UDC : 615.454.1 : 615.261.2
DOI: 10.15587/2519-4852.2021.234250

BIOPHARMACEUTICAL AND RHEOMETRIC STUDIES IN THE DEVELOPMENT OF A GEL COMPOSITION WITH DIMETHINDENE MALEATE

Tetiana Popova, Halyna Kukhtenko, Nataliia Bevz, Oleksandr Kukhtenko

Every year there is an increase in the number of cases of hypersensitivity to bites from various insects. A local allergic reaction to bites occurs within a few minutes and is accompanied by acute pain at the site of the bite, severe itching, hyperemia, the appearance of papules, tissue edema, and sometimes a small-point rash around. Considering the small number of drugs for local therapy of allergic manifestations and the unidirectional nature of their action, it is urgent to develop a drug containing the antihistamine dimethindene maleate and dexpanthenol, which plays the role of an anti-inflammatory, reparative and dermatoprotective substance.

The aim. *The aim of the study is to substantiate the delivery system of dimethindene maleate and dexpanthenol based on biopharmaceutical and rheometric research methods.*

Materials and methods. *To determine the component composition of the active ingredient delivery system, the type of dimetindene maleate administration was substantiated by studying its solubility. As a delivery system for active pharmaceutical ingredients, hydrogels were considered, which were made using high-molecular compounds of various origins: a natural substance – xanthan gum, a semi-synthetic substance – gyroxypropyl methylcellulose, and a synthetic substance – carbomer. The rate of release of dimethindene maleate from hydrogels was estimated by studying the kinetics of release through a semipermeable membrane. The assessment of the viscoelastic properties of hydrogels was carried out by performing an oscillatory rheometry test, which makes it possible to quantitatively determine the viscous and elastic components, as well as to characterize the bioadhesive properties.*

Results. *Based on the results of studying the solubility of dimethindene maleate in hydrophilic non-aqueous solvents, it was determined that propylene glycol is optimal for ensuring the introduction of a substance into hydrogel bases as a solution. As a result of studying the kinetics of the release of dimethindene maleate from hydrogels, it was found that the use of carbomer as a delivery system provides the release of 28.33 % of dimethindene maleate, xanthan gum – 25 %, hydroxypropyl methylcellulose – 7.33 %. When studying the viscoelastic properties by determining the values of the storage modulus G', the loss modulus G" and the damping (attenuation) factor tg δ, it was found that the carbomer-based hydrogel is a viscoelastic solid, the xanthan gum and hydroxypropyl methylcellulose-based hydrogels are a viscoelastic liquid. Bioadhesion on the surface of the skin during use has the advantage of carbomer hydrogel.*

Conclusions. *Based on the combination of biopharmaceutical and rheometric methods for substantiating the composition of the delivery system for dimetindene maleate and dexpanthenol, it is rational to use carbomer for further pharmacological and microbiological studies*

Keywords*: hydrogel, dimethindene maleate, dexpanthenol, hydroxypropyl methylcellulose (HPMC), xanthan gum, carbomer, G' storage modulus, G" loss modulus, viscoelastic properties*

Popova, T., Kukhtenko, H., Bevz, N., Kukhtenko, O. (2021). Biopharmaceutical and rheometric studies in the development of a gel composition with dimethindene maleate. ScienceRise: Pharmaceutical Science, 3 (31), 11–18. doi: http://doi.org/10.15587/2519-4852.2021.234250

1. Introduction

According to the World Allergy Organization (WAO), the prevalence of allergic pathology in the world population is from 10 % to 40 %. There are various types of allergies, one of which is insect allergy. It should be noted that up to 5 % of people in the world are prone to general reactions to insect bites [1, 2]. Every year there is an increase in the number of cases of hypersensitivity to various insects. This makes it advisable to develop new topical agents for local therapy of allergic reactions to insect bites or stings. The issue of treatment of the consequences of insect bites in children is especially acute, as the constant combing of bites is a threat of infection of wounds and delay their healing [3].

One of the ways of drug treatment of insect allergy, taking into account the severity of the reaction is the use of antihistamines of systemic and local action. Given the economic aspects of the cost of imported drugs currently in Ukraine, as well as the strong development of domestic industrial pharmacy, it is important to develop a gel with a combination of substances with antihistamines and reparative effects, namely dimethindene maleate and dexpanthenol.

Dimethindene maleate – a substance derived from phenylalkylamine, belongs to the group of antihistamines of the first generation, has antiallergic and antipruritic therapeutic effect, and blocks H1-receptors. Dimethindene maleate is a part of medicines of various dosage

forms. In the means of systemic action, the therapeutic dose is 1 mg / 1 tablet; in nasal forms 0.25 – 1 mg / 1 ml; in drugs of local dermatological action 1 mg / 1 g [3–5].

Dexpanthenol is a provitamin B5. Its action is similar to that of pantothenic acid, but it is better absorbed when applied topically. Pantothenic acid is a component of coenzyme A, which in the form of coenzyme acetyl-CoA plays an important role in cellular metabolism. Pantothenic acid is necessary for the formation and regeneration of the skin and mucous membranes. Dexpanthenol is used in topical agents in a dosage of 30–50 mg / 1 g [3, 6, 7].

The advantage of gels as carriers of drugs in the treatment of contact allergies is the additional provision of cooling and soothing effect on the affected areas of the skin.

