UDC 615.011/.014.2:615.477.66:615.322:615.015.12
DOI: 10.15587/2519-4852.2022.259877

EXPERIMENTAL RESEARCH ON THE DEVELOPMENT OF THE COMPOSITION OF THE TRANSDERMAL THERAPEUTIC SYSTEM OF ANTI-INFLAMMATORY ACTION BASED ON COMPOSITION OF NATURAL SUBSTANCES

Liliia Vyshnevska, Anastasia Olefir, Dmytro Lytkin, Liubov Bodnar

The aim of the work *is to develop the composition of the transdermal therapeutic system of anti-inflammatory action based on active pharmaceutical ingredients of natural origin.*
Materials and methods. *Selection of adhesive materials, plasticizers and solvents, the effect of introduction to the base of active pharmaceutical ingredients, determination of optimal temperature and drying time, pharmacological screening was performed by physicochemical, biopharmaceutical and biological research methods.*
Results. *The composition of the hydrophilic adhesive composition, which includes polyvinylpyrrolidone, eudragit (adhesives), PEO-400 (plasticizer), isopropyl alcohol (solvent) 50: 8: 12: 30, respectively. This composition has excellent organoleptic properties, is easily applied to the polymer base, holds its shape well (does not flow beyond the base), is applied in a thin layer and evenly distributed on the base. The optimal mode of drying of the adhesive composition based on PVP is 75 °C for 30 min, based on PVA – 75 °C for 35 min, the composition containing eudragit – 50 °C for 10 min. It is established that the addition of active substances to the adhesive composition does not adversely affect its properties.*
The study of antiexudative activity using different combinations of substances of natural origin as API and found that the best anti-inflammatory properties (25 %) have a sample No. 4, which includes dry extracts of white willow bark and sage leaves and quercetin 3:1:3 in accordance.
Conclusions. *Based on physicochemical, biopharmaceutical and pharmacological studies, the composition of the transdermal therapeutic system of anti-inflammatory action with active pharmaceutical ingredients of natural origin has been developed*
Keywords: *transdermal patches, composition, extract of white willow bark, sage extract of medicinal leaves, quercetin*

How to cite:
Vyshnevska, L., Olefir, A., Lytkin, D., Bodnar, L. (2022). Experimental research on the development of the composition of the transdermal therapeutic system of anti-inflammatory action based on composition of natural substances. ScienceRise: Pharmaceutical Science, 3 (37), 12–18. doi: http://doi.org/10.15587/2519-4852.2022.259877

1. Introduction

Inflammatory connective tissue diseases, namely arthritis, are quite common among people of all ages, but are most common in people over 40 years, with women getting sick 3 times more often than men. In general, arthritis of various etiologies affects about 5 % of the world's population [1].

In most cases, arthritis is chronic and requires long-term etiotropic, pathogenetic and symptomatic therapy. The basis of pathogenetic therapy is the principle of combating inflammation at different stages. The main stages of inflammation are alteration, exudation, and proliferation. Most topical anti-inflammatory drugs are aimed at eliminating the inflammatory process at the stage of exudation. For this purpose, drugs are used, the active substances of which are usually non-steroidal anti-inflammatory drugs, the main disadvantage of which is the presence of ulcerogenic effect [2, 3]. However, given the long course of therapy, it is important to replace the classic synthetic anti-inflammatory active pharmaceutical ingredients (API) with their alternatives of natural origin [4].

Medicines in the form of ointments, creams, gels, patches, lotions, etc. are used for local therapy of arthritis. The most promising among them are means in the form of transdermal patches, which could have not only local but also systemic effect [5, 6]. Their main advantages are ease of use and increased compliance with patients. The patches are transdermal, or they are also called transdermal therapeutic systems (TTS), usually consist of a base – an external light-protective covering which is impermeable to water and medicinal substances; a carrier of a medicinal product containing the active substance (reservoir or matrix, depending on the type of TTS structure); liner – a temporary protective film, which is removed before the application of TTS (the liner on one or two sides should be applied anti-adhesive coating) [7, 8]. Transdermal patches are elastic drugs of different sizes that contain one or more active substances [9, 10]. Their purpose is to transfer the active substance through the skin barrier into the systemic circulation when applied to intact skin [11, 12].

The aim of the study is to develop the composition of the transdermal therapeutic system of anti-in-

flammatory action with the content of active pharmaceutical ingredients of natural origin.

2. Research planning (methodology)

Anti-inflammatory TTS are represented on the Ukrainian pharmaceutical market by synthetic active substances [13], so the prospect of using herbal active substances in anti-inflammatory patches is extremely high. As an API, it is advisable to use plant extracts or other natural substances with anti-inflammatory action. For example, promising from this point of view are extracts from medicinal plant raw materials, which has a long history in pharmacy: white willow bark, sage leaves.

