective TTS should be able to temporarily reduce or bypass skin barrier inhibition as a result of improved drug delivery to achieve therapeutic plasma drug concentrations [67].

In view of the prospective use for the transdermal route of administration of known antihypertensive drugs, in particular, ACE inhibitors, we focused on the first-generation drugs – enalapril maleate, lisinopril dihydrate, and captopril – which are the most studied according to clinical data [27, 68].

According to the classification of ACE inhibitors depending on the chemical structure (Fig. 1), captopril belongs to the group of sulfhydryl-containing compounds, and enalapril maleate and lisinopril belong to the substances – derivatives of dicarboxylic acids [69, 70]. These functional groups are partly responsible for the differences in the pharmacokinetic and safety profiles of the mentioned drugs. Captopril and lisinopril are the only ACE inhibitors that are not prodrugs that require activation by hepatic biotransformation. Lisinopril is the only ACE inhibitor that does not undergo metabolism in the liver [71, 72].



N,N-(1S)-3-Phenyl-1-(ethoxycarbonyl)propyl-L-alanyl-L-proline maleate (1:1)
$C_{24}H_{32}N_2O_5$, M.м. 492,5

Enalapril Maleate

(S)-1-[N2-(1-carboxy-3-phenylpropyl)-lysyl-proline dihydrate
$C_{21}H_{31}O_5N_3 \cdot 2H_2O$, M.м. 441,52

Lisinopril dihydrate

(2S)-1-[(2S)-2-Methyl-3-sulfanylpropanoyl]-pyrrolidine-2-carboxylic acid
$C_9H_{15}NO_3S$, M.м. 217,3

Captopril

Fig. 1. Structural and molecular formulas of ACE inhibitors

All compounds are APIs of synthetic origin and have a crystalline structure. The selected molecules have a number of different physicochemical properties: molecular size, partition coefficient (LogP), acid dissociation constant (pKa), melting point, and solubility in water (Table 1) [73, 74].

Table 1

Physicochemical characteristics of API molecules ACE inhibitors

API	Molecular size, Da	Partition coefficient, log$P_{o/w}$	Acid dissociation constant, pK_a	Melting point, °C	Solubility in water at pH 7.4 (mg/mL)
Captopril	217.29	1.13	9.8	104–108	160
Enalapril maleate	492.52	2.45	3.0; 5.4	143–147	25
Lisinopril dihydrate	441.5	–1.22	2.5; 4.0; 6.7; 10.1	148	20

Within these physicochemical properties of existing drugs, the selected molecules cover the entire range of values [75, 76]. Most ACE inhibitors contain both proton acceptor and proton donor groups, which can be ionized or protonated, respectively. Dicarboxylated ACE inhibitors behave as strong acids at a physiological (7.4) pH value [77]. Thiol-containing captopril is a weak acid (pKa 9.8) [78]. Most ACE inhibitors are prodrugs and are hydrolyzed to acidic active metabolites after administration, with the exception of lisinopril, which is already in an acidic form [79].

It is important to divide ACE inhibitors into lipo- and hydrophilic, as the differences between these drugs are fundamental and important. Lipophilicity is characterized by the *n*-octanol/water partition coefficient (log$P_{o/w}$). Lipophilicity is one of the most important properties of biologically active substances [80, 81] and affects absorption, distribution, binding to blood plasma proteins, and elimination of drugs [82, 83].

According to the literature, a number of authors investigated the relationship between lipophilicity and pharmacological activity of ACE inhibitors, duration of action and absorption [84–86].

Lipophilic ACE inhibitors (captopril, quinapril, perindopril, enalapril) dissolve well in fats, penetrate cell membranes and inhibit the renin-angiotensin system tissue. As a result, they can have a slightly greater activity than hydrophilic ACE inhibitors in the low-renin form of hypertension, in which mainly the tissue of the renin-angiotensin system is activated. On the other hand, lipophilic drugs easily penetrate the blood-brain barrier, which is manifested by a greater number of side effects from the central nervous system. Unlike lipophilic drugs, the hydrophilic ACE inhibitor lisinopril does not penetrate into tissues and cells, and its greater concentration is stored in the blood, which allows, on the one hand, to use it in smaller doses, on the other hand, it does not penetrate into adipose tissue, which is especially important for overweight patients. In fact, lisinopril has advantages over other ACE inhibitors in terms of effectiveness in patients with obesity and metabolic syndrome [87].

ACE inhibitors and their metabolites mostly have low lipophilicity. The lipophilic outer layer of the skin allows only moderately lipophilic, potent, and small molecules to passively penetrate into the deeper layers. This significantly limits the transdermal delivery of high molecular weight compounds, but for selected low molecular weight substances, it will not be a determining factor [88].

Selected molecules have advantageous starting positions for transdermal delivery. This is confirmed by many studies of transdermal forms of these drugs.

In the work (Darren R. Gullick et al.), for the optimal release of the drug, a dosage form of a patch with ethyl ether of captopril was developed using two commercially available bioadhesive polymers. The results of diffusion through the model membranes showed an increase in the flow of the substance with an increase in the thickness of the patch and its values reaching the therapeutic level. Captopril ethyl ether has been shown to penetrate human skin better than the parent drug. This study demonstrated that adhesion and drug loading are important factors in optimizing topical patch formulations for the delivery of captopril prodrugs [89].

A study of captopril as a possible candidate for transdermal drug delivery was also conducted in the development of transdermal patches using ethyl cellulose (EC), polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), polyethylene glycol-6000 (PEG6000). In vitro skin permeation studies showed that the matrix-type film (PVA: PEG6000: DMF) was found to be an effective system and showed the highest flux of 0.102 mg/cm^2/h [90].