According to the classification of drugs on the basis of their equivalence, the drug under development belongs to group A.3 – the original drug with a fixed combination [8]. The therapeutic dose of dimethindene maleate in the gel is 1 mg / 1 g, dexpanthenol – 30 mg / 1 g.

The effectiveness of topical drugs depends on the rate of release of the active substance from the base and penetration through the stratum corneum, i.e. the delivery system and the physical state of the drug itself [9].

The aim of the work is the design and development of a gel composition for the treatment of contact allergy containing dimethindene maleate and dexpanthenol on the basis of biopharmaceutical and rheometric studies.

2. Research planning (methodology)

The plan of the experiment is shown in Fig. 1 in the form of a decision tree or a diagram of Ishikawa and provides for research aimed at substantiating the type of introduction of API into the delivery system; justification for the choice of the delivery system itself through the use of various macromolecular substances and their concentration; study of the influence of the used delivery system on the kinetics of API release and evaluation of their viscoelastic properties.

Hydrogels made on the basis of various macromolecular substances: carbomer, hydroxypropylmethylcellulose (HPMC) and xanthan gum were considered as delivery systems of active substances.

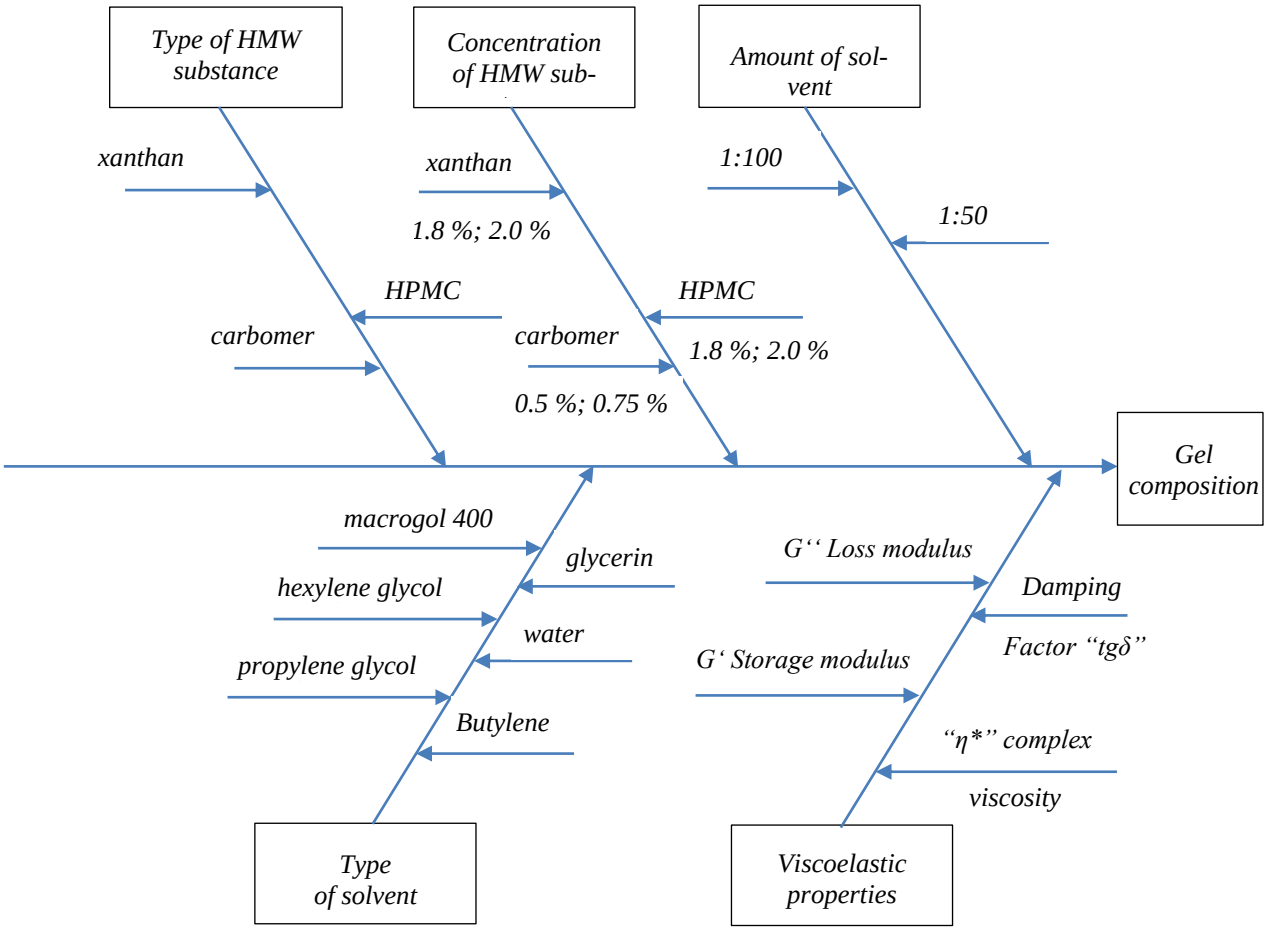

Fig. 1. Decision tree

3. Materials and methods

Methods for studying the solubility of dimethindene maleate

Purified water, macrogol 400 and polyhydric alcohols: propylene glycol, hexylene glycol, butylene glycol and glycerin were used as solvents to study the solubility of dimethindene maleate (CAS number 5636-83-9). Samples were prepared by weight in the ratio of dimethindene maleate: solvent as 1:50 and 1:100. Solubility was studied at room temperature 15–25 °C and heating,

thermostating time at each temperature was 30 minutes. Solubility was assessed visually. The research was conducted in accordance with the recommendations of SpHU 2nd edition, p. 1.4. [10–12]

Method of preparation of HPMC gels (brand Metolose SR-90SH-100000SR, Ph. Eur. 9.2)

To prepare HPMC gels, 1/3 of the prescript purified water was heated to 80 °C and the polymer was added with stirring for 30 minutes, then the remaining purified room temperature water was added. The concentration of HPMC in the test samples was 1.8 % and 2.0 %. 30 minutes after preparation of the base, the active substances were added. the pH of the gel was 5.7±0.1.