The properties of white willow bark are related to the chemical content of salicin in its chemical composition. Salicin has antipyretic, analgesic, diaphoretic effect, and prevents thrombosis. Compared to synthetic salicylates, the effect is slower, but lasts longer and has no negative effect on the gastrointestinal tract. The absence of ulcerogenic action, natural origin, as well as the presence of additional effects, hemostatic, disinfectant, antirheumatic, etc., are the undeniable advantages of using a dry extract of white willow bark as an active substance [14].

Sage leaves have powerful anti-inflammatory, as well as analgesic, antipyretic, antispasmodic, antiseptic activity due to the content of the plant antibiotic salvin. Sage leaves are widely used in both folk and traditional medicine (drug "Salvin") [15, 16].

We were also interested in quercetin – a flavonoid of plant origin, which is characterized by anti-edema, antispasmodic, antihistamine, anti-inflammatory effect. In combination with nonsteroidal anti-inflammatory drugs could be used to enhance the effect of the latter and minimize ulcerogenic action [17, 18].

Also, to accelerate the action of the patch at the initial stage, it would be advisable to use mustard powder. Mustard has an irritating effect, which leads to dilation of blood vessels at the site of application of the drug and could promote faster entry of API into the bloodstream [19].

Thus, the design of our research was to develop the optimal composition of the patch base and to experimentally select the quantitative ratio of dried white willow extract, dried sage extract, quercetin, and mustard powder.

3. Materials and methods

The composition was developed using adhesives of polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), isopropyl alcohol (IPA), 2 % aqueous solution of polyacrylamide (PAA), eudragit, hydroxypropylmethylcellulose (HPMC) and and their combinations. Purified water, ethanol, glycerin, isopropyl alcohol were used as solvents, macrogol 400 and glycerin were used as plasticizers (Table 1).

To obtain samples in the laboratory used the following technology: after weighing and measuring all the components dissolved the adhesive in a suitable solvent, added plasticizer, using a homogenizer (Daihan HG-15A) mixed the mass to homogeneity, a spatula applied a thin layer of polymer, dried according to the established mode for each adhesive, after complete cooling applied anti-adhesive coating.

Table 1

The composition of model samples of hydrophilic adhesive compositions

Component, % / Sample	PVP	PVA	PAA	Eudragit	Glycerin	Pur. water	Ethanol	Macrogol 400	IPA	HPMC
No. 1	30	–	–	–	10	–	60	–	–	–
No. 2	40	–	–	–	10	–	50	–	–	–
No. 3	50	–	–	–	10	–	40	–	–	–
No. 4	60	–	–	–	10	–	30	–	–	–
No. 5	30	–	–	–	–	–	60	10	–	–
No. 6	40	–	–	–	–	–	50	10	–	–
No. 7	50	–	–	–	–	–	40	10	–	–
No. 8	–	5	–	–	90	–	–	5	–	–
No. 9	–	10	–	–	85	–	–	5	–	–
No. 10	–	15	–	–	80	–	–	5	–	–
No. 11	–	20	–	–	75	–	–	5	–	–
No. 12	20	5	–	–	35	–	35	5	–	–
No. 13	20	10	–	–	30	–	35	5	–	–
No. 14	10	20	–	–	30	–	35	5	–	–
No. 15	20	20	–	–	25	–	30	5	–	–
No. 16	5	20	–	–	35	–	35	5	–	–
No. 17	–	10	10	–	75	–	–	5	–	–
No. 18	10	–	10	–	–	–	80	–	–	–
No. 19	10	10	10	–	20	–	50	–	–	–
No. 20	10	10	10	–	20	–	45	5	–	–
No. 21	50	–	–	8	–	–	–	12	30	–
No. 22	–	20	–	10	10	45	–	–	–	–
No. 23	–	10	–	10	10	55	–	–	–	15

To select a sample for further research, a visual comparison of the organoleptic properties of the model compositions was performed immediately after preparation and after drying. Criteria for evaluating the properties were consistency, homogeneity, ease of application on a polymer base (polyethylene terephthalate film with a thickness of 50 μm), uniformity of distribution on the polymer base, appearance after drying. For clarity and to facilitate the selection of the sample, its own scale for evaluating indicators from 0 to 5 was developed, where:

– consistency – 0 – too thin or too thick consistency, which prevents further use of the model composition, 5 – adhered to the balance, in which the composition could be easily applied to the base, without spreading beyond it (as too liquid) and not have large losses when applied due to the delay on the spatula (as too thick);

– homogeneity – 0 – inhomogeneous mass with a large number of lumps or air bubbles, which stratifies, 5 – completely homogeneous mass;

– ease of application on a polymeric basis – 0 – the mass is difficult to apply, stretches on a spatula, a large number of it remains on the spatula, 5 – the mass is easily applied to the base, evenly distributed, does not linger on the spatula;

– uniformity of distribution on a polymeric basis – 0 – distribution is uneven, weight in some places gathers

in lumps, forming roughness of a surface, 5 – the mass is distributed in a uniform thin layer, forming a smooth flat surface;

– appearance after drying – 0 – deformed base, dull surface, the presence of cracks or undried areas, 5 – evenly dried, smooth shiny surface without changing the colour of the mass and shape of the base.