The aim of the work (Pravin Uttekar et al.) was the development of matrix-type TTS containing the drug captopril using hydroxypropylmethylcellulose E-15 (HPMC E-15) and Eudragit RS 100 as polymers that control the release of captopril for a maximum period of time. The results indicate that the captopril-containing transdermal patch is a promising therapeutic approach to achieve maximum bioavailability and prolong the release of the drug [91].

Evaluation of formulations of transdermal patches made using another combination of HPMC K-15M with PVPK30 and EC in different ratios in captopril release experiments *in vitro* showed prolonged release of the drug within 24 h. It was found that the penetration of captopril from the developed transdermal patches occurs by the diffusion mechanism and is subject to zero-order release [92]. The pharmacodynamic activity of these transdermal patches containing captopril was evaluated in rats by measuring systolic blood pressure over 24 hours using the tail-cuff method. Blood pressure, heart rate, body and heart weight, and body and heart weight ratio were determined. The content of lactate dehydrogenase (LDH), creatine phosphokinase (CPK), glutathione (GSH), malondialdehyde (MDA), myeloperoxidase (MPO) and Na^+, K^+-ATPase was determined in the blood serum of rats. A histopathological evaluation of the heart tissue was carried out to determine any tissue damage. Blood pressure indicators in the arterial hypertension group, which received TTS with captopril, significantly decreased and became almost the same as the blood pressure indicators in the control group. These results suggest that matrix-type transdermal patches made of Eudragit RL 100 and RS 100 polymers containing captopril may be considered as transdermal therapeutic systems for the chronic treatment of arterial hypertension and congestive heart failure. Thus, it can be concluded that the transdermal delivery system can be used as a drug for captopril [93].

The patch with enalapril maleate based on hydroxypropylmethylcellulose was characterized by such physicochemical characteristics as thickness, mass change, drug content, and resistance to bending. *Ex vivo* skin permeation studies were performed using a Franz diffusion cell. The obtained data showed that the release of the active substance occurred according to the principle of diffusion according to the kinetics of the zero-order equation.

The results of the study show that enalapril maleate can be administered transdermally with matrix-type TTS for the effective control of arterial hypertension and the treatment of congestive heart failure and angina pectoris [94].

Pravin Gavali et al. investigated the possibility of using different concentrations and polymer grades of hydroxypropylmethylcellulose (K4M, K15M and K100M) for the development of transdermal delivery of enalapril maleate. The matrix films were evaluated by physicochemical characteristics followed by *in vitro* evaluation. *In vitro* drug release follows Higuchi kinetics, as the correlation coefficient of the values prevails over first-order kinetics. *In vitro* dissolution profiles using rat skin and human skin showed a slow and controlled release, indicating that it occurs by diffusion. The maximum release of the drug from this composition is 108.13 % up to 24 hours [95].

M Aqilet et al. developed a transdermal therapeutic system (TTS) of enalapril maleate (EM) using Eudragit E100 polymers, polyvinylpyrrolidone K-30 in various ratios and a penetration enhancer – piperidine hydrochloride. TTS EM evaluated drug release *in vitro* and skin permeation *ex vivo*. The transdermal form of the drug showed positive results of preclinical bioavailability and antihypertensive efficacy using the white rat model. The optimized composition provides enalapril maleate release *in vitro* at the level of 87.3 % and a flux of 380 μg/cm^2/h for 48 h. No chemical interaction between the drug and excipients and no signs of skin irritation were detected when using the patch. The developed composition was stable, with a preliminary shelf life of two years. In experimental hypertensive rats, a significant decrease in blood pressure was observed (p<0.001), which was maintained for 2 days. A three-fold improvement in the bioavailability of TTS was observed compared to commercially available tablets (AUC (from 0 to t): 1253.9 ng-h/mL compared to 422.88 ng-h/mL). These preclinical studies indicate the feasibility of EM matrix-type TTS for the two-day treatment of hypertension [96].

Enalapril maleate transdermal patch made using rosin and PVP in the form of a separate polymer film showed a stable release rate for 16 h and a drug release rate of 89.23 %. The data of *in vitro* studies, which were entered into various kinetic models, allowed us to assume that the release is subject to zero order. Thus, it was concluded that enalapril maleate transdermal patch may be a potential candidate for safe and effective controlled drug delivery over a long period of time [97].

As a transdermal route for potential drug delivery, proniosomal gel delivery has attracted attention because both nonionic surfactants and phospholipids themselves act as penetration enhancers. After applying proniosomes to the skin, they hydrate to form niosomal vesicles, and a high thermodynamic gradient of activity develops at the point of contact, which increases the permeability of the drug. The ratio of nonionic surfactants to cholesterol can change both the release characteristics and the encapsulation efficiency of entrapped drugs. It also improves the release and penetration of active substances through the skin and regulates the rate of the drug release mechanism. Reducing the size of vesicles due to nanoproniosomal technology can be the reason for increasing the rate and degree of drug diffusion. The main goal of the study (M. Sabareesh et al.) was to create a nanoproniosomal gel of enalapril maleate for the effective treatment of arterial hypertension by the transdermal route and to ensure better bioavailability. The study of penetration through the skin ex vivo showed that the highest percentage of penetration of the active substance from the drug was about 89.72 %.

