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Original article

Study of the effect of active pharmaceutical ingredients of various classes of BCS on the parameters of thermosensitive systems based on poloxamers

E.O. Bakhrushina, A.I. Khodenok *, V.S. Pyzhov, P.G. Solomatina, N.B. Demina, T.V. Korochkina, I.I. Krasnyuk

I.M. Sechenov First Moscow State Medical University (Sechenov University), A.P.Nelyubin Institute of Pharmacy, Department of Pharmaceutical Technology, 96 Vernadsky Avenue, building 1 119571, Moscow, Russia

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ABSTRACT

Introduction: The development of thermosensitive *in situ* systems has become widespread and prospective due to the optimal parameters of the phase transition - in the temperature range from room to physiological. Those properties can provide thermosensitive polymers, for example, poloxamers - as the most common.

It is worth noting that the addition of active pharmaceutical ingredients (APIs) changes the parameters of *in situ* systems, but no systematic study of the effect of APIs has been conducted. *The aim of this work* was to develop a systematic approach to studying the effect of APIs on the *in situ* rheological properties of poloxamer compositions.

Materials and methods: The biopharmaceutical classification system (BCS) was chosen as the basis. Accordingly, the following APIs were selected for the experiment: BCS class I - lidocaine hydrochloride and ketorolac tromethamine, class II - ibuprofen and diclofenac, class III - pyridoxine hydrochloride and ribavirin, class IV - furosemide and abiraterone. To create thermoreversible compositions, previously studied for stability combinations of poloxamer 407, poloxamer 188 and PEG 1500 were used.

At the stage of preparation of experimental samples formulations with APIs of classes II and IV of BCS were excluded, since the solubilizing ability of poloxamers is not enough to obtain stable combined complexes.

Results: In the course of the work, the following results were obtained: BCS class I APIs significantly reduced the phase transition temperature of the matrix of poloxamers 407 and 188, while the addition of PEG 1500 eliminated the effect of APIs on gels; BCS class III APIs practically did not affect the rheological properties of the studied combinations; the phase transition temperature of the gel based on poloxamer 407 did not change with the addition of Class I and Class III APIs.

Nevertheless, the obtained results made it possible to reveal the regular behavior of *in situ* complexes of poloxamer matrices depending on the class of BCS of the API. Further research is required.

1. Introduction

Currently, one of the most promising areas in pharmaceutical technology is the development of *in situ* systems for targeted drug delivery. The popularity of these systems is justified by a number of their advantages: targeting of action, minimizing adverse events, the greatest bioavailability compared to other methods of drug administration, prolongation of action.

In situ delivery systems form their final dosage form directly at the place of application. The phase transition can be potentiated by changes in temperature, humidity, pH, redox and photochemical reactions (Bakhrushina 2022). Due to the versatility of the stimulus, thermosensitive systems that change their viscosity in response to temperature changes – from room (or other storage temperature of the drug) to physiological or pathological have been widely used. Upon contact with the mucous tissue or target organ, the thermosensitive matrix performs a phase transition for

* Corresponding author.
E-mail address: angelinahodenok@gmail.com (A.I. Khodenok).

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some time (from several seconds to several minutes), due to which a gel of different viscosity and density is formed, contributing to better adhesion to the site of exposure, longer application and, as a consequence, prolongation of the pharmacological effect.

Thermosensitive polymers are capable of providing a sol–gel transition at different temperature values – these conditions can be adjusted by adding additional auxiliary components or directed synthesis of polymers with different component compositions. The temperature of the phase transition and the sol–gel transition rate are also affected by the active components introduced into the matrices (Tobin et al., 2023, Khanliq et al., 2023, Lupu et al., 2023, Javed et al., 2022).

Poloxamers (pluronics), symmetrical linear copolymers whose macromolecules consist of regularly or statistically alternating homopolymer blocks of ethylene oxide (EO) and propylene oxide (PO), have become the most widespread among the thermosensitive components of *in situ* systems.