To determine the optimal temperature and drying time, drying in a thermostat (ST-50C) was performed at temperatures that are characteristic of each adhesive, selecting the optimal time that provides complete and uniform drying. For samples containing PVP and PVA – 75 °C for 15, 20, 25, 30, 35, 40 and 45 minutes. For samples containing eudragit – 50 °C for 5, 10, 15, 20 minutes.

When the API is introduced into the adhesive base, its rarefaction or, conversely, thickening can be observed, which in both cases leads to the difficulty of applying the mass to the polymer base. Studies of the effect of API administration were also performed by visual organoleptic control, compared with the original sample.

Dry plant extracts were obtained in previous studies at the Department of Pharmaceutical Technology of Medicines of the National University of Pharmacy: aqueous extract of white willow bark (series No. 178616), alcoholic extract of sage (series No. 178712).

Pharmacological studies were performed on 60 adult male rats weighing 160–180 g.

The design of the study included the formation of 6 groups of 6 animals in each: 1 – positive control (PC) – untreated animals with reproduced pathology; 2–6, – animals to which objects No. 1–5, respectively, were used against the background of pathology.

Transdermal patches under the codes No. 1–5 were applied to the injured paw 1 h before the introduction of phlogogen in an empirical dose of 250 mg/kg. The effectiveness of the samples was evaluated by inhibiting the development of limb edema in the dynamics after 1, 2, 3, 4 and 5 h in comparison with animals of the CP group and comparison drugs.

The results were presented as the difference between the foot volumes at the time of measurement and its initial value in ml. The volume of the foot was determined using a plethysmometer (PanLabLE7500, Spain). To integrate the effectiveness of the use of the studied objects in this pathology, the indicator of their anti-exudative activity (AEA, %) was calculated by the formula:

$$AEA=((\Delta Vc-\Delta Vd)/\Delta Vc)*100\ \%,$$

where AEA – antiexudative activity, an indicator of inhibition of edema in experimental animals in comparison with animals of the CP group, %;

ΔVd і ΔVcp – the difference between the volume of swollen and non-swollen foot in the experiment and in control, respectively, ml.

The obtained data were presented as the average value and its error ($M\pm m$). Comparisons between the experimental groups were performed using the nonparametric Kruskal-Wallis method and the Mann-Whitney test. Differences between study groups were considered statistically significant at $p<0.05$. The basic software package "Statistica 6" and Excel 2007 were used for statistical data processing [20].

4. Research results

Based on the results of the evaluation of the organoleptic properties of the studied samples, petal diagrams were constructed, which allow to choose the sample that has the best properties (Fig. 1–6).

In Figs. No. 1 and No. 2 we could see that among the samples based on PVP the best properties have samples that contain 50 % PVP, regardless of the plasticizer. The lower the adhesive content, the worse the ease of application to the polymer base and uniform distribution. Increasing the amount of adhesive adversely affects the quality of the sample after drying, and even with the addition of 60 % PVP, the sample becomes unsuitable for further use (shrinks, hardens and loses adhesive properties).