During *in vivo* antihypertensive studies, it was established that the proniosomal gel composition of EM significantly (p<0.001) reduced blood pressure within limits close to normal values, and this level was maintained for 24 hours. This indicates that the drug penetrated and was constantly released into the systemic circula-

tion for up to 24 hours in the body of rats. At the same time, blood pressure indicators after treatment in the main group (D) were comparable to the control group (A). The drug was successful in returning the rats' blood pressure to normal values. The above results suggest that the proniosomal gel formulation of enalapril maleate has a promising future for the treatment of hypertension, which needs to be confirmed by clinical trials [98].

The results obtained (Jitendra Banweer et al.) of the study of the *in vitro* release of lisinopril dihydrate from a matrix-type plaster based on hydroxylpropyl methylcellulose (HPMC) and polyvinyl acetate (PVA) containing oleic acid and isopropyl alcohol in a 1:1 ratio showed the most promising flow of the medicinal substance in vitro and possessing excellent physicochemical properties at normal and accelerated temperature regimes [99].

The purpose of the work (Rajendra Messa, Srinivas Ampati) is to obtain transdermal films for the treatment of arterial hypertension with lisinopril dihydrate. The main interest of the authors in such a dosage form was to direct the drug to the site of its absorption, controlling the release of the drug in the therapeutic range for a longer time. Transdermal films of lisinopril dihydrate were obtained using HPMC K4M, HPMC K15M, Eudragit RS 100 and Eudragit RL 100 as polymers. Propylene glycol was used as a plasticizer, and SPAN20 as a penetration enhancer. The evaluation of their physicochemical properties and the study of release kinetics gave satisfactory results. The drug showed a high and controlled release activity both according to the in vitro drug diffusion profile and according to physicochemical parameters. In zero-order kinetics, the regression value of the drug was 0.992. The maximum diffusion of the medicinal product is achieved after 12 h when using the drug [100].

A transdermal patch based on the transphenosomal composition (Aparanjitha R. et al.) of lisinopril dihydrate was developed and evaluated. Lisinopril was encapsulated in a vesicle by the method of film hydration using various surfactants and characterized by transferase morphology, particle size, drug capture and release efficiency. The optimized transferase suspension was produced in the form of a transdermal patch by solvent casting and evaluated *in vitro*. Based on penetration studies, it was determined that the flux is 26.72±0.23 (μg/cm^2/h), and the cumulative amount of penetrating substance is (Q24) 751±0.94 μg/cm^2. The release of the substance from the patch was 84 %, which is better compared to the oral bioavailability of lisinopril [101].

Study limitations. The analysis of research conducted in the article on the development of transdermal forms of delivery of antihypertensive drugs is limited to the coverage of the use of only certain representatives of one group of APIs, in particular, ACE inhibitors.

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

6. Conclusions

The review of domestic and foreign literature confirmed the relevance of biopharmaceutical research in the field of development of innovative dosage forms – transdermal therapeutic systems for the treatment of hypertension.

The choice of promising antihypertensive APIs of the ACE group (enalapril maleate, lisinopril dihydrate, and captopril) is justified, considering their specific physicochemical properties that are suitable for penetration through the skin.

The market for transdermal drug delivery is increasing, and there is a prospect of higher growth rates in this market in the coming years.

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.

Financing

The research was funded by the Ministry of Health of Ukraine from the state budget according to the topic "Preformulation studies of biopharmaceutical properties of active pharmaceutical ingredients with antihypertensive action for the creation of innovative transdermal drug delivery systems" (state registration number: 0122U001605).

Data availability

The manuscript has no associated data.

References

1. Whelton, P. K., Carey, R. M., Aronow, W. S., Casey, D. E., Collins, K. J., Dennison Himmelfarb, C. et al. (2018). 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation, 138 (17), e426–e483. doi: https://doi.org/10.1161/cir.0000000000000597

2. Mills, K. T., Stefanescu, A., He, J. (2020). The global epidemiology of hypertension. Nature Reviews Nephrology, 16 (4), 223–237. doi: https://doi.org/10.1038/s41581-019-0244-2

3. Hypertension (2022). World Health Organization (WHO). Available at: https://www.who.int/health-topics/hypertension/#tab=tab_1

4. Stierman, B., Afful, J., Carroll, M. D., Chen, T. et al. (2021). National Health and Nutrition Examination Survey 2017 – March 2020 Prepandemic Data Files Development of Files and Prevalence Estimates for Selected Health Outcomes. National Center for Health Statistics (U.S.), NHSR No. 158. Available at: https://stacks.cdc.gov/view/cdc/106273

5. Marushko, Yu.V., Hyshchak, T.V. (2018). Arterialna hipertenziia u ditei ta pidlitkiv. Zdorov'ia Ukrainy. Pediatriia, 4 (47), 53–58. Available at: https://health-ua.com/multimedia/3/9/2/3/5/1547021303.pdf

6. Shlimkevych, I. V., Lembryk, I. S., Tsytsiura, O. O., Alekseieva, Yu. I., Zhyliak, O. V. (2022). Arterial hypertension in children and adolescents: a modern view at the problem (a literature review). Part 1. Zaporozhye Medical Journal, 24 (2), 248–253. doi: https://doi.org/10.14739/2310-1210.2022.2.235489

7. Senatorova, H. S., Honchar, M. O., Alenina, I. S. et al.; Senatorova, H. S. (Ed.) (2018). Arterialna hipertenziia u ditei. Kharkiv: PLANETA-PRYNT, 108.