Method of preparation of xanthan gum hydrogels (brand Ziboxan F200, Ph. Eur. 9.2)

Xanthan gum was added to the purified room temperature calculated according to the recipe and stirred for 30 minutes. Gel samples with a xanthan gum content of 2.0 % and 2.5 % were prepared. 30 minutes after preparation of the base, the active substances were added. The pH of the gel was 5.3±0.1.

Method of preparation of carbomer hydrogels (brand Carbopol™ Polymers Ultrez 10 NF, USP32–NF27)

Carbomer was added to the purified room temperature calculated according to the recipe, dispersed for 30 min, then neutralized with a solution of trometamol (40 %) to a pH of the dispersed system of 6.0±0.1 [13, 14]. The concentration of carbomer in the samples was 0.5 % and 0.75 %. 30 minutes after preparation of the base, the active substances were added. The pH of the gel was 5.8±0.1.

Methods for studying the kinetics of dimethindene maleate release from gels

The release of dimethindene maleate from the gels was determined by the degree of diffusion through the semipermeable membrane into the phosphate buffer solution with a pH corresponding to the pH of the test gel. Used a dialysis chamber, as a membrane – inert porous cellulosic material – Cuprophan, type 150 pm, 11±0.5 μm thick. The portion of the gel sample was 3.0 g (exact portion). In the process of dialysis through the membrane is the diffusion of dimethindene maleate into a system with a higher concentration of kinetically active units – molecules or ions. Dialysate samples with a volume of 10 ml were taken with a pipette at regular intervals (1 hour), adding the same volume of buffer solution to the chamber. The study was performed at a temperature of (34±0.5) °C.

The concentration of dimethindene maleate in the resulting dialysis solutions was calculated by the formula:

$$\boldsymbol{C} = \frac{A \cdot m_w^{st} \cdot 1 \cdot V_s \cdot 1000}{A_{st} \cdot m_w \cdot 100 \cdot 100},$$

where C – the concentration of dimethindene maleate in the test solution, mg / ml; A – optical density of the test solution; A_{st} – optical density of standard solution; m_w^{st} – weight of the standard sample, g; m_w – weight of the test sample, g; V_s – total volume of solution in the dialysis chamber, ml.

When calculating the total amount of dimethindene maleate, which went into solution, took into account its amount, which was contained in the previously selected samples:

$$X_n = C_n \cdot V_s + \frac{X_{n-1}}{V_s} \cdot V_a,$$

where X_n – the total amount of dimethindene maleate, which went into solution for n hours of the experiment; C_n – the concentration of dimethindene maleate in the dialysate after n hours of the experiment (mg / ml); X_{n-1} – the total amount of dimethindene maleate, which went into solution for n-1 hours of the experiment, mg; V_a – volume of aliquot selected for analysis (1 ml).

The concentration of dimethindene maleate in dialysate samples was determined by absorption spectrophotometry in the ultraviolet region of the spectrum in a phosphate buffer solution with a pH of 5.8±0.1. Preliminary studies show that in the range from 200 nm to 300 nm 0.001 % solution of a standard sample of dimethindene maleate in a phosphate buffer solution with a pH of 5.8±0.1 is characterized by the presence of a maximum absorption at wavelengths of 258 nm (Fig. 2).

The maximum wavelength of 258 nm was chosen as the analytical wavelength for further testing, as the subordination of solutions of dimethindene maleate in phosphate buffer solution with a pH of 5.8±0.1 to the basic law of light absorption is observed in the concentration of active substance from 0.002 mg / ml to 0.02 mg/ml (Fig. 3).

Further study was performed spectrophotometrically in a phosphate buffer solution with a pH of 5.8±0.1 at a wavelength of 258 nm. The calculation of the amount of dimethindene maleate transferred to the solution was performed by the standard method.