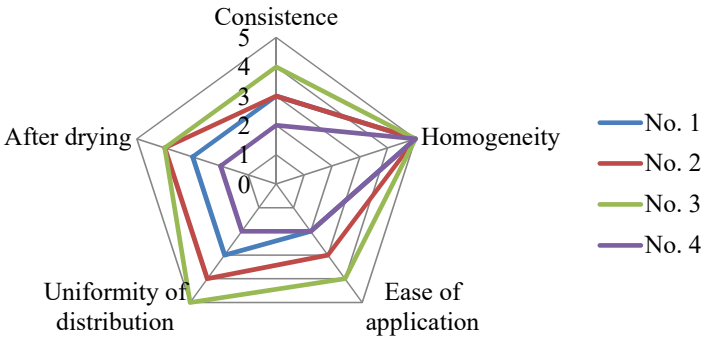

Fig. 1. Properties of samples based on PVP with glycerin

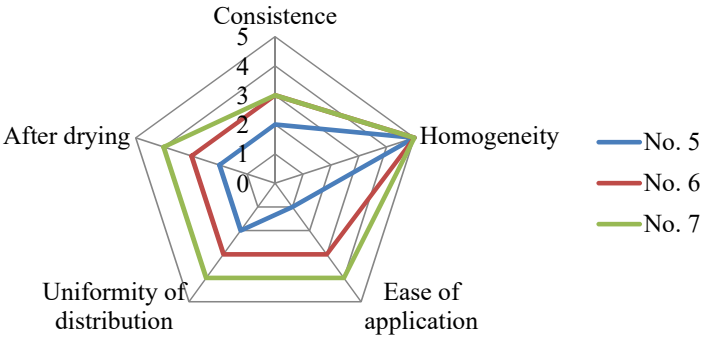

Fig. 2. Properties of samples based on PVP with a macrogol of 400

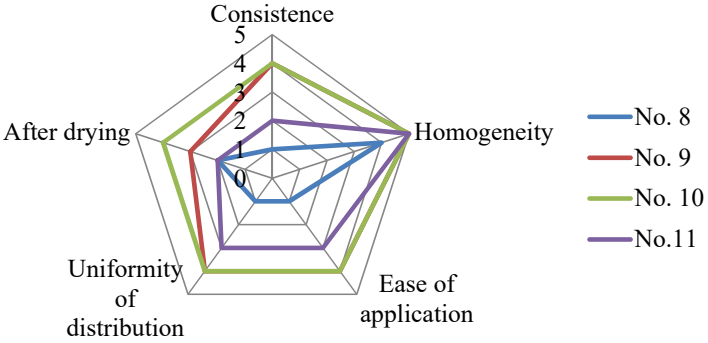

Fig. 3. Properties of samples based on PVA

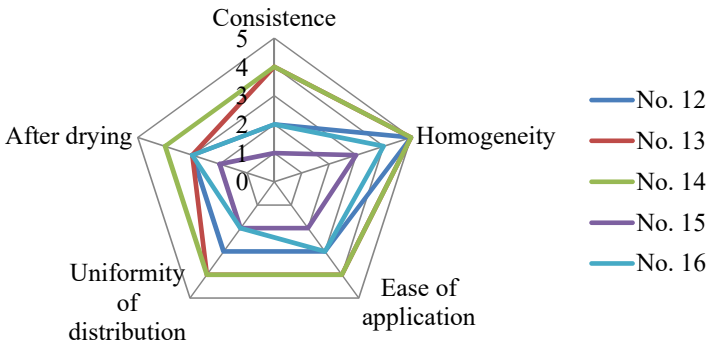

Fig. 4. Properties of samples based on the combination of PVP with PVA

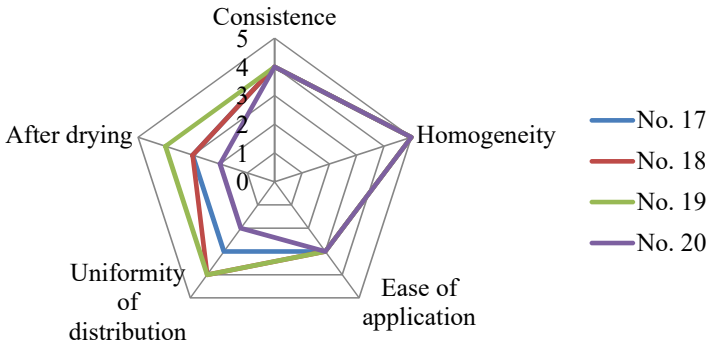

Fig. 5. Properties of samples based on combinations with PAA

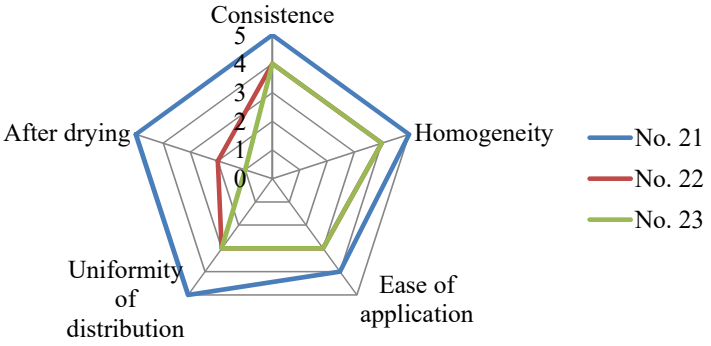

Fig. 6. Properties of samples based on combinations with eudragit

For samples based on PVA (Fig. 3) or its combination with PVP (Fig. 4), samples with 15 % PVA (plasticizer macrogol 400 in the amount of 5 %) and with a content of PVP+PVA – 10+20 % (plasticizer macrogol 400 in the amount of 5 %) proved to be relatively good. Unlike other samples, which include PVA, they had a satisfactory consistency, small losses during application, more evenly distributed on a polymer basis. The disadvantage is the greater thickness of the applied layer, compared to samples based on other adhesives.