8. Vsesvitnii den borotby z arterialnoiu hipertenziieiu. Derzhavna ustanova «Tsentr hromadskoho zdorov'ia Ministerstva okhorony zdorov'ia Ukrainy». Available at: https://www.phc.org.ua/news/vsesvitniy-den-borotbi-z-arterialnoyu-gipertenzieyu

9. Kumar, G., Virmani, T., Pathak, K., Alhalmi, A. (2022). A Revolutionary Blueprint for Mitigation of Hypertension via Nanoemulsion. BioMed Research International, 2022, 1–12. doi: https://doi.org/10.1155/2022/4109874

10. Li, C., Wang, J., Wang, Y., Gao, H., Wei, G., Huang, Y. et al. (2019). Recent progress in drug delivery. Acta Pharmaceutica Sinica B, 9 (6), 1145–1162. doi: https://doi.org/10.1016/j.apsb.2019.08.003

11. Bird, D., Ravindra, N. M. (2020). Transdermal drug delivery and patches – An overview. Medical Devices & Sensors, 3 (6). doi: https://doi.org/10.1002/mds3.10069

12. Zhao, Z., Ukidve, A., Kim, J., Mitragotri, S. (2020). Targeting Strategies for Tissue-Specific Drug Delivery. Cell, 181 (1), 151–167. doi: https://doi.org/10.1016/j.cell.2020.02.001

13. Lee, H., Song, C., Baik, S., Kim, D., Hyeon, T., Kim, D.-H. (2018). Device-assisted transdermal drug delivery. Advanced Drug Delivery Reviews, 127, 35–45. doi: https://doi.org/10.1016/j.addr.2017.08.009

14. Steven, J. M. (2019). Press Release Transdermal Drug Delivery Market – Global Drivers, Restraints, Opportunities, Trends, and Forecasts, 2017–2023.

15. Ramadon, D., McCrudden, M. T. C., Courtenay, A. J., Donnelly, R. F. (2021). Enhancement strategies for transdermal drug delivery systems: current trends and applications. Drug Delivery and Translational Research, 12 (4), 758–791. doi: https://doi.org/10.1007/s13346-021-00909-6

16. Guo, D., Dou, D., Li, X., Zhang, Q., Bhutto, Z. A., Wang, L. (2017). Ivermection-loaded solid lipid nanoparticles: preparation, characterisation, stability and transdermal behaviour. Artificial Cells, Nanomedicine, and Biotechnology, 46 (2), 255–262. doi: https://doi.org/10.1080/21691401.2017.1307207

17. Vargason, A. M., Anselmo, A. C., Mitragotri, S. (2021). The evolution of commercial drug delivery technologies. Nature Biomedical Engineering, 5 (9), 951–967. doi: https://doi.org/10.1038/s41551-021-00698-w

18. Facts About Hypertension (2022). Centers for Disease Control and Prevention. Atlanta: Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/bloodpressure/facts.htm

19. Vsesvitnii den borotby z arterialnoiu hipertenziieiu (2022). Available at: https://www.oblses.ck.ua/index.php?view=article&catid=41%3A2013-05-13-02-14-47&id=2898%3Avsesvitnii-den-borotby-z-arterialnoiu-hipertenziieiu&format=pdf&option=com_content&Itemid=57

20. Khyts, A. (2021). Suchasni mozhlyvosti likuvannia arterialnoi hipertenzii: fokus na ostanni rekomendatsii ISH 2020. Ukrainskyi medychnyi chasopys. Available at: https://www.umj.com.ua/article/208823/suchasni-mozhlivosti-likuvannya-arterialnoyi-gipertenziyi-fokus-na-ostanni-rekomendatsiyi-ish-2020

21. Korol, S. V. (2021). Arterialna hipertenziia: ohliad suchasnykh rekomendatsii. Zdorov'ia Ukrainy 21 storichchia, 11-12 (504-505). Available at: https://health-ua.com/multimedia/6/6/2/4/2/1626685365.pdf

22. Guideline for the pharmacological treatment of hypertension in adults (2021). Geneva: World Health Organization. Available at: https://apps.who.int/iris/bitstream/handle/10665/344424/9789240033986-eng.pdf

23. Kulkarni, S., Graggaber, J. (2022). How to improve compliance to hypertension treatment. European Society of Cardiology, 22 (6). Available at: https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-22/how-to-improve-compliance-to-hypertension-treatment

24. Mishchenko, L. A., Hulkevych, O. V. (2021). Nekontrolovana arterialna hipertenziia: dodatkovi mozhlyvosti pokrashchennia arterialnoho tysku ta yakosti zhyttia patsiientiv. Zdorov'ia Ukrainy 21 storichchia, 6 (499), 45–47. Available at: https://health-ua.com/multimedia/6/4/7/0/4/1619439395.pdf

25. Unger, T., Borghi, C., Charchar, F., Khan, N. A., Poulter, N. R., Prabhakaran, D. et al. (2020). 2020 International Society of Hypertension global hypertension practice guidelines. Journal of Hypertension, 38 (6), 982–1004. doi: https://doi.org/10.1097/hjh.0000000000002453

26. Chen, Y. J., Li, L. J., Tang, W. L., Song, J. Y., Qiu, R., Li, Q. et al. (2018). First-line drugs inhibiting the renin angiotensin system versus other first-line antihypertensive drug classes for hypertension. Cochrane Database of Systematic Reviews, 2018 (11). doi: https://doi.org/10.1002/14651858.cd008170.pub3

27. Herman, L. L., Padala, S. A., Ahmed, I., Bashir, K. (2022). Angiotensin Converting Enzyme Inhibitors (ACEI). StatPearls. Treasure Island (FL). Available at: https://www.ncbi.nlm.nih.gov/books/NBK431051/

28. Goyal, A., Cusick, A. S., Thielemier, B. (2022). ACE Inhibitors. StatPearls. Treasure Island. Available at: https://www.ncbi.nlm.nih.gov/books/NBK430896/

29. Fountain, J. H., Lappin, S. L. (2022). Physiology, Renin Angiotensin System. StatPearls. NCBI Bookshelf version. StatPearls Publishing.