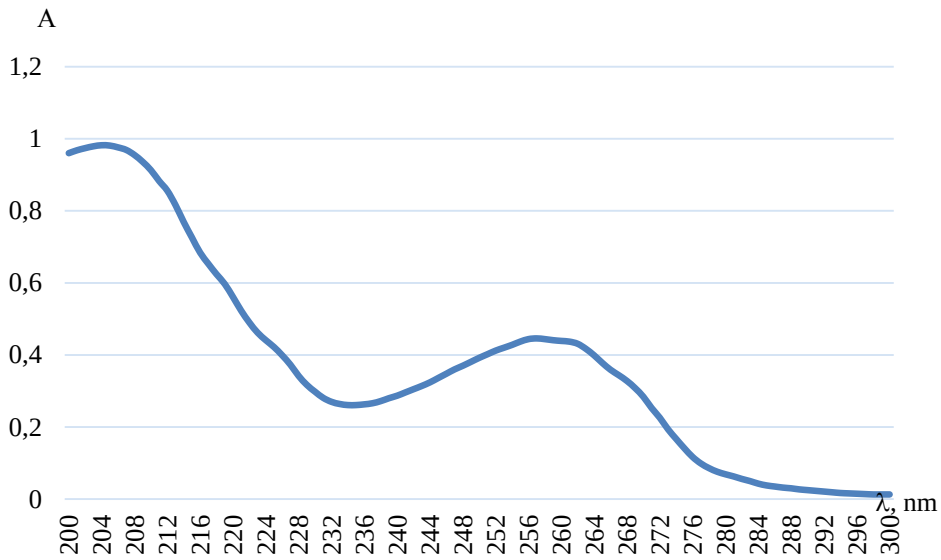

Fig. 2. Ultraviolet absorption spectrum of 0.001 % solution of dimethindene maleate in phosphate buffer solution with pH 5.8±0.1

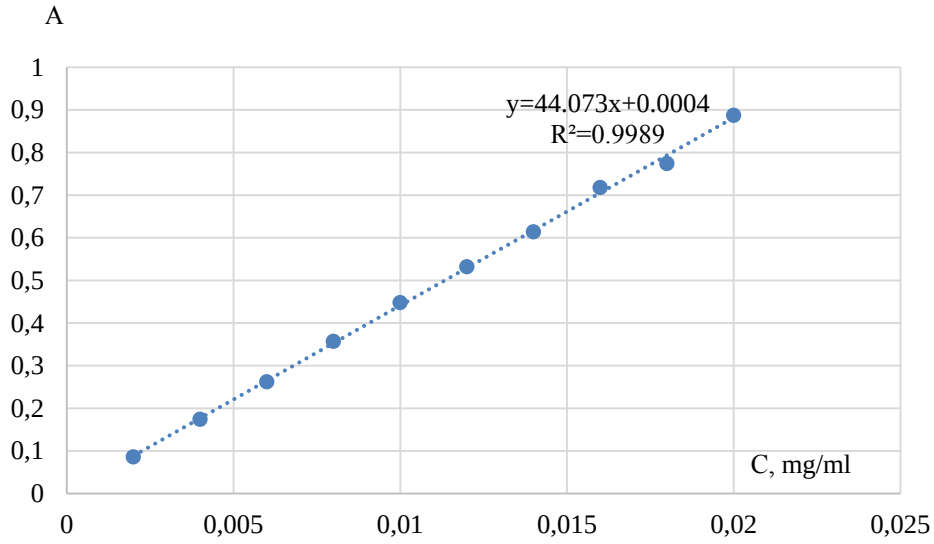

Fig. 3. Graph of the dependence of the optical density on the concentration of standard solutions of dimethindene maleate

Methods for studying the viscoelastic properties of gels

The evaluation of viscoelastic properties was determined using a rheometer MCR 301, Anton Paar, Austria with a plate-to-plate geometry with a diameter of 25 mm, a gap between the plates of 0.209 mm. The study of viscoelastic properties was performed in two stages: amplitude and frequency scanning.

First, an amplitude scan was performed to determine the range of linear viscoelasticity of the samples (LVE range) in which the structure of the gels does not break under the influence of the deforming force. To determine the LVE range, an amplitude scan in the range of 0.01–100 % with a constant angular frequency of 10 rad / s was performed. The next step at a defined and fixed deformation force within the LVE range was set to the frequency sweep range from 100 to 0.1 rad / s, the study was performed at 25 °C.

The research results are presented in the form of mechanical spectra, according to the nature of the arrangement of mechanical spectra, a conclusion is made about the viscoelastic properties of the dispersed system.

4. Research results

The effectiveness of topical drugs depends on the type of API included into the delivery system, the components on which the delivery system itself is designed, and the excipients that help release APIs and penetrate the skin barrier. Therefore, the first step in substantiating the composition of the gel was the study of the solubility of dimethindene maleate – a white solid powder [15]. The results of the studies are presented in Tab. 1. Dexpanthenol is a viscous liquid, so it was introduced into the gel directly by adding the required amount and dissolving in the gel base [16].

Table 1

The results of the study of the solubility of dimethindene maleate

Solvent	The ratio of dimethindene maleate: solvent / dissolution temperature							
	40±1 °C		45±1 °C		50±1 °C		55±1 °C	
	1:50	1:100	1:50	1:100	1:50	1:100	1:50	1:100
Purified water	+	+	+	+	+	+	+	+
Propylene glycol	+	+	+	+	+	+	+	+
Hexylene glycol	–	–	–	–	±	+	+	+
Butylene glycol	–	–	±	+	+	+	+	+
Macrogol 400	–	–	±	+	+	+	+	+
Glycerin	–	–	–	–	–	–	–	–

Note: «+» – soluble; «±» – slightly soluble; «–» – practically insoluble

At the stage of substantiation of the local API delivery system, the method of studying the release kinetics of the active substance through a semipermeable membrane is widely used, which simulates the process of penetration of active components through the stratum corneum [17–19]. The results of the study are shown in Fig. 4.

The next step in the substantiation of the choice of API delivery system was research to study the viscoelastic characteristics of the studied gels, which can predict the stability of the dispersed system during storage and the ability to bioadhesion on the skin surface when using them [20–22]. The research results are shown in Fig. 5 and 6, Table 2.