In Fig. 5 shows the properties of indicators based on combinations of PVP and PVA with 2 % aqueous solution of PAA. Satisfactory properties in this case have a sample, which includes 10 % of each of the adhesives without adding macrogol 400 as a plasticizer. Combinations of PAA with PVP only or with PVA only have insufficiently uniform distribution when applied to the polymer base and relatively low quality after drying (the adhesive composition is compressed from the edges to the center of the polymer base under the action of high temperature).

In Fig. 6 sample No. 21 based on eudragit with PVP has the best performance for each criterion, mass is homogeneous, consistency is moderately thick, which provides ease of application and perfect uniform distribution on a polymer basis, after drying the surface is smooth, without signs of deformation.

Therefore, according to the results of organoleptic control, for further studies we used the sample No. 21.

When determining the optimal drying regime, the properties, and limits of permissible temperature regimes for the adhesives included in the compositions were taken into account. The mode in which the composition based on PVP based on PVP does not lose its shape and adhesive properties, dries evenly and completely, is 75 °C for 30 minutes. The drying process in this case is based on the “soft” evaporation of the volatile ethanol solvent to the required consistency of the adhesive base, time less than 30 minutes does not ensure complete evaporation of ethanol, and more – dries and leads to loss of adhesive properties. For PVA-based samples the optimal mode is 75 °C for 35 minutes. In this case, the role of non-evaporation of the solvent plays a role, because glycerin is not a volatile solvent, the main thing is the process of plasticization under the action of elevated temperature. Insufficient exposure does not provide proper drying, the mass remains sparse, exposure for more than 35 min leads to a decrease in adhesive properties, and the mass acquires a rubbery consistency. The introduction of eudragit into the adhesive base leads not only to the improvement of organoleptic properties, but also to a decrease in temperature and acceleration of drying. The optimal mode for such samples is 50 °C for 10 minutes. Keeping the samples in the thermostat for more than 10 min, or at a temperature above 50 °C, leads to significant overdrying of the adhesive base, a film devoid of adhesive properties is formed, which completely lags behind the polymer base.

Introduction to the API was performed by pre-dispersing dry extracts and quercetin with half the amount of solvent. When comparing the organoleptic properties of the primary adhesive base without active substances and the sample, which includes API, it was found that they do not adversely affect the properties of the adhesive base, even though its composition was proportionally adjusted due to increased dry matter. Both samples have a satisfactory consistency, are easily applied to the polymer base, have no significant losses during application, are evenly and thinly distributed on the polymer base, after drying with the optimal mode are not deformed, do not lose adhesive properties, the surface remains smooth, shiny (Fig. 7).

Plant active extracts of anti-inflammatory action were chosen as active substances: dry extract of white willow bark, dry extract of sage leaves, quercetin, the

beneficial effects of which are, first, anti-edema and anti-inflammatory, mustard powder as an irritant and vasodilator to accelerate the action of the patch at the initial stage. The concentration of API was selected according to the instructions of soft drugs and solutions for external use available on the market, as well as based on the analysis of patents and publications of other scientists [21]. This is 1 % for sage leaf extract and 3 % for white willow bark extract, quercetin 30 mg/g, mustard powder 0.3–0.5 % [22, 23], so that in case of prolonged stay on the skin the drug does not cause discomfort. and irritation (Table 2).

The formed model compositions were provided for pharmacological research. The results of pharmacological screening are given in Table 3.

As could be seen from the Table 3, the dynamics of edema in the PC group is characteristic of this experimental model [24]. Already 1 h after the introduction of phlogogen observed the development of edema, which gradually increased. The maximum value of edema was observed 5 h after administration of carrageenan. The transdermal route of API patches under ciphers No. 1–5 showed no activity 1 h after phlogogen administration in all subjects. However, after 2 hours of local use of the objects, the activity of the patches showed a positive trend (except for the patch No. 5). During the prostaglandin phase (3–5 h) – patches numbered No. 1–5 showed the following average activity – 24.3, 18.4, 21.8, 35.7 and 22.4 %, respectively. During the experiment, the patches numbered No. 1–5 showed the following average anti-exudative effect – 14.5, 10.4, 11.4, 25 and 10 %, respectively. Plaster No. 4 showed the best results – the average anti-exudative effect was 25 %.