30. Angiotensin Converting Enzyme (ACE) Inhibitors. Clinical Pharmacology (2021). Elsevier.

31. Sirenko, Yu. M., Radchenko, H. D. (2004). Rol inhibitoriv anhiotenzynperetvoriuiuchoho fermentu v suchasnomu likuvanni khvorykh z arterialnoiu hipertenziieiu. Ukraynskyi kardyolohycheskyi zhurnal.

32. Emilie, W. (2022). ACE Inhibitors: A Class and Utilization Review. Cardiology ADVISOR. Available at: https://www.thecardiologyadvisor.com/ddi/ace-inhibitors/

33. Sirenko, Yu. M. (2006). Rol inhibitoriv anhiotenzynperetvoriuiuchoho fermentu v suchasnomu likuvanni sertsevo-sudynnykh zakhvoriuvan. Ratsionalna farmakoterapiia, 1 (1). Available at: https://rpht.com.ua/ua/archive/2006/1%281%29/article-4/rol-ingibitoriv-angiotenzinperetvoryuyuchogo-fermentu-v-suchasnomu-likuvanni-sercevo-sudinnih-zahvoryuvan#

34. Rohman, M. S., Fajar, J. K., Kuncahyo, B. H., Yunita, L., Sidarta, E. P., Saka, P. N. B. et al. (2018). Angiotensin-converting enzyme (ACE) I/D and bradykinin B2 receptor T/C genes polymorphism in patients with ACE inhibitors-related cough. Egyptian Journal of Medical Human Genetics, 19 (4), 307–313. doi: https://doi.org/10.1016/j.ejmhg.2018.05.006

35. Rahman, M., Pressel. S., Davis, B. R., Nwachuku, C. et al. (2005). Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Archives of Internal Medicine, 165 (8), 936–946. doi: https://doi.org/10.1001/archinte.165.8.936

36. Anthony, A. B. (2016). Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – ALLHAT. American College of Cardiology. Available at: https://www.acc.org/latest-in-cardiology/clinical-trials/2014/02/25/15/55/allhatnbsp8212nbsppresented-at-aha-2009

37. Unger, T., Paulis, L., Sica, D. A. (2011). Therapeutic perspectives in hypertension: novel means for renin-angiotensin-aldosterone system modulation and emerging device-based approaches. European Heart Journal, 32 (22), 2739–2747. doi: https://doi.org/10.1093/eurheartj/ehr253

38. Voronkov, L. H. (2007). Inhibitory APF ta adrenoblokatory u likuvanni khronichnoi sertsevoi nedostatnosti: klinichna rol ta metodolohiia zastosuvannia. Ratsionalna farmakoterapiia, 2 (3). Available at: https://rpht.com.ua/ua/archive/2007/2%283%29

39. Choi, I. S., Park, I. B., Lee, K., Ahn, T. H., Kim, J. H., Ahn, Y. et al. (2018). Angiotensin-Converting Enzyme Inhibitors Provide Better Long-Term Survival Benefits to Patients With AMI Than Angiotensin II Receptor Blockers After Survival Hospital Discharge. Journal of Cardiovascular Pharmacology and Therapeutics, 24 (2), 120–129. doi: https://doi.org/10.1177/1074248418795897

40. Enalapril: Uses, Interaction, Mechanism of Action (2022). DrugBank: a knowledgebase for drugs, drug actions and drug targets. Available at: https://go.drugbank.com/drugs/DB00584

41. Lam, P. H., Packer, M., Fonarow, G. C., Faselis, C., Allman, R. M., Morgan, C. J., Singh, S. N., Pitt, B., Ahmed, A. (2020). Early Effects of Starting Doses of Enalapril in Patients with Chronic Heart Failure in the SOLVD Treatment Trial. The American Journal of Medicine, 133 (2), e25–e31. doi: https://doi.org/10.1016/j.amjmed.2019.06.053

42. Enalaprilum. Kompendium. Likarski preparaty. Available at: https://compendium.com.ua/dec/270895/#

43. Olvera, L. E., Parmar, M., Pendela, V. S., Jamie M. Terrell (2022). Lisinopril. StatPearls. Treasure Island, StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK482230/

44. Soloshenko, O. S., Serhyenko, O. M. (2011). Vibor preparata hruppi ynhybytorov APF: effektyvnost, bezopasnost y dostupnost dlia patsyenta. Ukrainskyi Medychnyi Chasopys. Likariu-praktyku, 1 (81), 60–64. Available at: https://www.umj.com.ua/article/9848/vybor-preparata-gruppy-ingibitorov-apf-effektivnost-bezopasnost-i-dostupnost-dlya-pacienta#list

45. Lizynopryl (Lisinopril). Kompendium. Likarski preparaty. Available at: https://compendium.com.ua/uk/akt/76/3045/lisinoprilum/

46. Obied, A. H. H., Ahmed, A. A. E. (2021). Evaluation of the clinical outcome of captopril use for hypertensive urgency in Khartoum State's emergency centres. African Journal of Emergency Medicine, 11 (1), 202–206. doi: https://doi.org/10.1016/j.afjem.2020.10.003

47. Chekman, I. S., Horchakova, N. O., Kazak, L. I. et al.; Chekman, I. S. (Ed.) (2017). Farmakolohiia. Vinnytsia: Nova Knyha, 784.