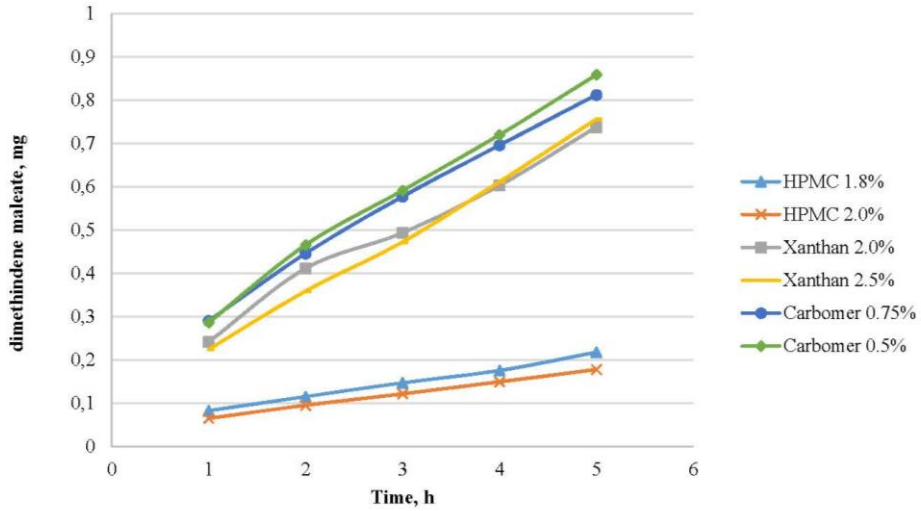

Fig. 4. Kinetics of dimethindene maleate release from hydrogels

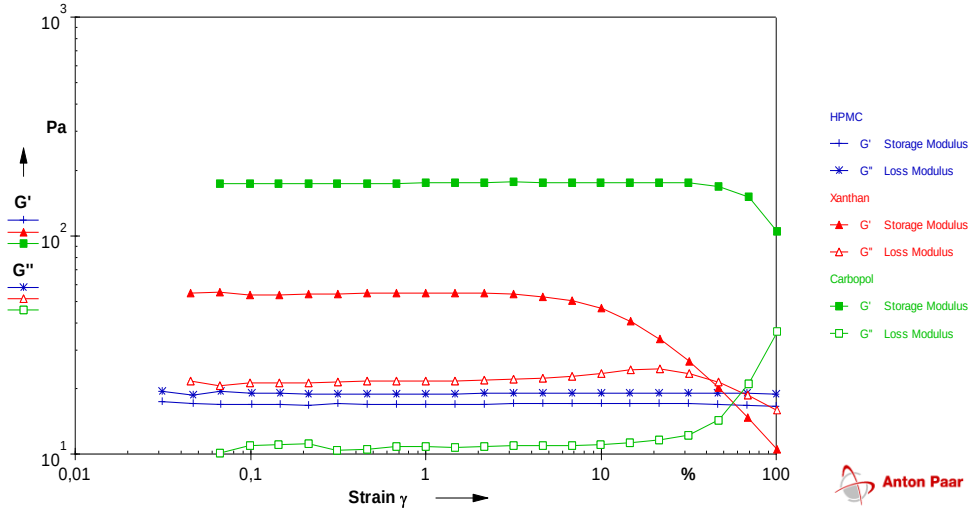

Fig. 5. Linear viscosity range for test gels (LVE range)

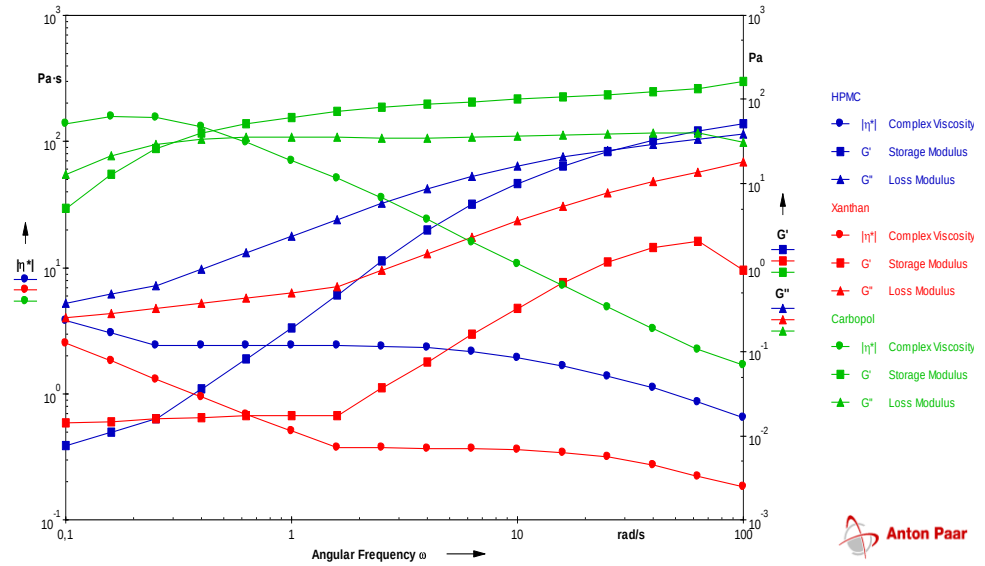

Fig. 6. Mechanical spectra of the modulus of elasticity G′, the modulus of losses G″ and the complex viscosity η* depending on the frequency (ω, rad / s) at a constant amplitude γ=1 %