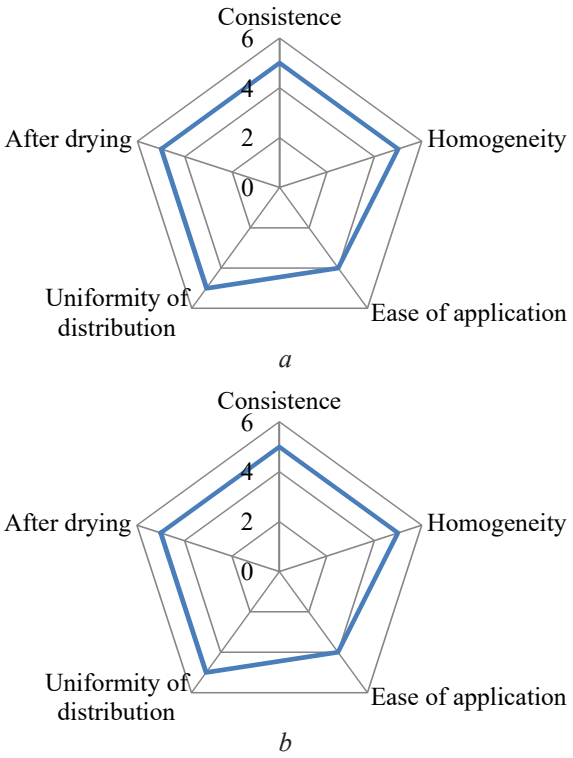

Fig. 7. Comparative characteristics of organoleptic properties: *a* – adhesive base; *b* – sample base with API

Table 2

The composition of model samples of transdermal therapeutic system of anti-inflammatory action

Component, % / Sample	PVP	Eudragit	Macrogol 400	IPA	Dry extract of willow bark	Dry extract of sage leaves	Quercetin	Mustard powder
No. 1	48.0	7.5	9.6	27.5	3.0	1.0	3.0	0.4
No. 2	49.5	8.0	11.0	28.1	3.0	1.0	–	0.4
No. 3	48.5	8.0	10.0	27.1	3.0	–	3.0	0.4
No. 4	48.0	7.5	10.0	27.5	3.0	1.0	3.0	–
No. 5	49.5	8.0	11.0	27.1	–	1.0	3.0	0.4

Table 3

The effect of test samples on the activity of prostaglandins and kinins in the presence of carrageenan edema of the foot in rats (M±*m*), *n*=6

Experimental conditions, samples 1		Dynamics of inflammation. h					Average value AEA, %
		2	3	4	5		
PC	ΔV, ml	0.49±0.02	0.94±0.05	1.30±0.07	1.42±0.07	1.46±0.09	–
No. 1	ΔV, ml	0.53±0.07	0.86±0.06	1.06±0.12^{1T}	1.07±0.12^{1T}	1.02±0.13^{1}	14.5
	AEA, %	–9.3	9.0	18.0	24.8	30.0	
No. 2	ΔV, ml	0.51±0.03^{1T}	0.093±0.08	1.15±0.07	1.13±0.09^{1}	1.11±0.09$^{1/2T/3T}$	10.4
	AEA, %	–4.8	1.6	11.1	20.6	23.5	
No. 3	ΔV, ml	0.54±0.08	0.93±0.05	1.12±0.04^{2T}	1.10±0.08^{1}	1.03±0.09^{1}	11.4
	AEA, %	–10.3	1.6	13.4	23.0	29.1	
No. 4	ΔV, ml	0.49±0.05	0.78±0.08	0.93±0.07$^{1/4T/5T/6/7}$	0.91±0.09^{1}	0.83±0.09$^{1/6T}$	25.0
	AEA, %	–0.3	17.8	28.3	36.4	42.3	
No. 5	ΔV, ml	0.55±0.06	0.99±0.07$^{2T/4}$	1.10±0.04^{1}	1.08±0.05^{3T}	1.06±0.05$^{1/2/3}$	10.0
	AEA, %	–12.4	–5.1	15.4	24.4	27.4	

Note: [1] – differences are statistically significant for the group of sample 1, p<0.05 (Mann-Whitney test); [2] – differences are statistically significant for the group of sample 2, p<0.05 (Mann-Whitney test); [3] – differences are statistically significant for the group of sample 3, p<0.05 (Mann-Whitney test); [4] – differences are statistically significant for the group of sample 4, p<0.05 (Mann-Whitney test); [T] – differences statistically go to the probable, 0.05<p<0.100 (Mann-Whitney test); AEA – antiexudative activity; ΔV – the difference between the volume of the swollen and non-swollen paw, ml; n – the number of animals in each group

Thus, the study of antiexudative activity of the studied samples in the model of inflammation indicates the presence of only the patch No. 4 anti-inflammatory properties, the mechanism of which is a moderate effect on prostaglandin activity – the average antiexudative effect of this sample is 25.0 %.

5. Discussion of research result

According to the results of experimental studies, it was determined that the model sample No. 21 based on eudragit with PVP has the best performance according to the proposed criteria, the mass is homogeneous, the consistency is moderately thick, which ensures ease of application and perfect uniform distribution on a polymer basis. smooth, without signs of deformation. Pharmacological studies have shown that sample No. 4, which contains as an API extracts of dried white willow bark, sage and quercetin, is more effective than the other samples. The introduction of mustard powder as a vasodilator component did not give the expected effect.