48. Kaptopryl (Captoprilum). Kompendium. Likarski preparaty. Available at: https://compendium.com.ua/akt/67/3102/captoprilum/#toc-0

49. Park, S. (2019). Ideal Target Blood Pressure in Hypertension. Korean Circulation Journal, 49 (11), 1002–1009. doi: https://doi.org/10.4070/kcj.2019.0261

50. Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E., Azizi, M., Burnier, M. et al. (2018). 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal, 39 (33), 3021–3104. doi: https://doi.org/10.1093/eurheartj/ehy339

51. Abegaz, T. M., Shehab, A., Gebreyohannes, E. A., Bhagavathula, A. S., Elnour, A. A. (2017). Nonadherence to antihypertensive drugs: A systematic review and meta-analysis. Medicine (Baltimore), 96 (4), e5641. doi: https://doi.org/10.1097/md.0000000000005641

52. Abbas, H., Hallit, S., Kurdi, M., Karam, R. (2022). Non-adherence to antihypertensive medications in Lebanese adults hospitalized for hypertensive urgency and its cost. BMC Cardiovascular Disorders, 22 (1). doi: https://doi.org/10.1186/s12872-022-02907-z

53. Lane, D., Lawson, A., Burns, A., Azizi, M., Burnier, M., Jones, D. J. L. et al. (2022). Nonadherence in Hypertension: How to Develop and Implement Chemical Adherence Testing. Hypertension, 79 (1), 12–23. doi: https://doi.org/10.1161/hypertensionaha.121.17596

54. Tan, F. C. J. H., Oka, P., Dambha-Miller, H., Tan, N. C. (2021). The association between self-efficacy and self-care in essential hypertension: a systematic review. BMC Family Practice, 22 (1). doi: https://doi.org/10.1186/s12875-021-01391-2

55. Mali, A. D., Bathe, R., Patil, M. (2015). An updated review on transdermal drug delivery systems. International Journal of Advances in Scientific Research, 1 (6), 244–254. doi: https://doi.org/10.7439/ijasr.v1i6.2243

56. Pastore, M. N., Kalia, Y. N., Horstmann, M., Roberts, M. S. (2015). Transdermal patches: history, development and pharmacology. British Journal of Pharmacology, 172 (9), 2179–2209. doi: https://doi.org/10.1111/bph.13059

57. Singh, I., Morris, A. (2011). Performance of transdermal therapeutic systems: Effects of biological factors. International Journal of Pharmaceutical Investigation, 1 (1), 4–9. doi: https://doi.org/10.4103/2230-973x.76721

58. Jeong, W. Y., Kwon, M., Choi, H. E., Kim, K. S. (2021). Recent advances in transdermal drug delivery systems: a review. Biomaterials Research, 25 (1). doi: https://doi.org/10.1186/s40824-021-00226-6

59. Vons, B. V., Chubka, M. B., Hroshovyi, T. A. (2017). Transdermal drug delivery system. Pharmaceutical Review, 2, 106–112. doi: https://doi.org/10.11603/2312-0967.2017.2.7902

60. Pavan, K. Y., Saurabh M. (2017). Transdermal patch of an antihypertensive drug: its development and evaluation. World Journal of Pharmaceutical Research, 6 (4), 1355–1374. doi: https://doi.org/10.20959/wjpr20174-8214

61. Rastogi, V., Pragya, U. P. (2012). A Brief View on Antihypertensive Drugs Delivery through Transdermal Patches. International Journal of Pharmaceutical Sciences and Research, 3 (7), 1955–1970. Available at: https://www.academia.edu/35565081/

62. Al Hanbali, O. A., Khan, H. M. S., Sarfraz, M., Arafat, M., Ijaz, S., Hameed, A. (2019). Transdermal patches: Design and current approaches to painless drug delivery. Acta Pharmaceutica, 69 (2), 197–215. doi: https://doi.org/10.2478/acph-2019-0016

63. Sharma, P. K., Panda, A., Pradhan, A., Zhang, J., Thakkar, R., Whang, C.-H. et al. (2017). Solid-State Stability Issues of Drugs in Transdermal Patch Formulations. AAPS PharmSciTech, 19 (1), 27–35. doi: https://doi.org/10.1208/s12249-017-0865-3

64. Liu, C., Quan, P., Fang, L. (2016). Effect of drug physicochemical properties on drug release and their relationship with drug skin permeation behaviors in hydroxyl pressure sensitive adhesive. European Journal of Pharmaceutical Sciences, 93, 437–446. doi: https://doi.org/10.1016/j.ejps.2016.08.048

65. Chandrashekar, N., Shobha Rani, R. (2008). Physicochemical and pharmacokinetic parameters in drug selection and loading for transdermal drug delivery. Indian Journal of Pharmaceutical Sciences, 70 (1), 94–96. doi: https://doi.org/10.4103/0250-474x.40340

66. Kokate, A., Li, X., Jasti, B. (2008). Effect of Drug Lipophilicity and Ionization on Permeability Across the Buccal Mucosa: A Technical Note. AAPS PharmSciTech, 9 (2), 501–504. doi: https://doi.org/10.1208/s12249-008-9071-7

67. Rahbari, R., Ichim, I., Bamsey, R., Burridge, J., Guy, O. J., Bolodeoku, J., Graz, M. (2020). Characterisation of Drug Delivery Efficacy Using Microstructure-Assisted Application of a Range of APIs. Pharmaceutics, 12(12), 1213. doi: https://doi.org/10.3390/pharmaceutics12121213

68. M Elhaj, B., Hamad Farah, F., Saad Ali, H. (2021). Captopril: An Overview of Discovery, Development, and Post-marketingSurveillance as an Effective Anti-hypertensive Drug. Acta Scientific Pharmaceutical Sciences, 5 (4), 6–9. doi: https://doi.org/10.31080/asps.2021.05.0695