Table 2

The damping factor of gel bases (tg δ) depending on the frequency (ω, rad / s)

Angular Frequency, rad/s	Damping Factor		
	HPMC 1.8 %	Xanthan 2.0 %	Carbomer 0.5 %
100	0.743	19.3	0.186
63.1	0.799	6.7	0.295
39.8	0.899	6.06	0.326
25.1	1.05	6.62	0.337
15.8	1.28	8.21	0.351
10	1.62	11.1	0.363
6.31	2.17	14.5	0.376
3.98	3.13	19.3	0.392
2.51	4.87	25.4	0.429
1.58	7.87	34.3	0.49
1	12.4	28.8	0.595
0.631	18.5	25.2	0.684
0.398	26.7	22.7	0.835
0.251	38.1	20.7	1.13
0.158	43.1	19.2	1.64

5. Discussion of research results

Studies have shown that dimethindene maleate is poorly soluble in purified water and insoluble in hydrophilic non-aqueous solvents at room temperature. With a gradual increase in temperature above 25 °C with an interval of 5 °C there is a slow process of dissolution of dimethindene maleate. At a temperature of 40 °C dimethindene maleate is completely soluble in both purified water and propylene glycol, the dissolution process in these solvents does not depend on their ratio. In Macrogol 400 and butylene glycol dimethindene maleate is completely dissolved at a temperature of 45±1 °C, in hexylene glycol at 50±1 °C. When using Macrogol 400, butylene glycol and hexylene glycol, there is a dependence of the dissolution of dimethindene maleate on the amount of solvent used, the dissolution proceeds faster at a ratio of dimethindene maleate: solvent as 1:100.

Due to the plasticizing and antiseptic properties of propylene glycol, it is rational to use it as a solvent for dimethindene maleate [12, 17, 23]. Thus, in the development of samples of hydrogels of dimethindene maleate was introduced in the form of propylene glycol solution. pH of manufactured gel samples using carbomer, hydroxypropylmethylcellulose and xanthan gum is in the range of 5.0–6.0, which according to the literature is biocompatible with skin applications with minimal risk of irritation and bacterial contamination, and on the other hand promotes stability [18, 19]. The studied samples differed in the type of gelling agent used and its concentration, which was previously substantiated by conducting rheological studies on a rotary rheoviscometer [20, 24].

As can be seen from Fig. 3, which presents the results of the study of the kinetics of release of dimethindene maleate from hydrogels, the best biopharmaceutical properties have samples made on the basis of carbomer, which provide the release of dimethindene maleate 0.85 mg for 5 hours of the experiment, which is 28.33 % of the sample. The xanthan gum-based hydrogel is slightly lower at 0.75 mg (25 %), and the hydroxypropylmethylcellulose hydrogel releases 0.22 mg (7.33 %) of dimethindene maleate for 5 hours of the experiment. A common feature for all samples is the lack of significant dependence of the amount of released substance on the used concentration of carbomer, HPMC and xanthan gum; the obtained deviations are within the statistical error.

The peculiarity of oscillating rheometry in comparison with rotary viscometers is that the samples are not subject to mechanical destruction, and the indicators that are fixed, correspond to the native state of the sample, i.e. retain the structure of the studied samples [25, 26].

The results obtained at this stage are divided into elastic and viscous component (module) of viscoelastic behaviour of the sample: G´ – modulus of elasticity (or modulus of accumulation) and G´´ – modulus of viscosity or modulus of loss. The term “storage module” indicates that the voltage energy was temporarily stored

during the test, but it can be returned. The term "loss module" indicates that the energy used to initiate the flow, irreversibly converted into heat ("lost") [26].

The modulus of elasticity G' is the elastic part of the viscoelastic behaviour, which quasi-describes the "solid" part of the behaviour of the sample. The loss of modulus G" characterizes the viscous part of the viscoelastic behaviour, which can be considered as a "liquid" part of the behaviour of the sample. Viscous behaviour occurs due to internal friction between particles and molecules in a liquid. This friction is always associated with heating from friction in the sample, i.e. with the conversion of deformation energy into thermal energy. This part of the energy is absorbed by the sample, spent on internal friction processes and can no longer be used by the sample. On the contrary, the elastic part of the energy is stored in the deformed material, by expanding and stretching the internal bonds without destroying the interaction between the particles and without excessive stretching or destruction of the material. When a material returns to its original state, such unused accumulated energy acts as a driving force to return the material to its original form. In viscoelastic solids G' > G", i.e. they have a greater modulus of elasticity than the modulus of loss. On the other hand, viscoelastic fluids G" > G', i.e. they have a larger modulus of loss than the modulus of elasticity [26–28].

From the data of Fig. 5 shows that for carbomer hydrogels G' > G" predominates, for HPMC gels and xanthan gum G" > G'.

The damping factor or loss factor: tg δ = G" / G' indicates the ratio of viscous and elastic parts in the viscoelastic behaviour of the sample. The results of the calculation of tg δ are presented in Table 2. If the loss factor tg δ <1, then the sample is a viscoelastic body, when tg δ = 1 the sample will be at the point of gelation, and at values of tg δ> 1 – in a state of viscoelastic fluid [26, 29].