Recently, foreign scientists are also looking for a natural alternative to synthetic NSAIDs. A 2018 study by Indonesian scientists developing a transdermal patch with Sauropus androgynus leaf extract showed that plant-derived APIs were less effective than synthetic ones. Their efficiency could sometimes reach 66 % [25].

The studied transdermal patch with St. John's wort extract (China, 2021) in vivo in a model of chronic inflammation 2.5 hours after application showed anti-inflammatory activity, while the samples we studied began to show positive dynamics after 2 hours [26].

Study limitations. Pharmaceutical development of the drug involves a number of studies, including validation of the technological process of obtaining the drug and analytical methods.

Prospects for further research are to develop methods for identification and quantification of API, biopharmaceutical, technological and microbiological definitions.

6. Conclusions

Based on the research, the composition of the hydrophilic adhesive composition was developed, which includes polyvinylpyrrolidone, eudragit (adhesives), macrogol 400 (plasticizer), isopropyl alcohol (solvent) 50:8:12:30, respectively. The optimal mode of drying of adhesive compositions was determined: based on PVP – 75 °C for 30 min, based on PVA – 75 °C for 35 min, compositions with eudragit – 50 °C for 10 min.

The antiexudative activity of combinations of active pharmaceutical ingredients of natural origin was studied and it was found that the sample No. 4 has the best anti-inflammatory properties (25 %), which includes extracts of dried white willow bark and sage and quercetin 3:1:3, respectively.

The composition of the anti-inflammatory patch was developed: polyvinylpyrrolidone – 48.0, eudragit – 7.5, macrogol 400 – 10.0, isopropyl alcohol – 27.5, dry willow extract of white bark – 3.0, dry sage extract of medicinal leaves – 1.0, quercetin – 3.0.

Conflict of interests

The authors declare that they have no conflicts of interest.

Financing

The study was performed without financial support.

References

1. Musculoskeletal conditions. World Health Organization. Available at: https://www.who.int/news-room/fact-sheets/detail/musculoskeletal-conditions

2. Kriplani, P., Sharma, A., Aman, P. P., Chopra, B., Dhingra, A., Deswal, G. (2018). Formulation and evaluation of transdermal patch of diclofenac sodium. Global Journal of Pharmacy and Pharmaceutical Sciences, 4 (5). doi: http://doi.org/10.19080/gjpps.2018.04.555647

3. Zhang, Y., Cun, D., Kong, X., Fang, L. (2014). Design and evaluation of a novel transdermal patch containing diclofenac and teriflunomide for rheumatoid arthritis therapy. asian journal of pharmaceutical sciences, 9 (5), 251–259. doi: http://doi.org/10.19080/gjpps.2018.04.555647

4. Putri, F. R., Adjeng, A. N. T., Yuniar, N., Handoyo, M., Sahumena, M. A. (2019). Formulation and physical characterization of curcumin nanoparticle transdermal patch. International Journal of Applied Pharmaceutics, 11 (6), 217–221. doi: http://doi.org/10.22159/ijap.2019v11i6.34780

5. Kurakula, M., Ahmed, O. A., Fahmy, U. A., Ahmed, T. A. (2016). Solid lipid nanoparticles for transdermal delivery of avanafil: optimization, formulation, in-vitro and ex-vivo studies. Journal of liposome research, 26 (4), 288–296. doi: http://doi.org/10.3109/08982104.2015.1117490

6. Yang, Z., Teng, Y., Wang, H., Hou, H. (2013). Enhancement of skin permeation of bufalin by limonene via reservoir type transdermal patch: formulation design and biopharmaceutical evaluation. International journal of pharmaceutics, 447 (1-2), 231–240. doi: http://doi.org/10.1016/j.ijpharm.2013.02.048

7. Mahajan, N. M., Zode, G. H., Mahapatra, D. K., Thakre, S., Dumore, N., Gangane, P. S. (2018). Formulation development and evaluation of transdermal patch of piroxicam for treating dysmenorrhoea. Journal of Applied Pharmaceutical Science, 8 (11), 35–41.

8. Hafeez, A., Jain, U., Singh, J., Maurya, A., Rana, L. (2013). Recent Advances in Transdermal Drug Delivery System (TDDS): An Overview. Journal of Scientific and Innovative Research, 2 (3), 695–709.

9. Tin, W. W. (2014). Electrical, magnetic, photomechanical and cavitational waves to overcome skin barrier for transdermal drug delivery. Journal of Controlled Release, 193, 257–269. doi: http://doi.org/10.1016/j.jconrel.2014.04.045

10. Vijay, B. M., Vinay, K., Rajeev, K. (2019). An Overview of Transdermal Drug Delivery System. Journal of Drug Delivery & Therapeutics, 9, 773–778.

11. Derzhavna Farmakopeia Ukrainy. Vol. 2. Kharkiv: DP «Ukrainskyi naukovyi farmakopeinyi tsentr yakosti likarskykh zasobiv», 1113–1114.