69. Regulski, Mil. osz, Regulska, K., Stanisz, B., Murias, M., Gieremek, P., Wzgarda, A., Niz.nik, Bartl. omiej. (2015). Chemistry and Pharmacology of Angiotensin-Converting Enzyme Inhibitors. Current Pharmaceutical Design, 21 (13), 1764–1775. doi: https://doi.org/10.2174/1381612820666141112160013

70. Patel, R. N. (2016). Applications of Biocatalysis for Pharmaceuticals and Chemicals. Organic Synthesis Using Biocatalysis. Academic Press, 339–411. doi: https://doi.org/10.1016/b978-0-12-411518-7.00011-1

71. Panchyshyn, Yu. M. (2012). Praktychni aspekty zastosuvannia inhibitoriv APF u khvorykh iz kardiovaskuliarnoiu patolohiieiu. Ratsionalna farmakoterapiia, 3 (24), 22–29. Available at: https://rpht.com.ua/ua/archive/2012/3%2824%29/pages-22-29/praktichni-aspekti-zastosuvannya-ingibitoriv-apf-u-hvorih-iz-kardiovaskulyarnoyu-patologiieyu

72. Piepho, R. W. (2000). Overview of the angiotensin-converting-enzyme inhibitors. American Journal of Health-System Pharmacy, 57 (1), S3–S7. doi: https://doi.org/10.1093/ajhp/57.suppl_1.s3

73. Derzhavna Farmakopeia Ukrainy (2015). Kharkiv: Derzhavne pidpryiemstvo «Ukrainskyi naukovyi- farmakopeinyi tsentr yakosti likarskykh zasobiv», 1128.

74. European Pharmacopoeia. European Directorate for the Quality of Medicines (2019). Strasbourg, 4370.

75. Andújar-Sánchez, M., Cámara-Artigas, A., Jara-Pérez, V. (2004). A calorimetric study of the binding of lisinopril, enalaprilat and captopril to angiotensin-converting enzyme. Biophysical Chemistry, 111 (2), 183–189. doi: https://doi.org/10.1016/j.bpc.2004.05.011

76. Hillaert, S., Van den Bossche, W. (2000). Optimization of capillary electrophoretic separation of several inhibitors of the angiotensin-converting enzyme. Journal of Chromatography A, 895 (1-2), 33–42. doi: https://doi.org/10.1016/s0021-9673(00)00591-4

77. Remko, M. (2006). Acidity, Lipophilicity, Solubility, Absorption, and Polar Surface Area of Some ACE Inhibitors. Chemical Papers, 61 (2), 133–141. doi: https://doi.org/10.2478/s11696-007-0010-y

78. Spiller, H. A. (2014). Angiotensin Converting Enzyme (ACE) Inhibitors. Encyclopedia of Toxicology, 14–16. doi: https://doi.org/10.1016/b978-0-12-386454-3.00686-2

79. Foye, W. O., Lemke, T. L., Williams, D. A. (2008). Foye's principles of medicinal chemistry. Lippincott Williams & Wilkins. Available at: https://www.worldcat.org/title/foyes-principles-of-medicinal-chemistry/oclc/145942325

80. Di, L., Kerns, E. H. (2003). Profiling drug-like properties in discovery research. Current Opinion in Chemical Biology, 7 (3), 402–408. doi: https://doi.org/10.1016/s1367-5931(03)00055-3

81. Hartmann, T., Schmitt, J. (2004). Lipophilicity – beyond octanol/water: a short comparison of modern technologies. Drug Discovery Today: Technologies, 1 (4), 431–439. doi: https://doi.org/10.1016/j.ddtec.2004.10.006

82. Odovic, J., Markovic, B., Trbojevic-Stankovic, J., Vladimirov, S., Karljikovic-Rajic, K. (2013). Evaluation of ACE inhibitors lipophilicity using in silico and chromatographically obtained hydrophobicity parameters. Hemijska Industrija, 67 (2), 209–216. doi: https://doi.org/10.2298/hemind120522078o

83. Bruno, C. D., Harmatz, J. S., Duan, S. X., Zhang, Q., Chow, C. R., Greenblatt, D. J. (2021). Effect of lipophilicity on drug distribution and elimination: Influence of obesity. British Journal of Clinical Pharmacology, 87 (8), 3197–3205. doi: https://doi.org/10.1111/bcp.14735

84. Remko, M., Swart, M., Bickelhaupt, F. M. (2006). Theoretical study of structure, pKa, lipophilicity, solubility, absorption, and polar surface area of some centrally acting antihypertensives. Bioorganic & Medicinal Chemistry, 14 (6), 1715–1728. doi: https://doi.org/10.1016/j.bmc.2005.10.020

85. Stella, V. J., Borchardt, R. T., Hageman, M. J., Oliyai, R., Maag, H., Tilley, J. W. (Eds.) (2007). Prodrugs: Challenges and Rewards. Biotechnology: Pharmaceutical Aspects. New York: Springer Science, Business Media, 1464. doi: https://doi.org/10.1007/978-0-387-49785-3

86. Trbojevic, J., Odovic, J., Trbojevic-Stankovic, J., Stojimirovic, B., Jelic, R. (2017). The Evaluation of Angiotensin-Converting Enzyme Inhibitors in Renal Elimination with Selected Molecular Descriptors. Serbian Journal of Experimental and Clinical Research, 18 (2), 119–123. doi: https://doi.org/10.1515/sjecr-2016-0100