In summary, the carbomer gel is a viscoelastic body, the HPMC and xanthan gum-based gels are viscoelastic liquids. Accordingly, the best bioadhesive properties have a delivery system API using carbomer.

In the scientific literature there is the following interpretation of the results of the oscillation experiment: provided that G' > G" and the test is performed in the LVE range (Fig. 5), and if G' $\geq$ 10 Pa then we can assume some stability to gels, while G' $\leq$ 1 Pa, the stability associated with the practical use of the gel is hardly present. For the intermediate value of G' it is necessary to perform additional studies [28, 30]. For the studied samples of gels with dimethindene maleate and dexpanthenol G' is 174 Pa for carbomer gels, 54 Pa – for xanthan gum and 17 Pa – for HPMC gels, which indicates satisfactory predicted stability of dispersed systems.

Study limitations. Studies of the kinetics of dexpanthenol release from hydrogel bases have not been performed, which limits the breadth of conclusions.

Prospects for further research. The developed gel composition containing dimethindene maleate and dexpanthenol based on carbomer is at the stage of pharmacological study.

6. Conclusions

1. Based on the study of the solubility of dimethindene maleate, the use of propylene glycol as a solvent for the introduction of dimethindene maleate to the base of the hydrogel by type of solution is justified.

2. The kinetics of dimethindene maleate release from hydrogel delivery systems, which differed in the type of macromolecular substance used and its concentration, was studied. It was found that the use of carbomer as a delivery system provides the release of 28.33 % of dimethindene maleate, xanthan gum – 25 %, hydroxypropylmethylcellulose – 7.33 %.

3. The study of viscoelastic properties of the studied samples using oscillating rheological methods. The carbomer-based hydrogel was found to be a viscoelastic body, the xanthan gum and the hydroxypropylmethylcellulose hydrogel to be a viscoelastic liquid.

4. According to the combination of biopharmaceutical and rheometric studies, it is advisable to use a hydrogel delivery system of dimethindene maleate and dexpanthenol made on the basis of carbomer for further pharmacological and microbiological studies.

Conflict of interests

The authors declare that they have no conflicts of interest.

Financing

None

References

1. European Academy of Allergy and Clinical Immunology. EAACI. Available at: https://www.eaaci.org/organisation/about-us.html

2. World Allergy Organization. WAO. Available at: https://www.worldallergy.org/

3. Uter, W., Werfel, T., Lepoittevin, J.-P., White, I. R. (2020). Contact Allergy-Emerging Allergens and Public Health Impact. International Journal of Environmental Research and Public Health, 17 (7), 2404. doi: http://doi.org/10.3390/ijerph17072404

4. Derzhavnyi reiestr likarskykh zasobiv Ukrainy. Available at: http://www.drlz.com.ua

5. T Ryvak, T. B., Nepyivoda, O. M., Koval, A. Y. (2020). Pharmaceutical care for symptoms of allergy during pregnancy and lactation: rational choice and use of antihistamines. Zaporozhye Medical Journal, 22 (2), 192–199. doi: http://doi.org/10.14739/2310-1210.2020.2.200594

6. Eschler, D., Klein, P. (2010). An Evidence-based Review of the Efficacy of Topical Antihistamines in the Relief of Pruritus. Journal of Drugs in Dermatology, 9 (8), 992–997.

7. Kalkan, F., Parlakpinar, H., Disli, O. M., Tanriverdi, L. H., Ozhan, O., Polat, A. et. al. (2018). Protective and therapeutic effects of dexpanthenol on isoproterenol-induced cardiac damage in rats. Journal of Cellular Biochemistry, 119 (9), 7479–7489. doi: http://doi.org/10.1002/jcb.27058

8. Proksch, E., de Bony, R., Trapp, S., Boudon, S. (2017). Topical use of dexpanthenol: a 70th anniversary article. Journal of Dermatological Treatment, 28 (8), 766–773. doi: http://doi.org/10.1080/09546634.2017.1325310

9. Medicines. Pharmaceutical development (ICH Q8) (2011). ST-N MoHU 42-3.0:2011. Kyiv. Available at: https://compendium.com.ua/uk/clinical-guidelines-uk/standartizatsiya-farmatsevtichnoyi-produktsiyi-tom-1/st-n-mozu-42-3-0-2011/

10. Ul Ullah, F., Othman, M. B. H., Javed, F., Ahmad, Z., Akil, H. M. (2015). Classification, processing and application of hydrogels: A review. Materials Science and Engineering: C, 57, 414–433. doi: http://doi.org/10.1016/j.msec.2015.07.053