12. European Pharmacopoeia (2013). Strasbourg: European Department for the Quality of Medicines, 798–799.

13. Gaur, P. K., Mishra, S., Purohit, S. (2013). Solid Lipid Nanoparticles of Guggul Lipid as Drug Carrier for Transdermal Drug Delivery. BioMed Research International, 2013, 1–10. doi: http://doi.org/10.1155/2013/750690

14. Shara, M., Stohs, S. J. (2015). Efficacy and Safety of White Willow Bark (Salix alba Extracts. Phytotherapy Research, 29 (8), 1112–1116. doi: http://doi.org/10.1002/ptr.5377

15. Myha, M. M. et. al. (2019). Fitokhimichnyi profil ta protyzapalna aktyvnist sukhykh ekstraktiv z lystia shavlii likarskoi. Biolohiia ta farmatsiia, 4, 38–42.

16. Koshovyi, O. N., Vovk, G. V., Akhmedov, E. Yu., Komissarenko, A. N. (2015). The study of the chemical composition and pharmacological activity of Salvia officinalis leaves extracts getting by complex processing. Azerbaijan Pharmaceutical and Pharmacotherapy Journal, 15 (1), 30–34.

17. Hladkykh, F. V., Stepaniuk, N. H. (2014). New approaches to reduce ulcerogenity of nonsteroidal anti-inflammatory drugs: achievements, unsolved issues and ways to optimize. Zaporozhye Medical Journal, 2, 82–86. doi: http://doi.org/10.14739/2310-1210.2014.2.25437

18. Fan, M., Zhang, G., Hu, X., Xu, X., Gong, D. (2017). Quercetin as a tyrosinase inhibitor: Inhibitory activity, conformational change and mechanism. Food Research International, 100, 226–233. doi: http://doi.org/10.1016/j.foodres.2017.07.010

19. Luna-Vázquez, F., Ibarra-Alvarado, C., Rojas-Molina, A., Rojas-Molina, I., Zavala-Sánchez, M. (2013). Vasodilator Compounds Derived from Plants and Their Mechanisms of Action. Molecules, 18 (5), 5814–5857. doi: http://doi.org/10.3390/molecules18055814

20. Lapach, S. N., Chubenko, A. V., Babych, P. N. (2001). Statystycheskye metodi v medyko-byolohycheskykh yssledovanyiakh s yspolzovanyem Excel. Kyiv: Moryon, 320.

21. Kvertsetyn hranuly 0,04 h/1 h paket 2 h. Available at: https://compendium.com.ua/dec/260462/7207-233111/

22. Assalix®. Available at: https://compendium.com.ua/dec/267469/

23. SALVIN. Available at: https://mozdocs.kiev.ua/likiview.php?id=6865

24. Di Rosa, M., Giroud, J. P., Willoughby, D. A. (1971). Studies of the mediators of the acute inflammatory response induced in rats in different sites by carrageenan and turpentine. The Journal of Pathology, 104 (1), 15–29. doi: http://doi.org/10.1002/path.1711040103

25. Rise, D., Sri, L., Desy, S. A. (2018). Antiinflammatory Activity Patch Ethanol Extract Of Leaf Katuk (Sauropus Androgynus L. Merr). Jurnal Ilmu Kefarmasian Indonesia, 16 (1), 1–5. doi: http://doi.org/10.35814/jifi.v16i1.493

26. Quan, P., Jiao, B., Shang, R., Liu, C., Fang, L. (2021). Alternative therapy of rheumatoid arthritis with a novel transdermal patch containing Siegesbeckiae Herba extract. Journal of Ethnopharmacology, 265, 113294. doi: http://doi.org/10.1016/j.jep.2020.113294

Received date 17.05.2022
Accepted date 21.06.2022
Published date 30.06.2022

Liliia Vyshnevska, Doctor of Pharmaceutical Sciences, Professor, Head of the Department, Department of Pharmaceutical Technology of Drugs, National University of Pharmacy, Pushkinska st., 53, Kharkiv, Ukraine, 61002

Anastasia Olefir, Postgraduate Student, Department of Pharmaceutical Technology of Drugs, National National University of Pharmacy, Pushkinska st., 53, Kharkiv, Ukraine, 61002

Dmytro Lytkin, PhD, Deputy Director of Educational and Scientific Institute, Educational and Scientific Institute of Applied Pharmacy, National University of Pharmacy, Pushkinska st., 53, Kharkiv, Ukraine, 61002

Liubov Bodnar, Postgraduate Student, Department of Pharmaceutical Technology of Drugs, National University of Pharmacy, Pushkinska st., 53, Kharkiv, Ukraine, 61002

***Corresponding author:** Liliia Vyshnevska, e-mail: liliiavyshnevska@gmail.com*