87. Barna, O. N. (2015). Mistse Dyrotonu sered inhibitoriv APF: vid farmakokinetyky do farmakoekonomiky. Zdorov'ia Ukrainy. Medychni vydannia. Available at: https://health-ua.com/article/18708-mstce-dirotonu-sered-ngbtorv-apf-vd-farmakoknetiki-do-farmakoekonomki

88. Zheng, W., Tian, E., Liu, Z., Zhou, C., Yang, P., Tian, K. et al. (2022). Small molecule angiotensin converting enzyme inhibitors: A medicinal chemistry perspective. Frontiers in Pharmacology, 13. doi: https://doi.org/10.3389/fphar.2022.968104

89. Gullick, D. R., Pugh, W. J., Ingram, M. J., Cox, P. A., Moss, G. P. (2010). Formulation and characterization of a captopril ethyl ester drug-in-adhesive-type patch for percutaneous absorption. Drug Development and Industrial Pharmacy, 36 (8), 926–932. doi: https://doi.org/10.3109/03639040903585135

90. Duraivel, S., Rajalakshmi, A.N., Debjit B. (2014). Formulation and evaluation of captopril Transdermal Patches. Elixir Pharmacy, 76, 28209–28213.

91. Pravin, U., Akshata, K., Pravin, C., Manoj, D., Vishal, D. (2016). Formulation and Evaluation of Captopril Transdermal patches for the treatment of hypertension. Available online at www.scholarsresearchlibrary.com. Scholars Research Library. Der Pharmacia Lettre, 8 (5), 12–16.

92. Dhanabal, C. (2019). Formulation and Evaluation of Transdermal Delivery System Comprising Captopril as Antihypertensive Drug. Coimbatore: RVS College of Pharmaceutical Sciences.

93. Kerımoğlu, O., Şahbaz, S., Şehırlı, Ö., Ozdemır, Z. N., Şule Çetınel, Dortunç, B., Şener, G. (2015). Pharmacodynamical evaluation of matrix type transdermal therapeutic systems containing captopril. Acta Pol Pharm., 72 (4), 799–806. Available at: https://pubmed.ncbi.nlm.nih.gov/26647638/

94. Natrajan, R., Rajendran, N.N., Sabareesh, M., Selvaraj, S. (2011). Formulation and evaluation of transdermal delivery of enalapril maleate. International Journal of Pharmaceutical Research., 3, 73–78. Available at: https://www.researchgate.net/publication/287472077_Formulation_and_evaluation_of_transdermal_delivery_of_enalapril_maleate

95. Gavali, P., Gaikwad, A., Radhika, P. R., Sivakumar, T. (2010). Design and development of hydroxypropyl methylcellulose (HPMC) based polymeric film of enalapril maleate. InternationalJournal of PharmTech Research, 2 (1), 274–282. Available at: https://sphinxsai.com/sphinxsaivol_2no.1/pharmtech_vol_2no.1/PharmTech_Vol_2No.1PDF/PT%20=44%20(274-282).pdf

96. Aqil, M., Bhavna, Chowdhary, I., Sultana, Y., Talegaonkar, S., Ahmad, F. J., Ali, M. M. (2008). Transdermal Therapeutic System of Enalapril Maleate Using Piperidine as Penetration Enhancer. Current Drug Delivery, 5 (2), 148–152. doi: https://doi.org/10.2174/156720108783954860

97. Pramod, K. P., Ramesh, K., Rashmi, M. B., Rajarajan, S. (2019). Formulation and Evaluation of Transdermal Patches of an Antihypertensive Drug for Controlled Release. Journal of Emerging Technologies and Innovative Research (JETIR), 6 (6), 444–452. Available at: https://www.jetir.org/papers/JETIR1906210.pdf

98. Sabareesh, M., Yanadaiah, J. P., Chandra Sekhar, K. B. (2020). A Novel Vesicular Approach For Transdermal Administration Of Enalapril Maleate Loaded Nanoproniosomal Gel: Formulation, Ex Vivo Evaluation And In Vivo Antihypertensive Study. International Journal of Applied Pharmaceutics, 12 (5), 190–202. doi: https://doi.org/10.22159/ijap.2020v12i5.38463

99. Jitendra, B., Pathaka, A. K., Subhash. P. (2010). Development and Optimization of Transdermal System of Lisinopril dehydrate: Employing Permeation Enhancers. Iranian Journal of Pharmaceutical Sciences, 6 (4). Available at: http://www.ijps.ir/article_2166.html

100. Rajendra, M., Srinivas, A. (2015). Formulation and Characterization Transdermal Patches for Enhancing the Bio-Availability of Lisinopril Dihydrate. International Journal of Medicine and Nanotechnology, 2 (6), 306–310. Available at: https://www.researchgate.net/publication/296573307

101. Aparanjitha, R., Sunitha, R. M., Sarangapani, M. (2020). Formulation And In Vitro Evaluation of Transferosomal Patches for Enhanced Drug Delivery of Lisinopril Dihydrate. Journal of Scientific Research, 64 (3), 105–109. doi: https://doi.org/10.37398/jsr.2020.640318

Received date 20.03.2023
Accepted date 10.08.2023
Published date 18.08.2023

Tatyana Shyteyeva, PhD, Leading Researcher, State Research Laboratory for Quality Control of Medicinal Products, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Elena Bezchasnyuk, PhD, Associate Professor, State Scientific Research Laboratory for Quality Control of Medicines, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Oleg Kryskiv*, PhD, Associate Professor, Department of General Chemistry, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Vasyl Grynenko, PhD, Associate Professor, Department of Pharmaceutical Chemistry, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

***Corresponding author:** Oleg Kryskiv, e-mail: oleg.kryskiw@gmail.com*