11. Derzhavna Farmakopeia Ukrainy. Vol. 1 (2015). Kharkiv: Derzhavne pidpryiemstvo «Ukrainskyi naukovyi farmatsevtychnyi tsentr yakosti likarskykh zasobiv», 1128.
12. Derzhavna Farmakopeia Ukrainy. Vol. 2 (2014). Kharkiv: Derzhavne pidpryiemstvo «Ukrainskyi naukovyi farmatsevtychnyi tsentr yakosti likarskykh zasobiv», 724 s.
13. Handbook of Pharmaceutical Excipients. 8th ed. / eds. P. J. Sheskey, W. G. Cook, C. G. Cable. London : American Pharmacists Association, Pharmaceutical Press, 2017. 1216 p.
14. Neutralizing Carbopol® and Pemulen™ Polymers in Aqueous and Hydroalcoholic Systems, Technical Data Sheet (TDS-237) (2009). Cleveland: Lubrizol Advanced Materials, Inc. Cleveland.
15. Kukhtenko, H. P., Popova, T. V., Gladukh, Ie. V., Kukhtenko, O. S. (2020). Comparative analysis of carbomer polymers for pharmaceutical and cosmetic practice. Zaporozhye Medical Journal, 3, 431–436. doi: http://doi.org/10.14739/2310-1210.2020.3.204960
16. Dimethindene (2021). National Center for Biotechnology Information. PubChem Compound Summary for CID 21855. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/Dimethindene Last accessed: 11.04.2021
17. Dexpanthenol (2021). National Center for Biotechnology. Information PubChem Compound Summary for CID 131204. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/Dexpanthenol Last accessed: 11.04.2021
18. Suhail, M., Wu, P.-C., Minhas, M. U. (2020). Using Carbomer-Based Hydrogels for Control the Release Rate of Diclofenac Sodium: Preparation and In Vitro Evaluation. Pharmaceuticals, 13 (11), 399. doi: http://doi.org/10.3390/ph13110399
19. Babiy, E. V., Vashchenko, K. F., Vashchenko, O. O. (2014). Investigation of amixin release from semifsolid preparations. Ukrainian biopharmaceutical journal, 1 (30), 46–50.
20. Kukhtenko, O., Gladukh, Ie., Kukhtenko, H., Bevz, N. (2019). Pharmaceutical Studies on Development of Venotonic Action Gel Based on Plant Extract. Retsept, 22 (1), 34–42.
21. Lyapunov, A. N., Bezuglaya, E. P., Lyapunov, N. A., Kirilyuk, I. A. (2015). Studies of Carbomer Gels Using Rotational Viscometry and Spin Probes. Pharmaceutical Chemistry Journal, 49 (9), 639–644. doi: http://doi.org/10.1007/s11094-015-1344-3
22. De Souza Ferreira, S. B., Moço, T. D., Borghi-Pangoni, F. B., Junqueira, M. V., Bruschi, M. L. (2016). Rheological, mucoadhesive and textural properties of thermoresponsive polymer blends for biomedical applications. Journal of the Mechanical Behavior of Biomedical Materials, 55, 164–178. doi: http://doi.org/10.1016/j.jmbbm.2015.10.026
23. Kukhtenko, H., Gladukh, I., Kukhtenko, O., Soldatov, D. (2017). Influence of Excipients on the Structural and Mechanical Properties of Semisolid Dosage Forms. Asian Journal of Pharmaceutics, 11 (3), S575–S578. doi: http://doi.org/10.22377/ajp.v11i03.1462
24. Risaliti, L., Piazzini, V., Di Marzo, M. G., Brunetti, L., Cecchi, R., Lencioni, P. et. al. (2018). Topical formulations of delta-aminolevulinic acid for the treatment of actinic keratosis: Characterization and efficacy evaluation. European Journal of Pharmaceutical Sciences, 115, 345–351. doi: http://doi.org/10.1016/j.ejps.2018.01.045
25. Sosa, L., Calpena, A. C., Silva-Abreu, M., Espinoza, L. C., Rincón, M., Bozal, N. et. al. (2019). Thermoreversible Gel-Loaded Amphotericin B for the Treatment of Dermal and Vaginal Candidiasis. Pharmaceutics, 11 (7), 312. doi: http://doi.org/10.3390/pharmaceutics11070312
26. Carvalho, F. C., Calixto, G., Hatakeyama, I. N., Luz, G. M., Gremião, M. P. D., Chorilli, M. (2012). Rheological, mechanical, and bioadhesive behavior of hydrogels to optimize skin delivery systems. Drug Development and Industrial Pharmacy, 39 (11), 1750–1757. doi: http://doi.org/10.3109/03639045.2012.734510
27. Mazger, T. G. (2006). The Rheology Handbook: For users of rotational and oscillatory rheometers. Hannover: Vincentz Network, 299.
28. Alghooneh, A., Razavi, S. M. A., Kasapis, S. (2019). Classification of hydrocolloids based on small amplitude oscillatory shear, large amplitude oscillatory shear, and textural properties. Journal of Texture Studies, 50 (6), 520–538. doi: http://doi.org/10.1111/jtxs.12459
29. Savary, G., Gilbert, L., Grisel, M., Picard, C. (2019). Instrumental and sensory methodologies to characterize the residual film of topical products applied to skin. Skin Research and Technology, 25 (4), 415–423. doi: http://doi.org/10.1111/srt.12667
30. Kalouta, K., Eleni, P., Boukouvalas, C., Vassilatou, K., Krokida, M. (2019). Dynamic mechanical analysis of novel cosmeceutical facial creams containing nano- encapsulated natural plant and fruit extracts. Journal of Cosmetic Dermatology, 19 (5), 1146–1154. doi: http://doi.org/10.1111/jocd.13133

Received date 13.04.2021
Accepted date 01.06.2021
Published date 30.06.2021

Tetiana Popova, Postgraduate Student, Department of Cosmetology and Aromology, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Halyna Kukhtenko*, PhD, Associate Professor, Department of Cosmetology and Aromology, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

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

Oleksandr Kukhtenko, Doctor of Pharmaceutical Sciences, Professor, Head of Department, Department of Technologies of Pharmaceutical Preparations, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

**Corresponding author: Halyna Kukhtenko, e-mail: galinakukh@gmail.com*