Depending on the number of EO and PO groups, the physicochemical properties of the final polymers change. Thus, it was found that with an increase in the hydrophilicity of pluronics (i.e., the mass fraction of polyoxyethylene groups in the polymer), its viscosity and the turbidity temperature of its aqueous solution increase. The ratio of polypropylene oxide (PPO) and polyethylene oxide (PEO) in the molecule also affects the rate of dissolution of pluronics in water and the values of surface tension in their aqueous solutions (Abdirakhimov 2021).

The contribution of ethylene oxide and propylene oxide to the physicochemical properties of pluronics is most clearly shown by the value of the hydrophilic-lipophilic balance, since these polymers are nonionic surfactants.

Using the example of the block copolymers of PEO and PPO considered in this paper, whose characteristics are indicated in Table 1, the amount of hydrophilic-lipophilic balance (HLB) pluronics is influenced not so much by the amount of oxyethylene and oxypropylene components as by their percentage content in the polymer. With an increase in the mass fraction of EO in the block copolymer, its hydrophilicity increases (the value of HLB increases). At the same time, the critical concentration of micelle formation and the temperature of gelation of their 1% aqueous solutions increases.

One of the most important properties of pluronics is the ability of individual block copolymer molecules to assemble into micelles when the critical concentration of micelle formation (CMC) is reached in an aqueous solution. The PO core inside the micelles can include various lipophilic compounds due to its hydrophobicity (Dahanayake 2022).

As the concentration of the block copolymer increases, micelles form more densely packed structures and form gels when a certain threshold concentration is reached. These gels have a microheterogenic structure, swelling ability and biocompatibility. (Rey-Rico et al., 2018, Saadat et al., 2023, Ward et al., 2023, Bollenbach 2022).

The PO chains have a lower critical dissolution temperature, due to which both the micelles of pluronics and their gels have the thermoreversive properties. While the PO chains are hydrated and soluble in water at low temperatures, when the temperature rises and the critical temperature of micelle formation is reached, they dehydrate and become insoluble, which leads to the formation of micellar cores. Similarly, the formation of gels is observed only when the critical temperature of gelation (CTG) is reached (Chittari S. S. et al., 2023, Bakhrushina E.O. et al., 2023).

The structure of block copolymers has a strong influence on the processes of micelle formation and gelation. As the length of the hydrophobic block increases, the formation of micelles and gels becomes more favorable, which leads to lower values of CMC and critical temperature of micelle formation (CMT). Conversely, an increase in the length of the hydrophilic block of ethylene oxide (ETO) reduces the stability of micelles (Aparajay and Dev 2022). Thus, gelation in aqueous solutions of pluronics is affected by:

1) Mass concentration of block polymer in solution;

2) Molecular weight of the hydrophobic base of PPO;

3) The number of moles of ethylene oxide condensed with a hydrophobic base of PO (Kelly 2022).

In modern studies of the problem, the leading role of the influence of active ingredients on the parameters of thermosensitive systems is noted. However, these studies did not apply a systematic approach to the study of rheological behavior of *in situ* thermosensitive systems with active substances and placebo (Bakhrushina 2022). Understanding the principles of interaction of active ingredients and matrix components will allow us to approach the development of dosage forms systematically, rather than empirically, which will reduce financial and time costs.

The aim of the work is to develop a systematic approach to determining the influence of APIs on the rheological parameters of poloxamer compositions. The BCS was chosen as the criterion for the selection of the APIs.

2. Materials and methods

For obtaining experimental samples, Poloxamer 407 and Poloxamer 188 of the Kolliphor® brand of BASF, polyethylene glycol 1500 of the Pluriol® E 1500 brand were used. Pharmaceutical substances of Classes I, II, III and IV of the Biopharmaceutical Classification System (BCS) were used as active pharmaceutical ingredients (APIs) (Table 2).

Two most stable gel matrices (according to previously conducted studies (Bakhrushina et al., 2022)) and a monopolymeric

Table 2
Classification of experimental APIs according to the BCS.

BCS class	API
I	Lidocaine hydrochloride [Dishman Pharmaceutical Chemicals Limited, India] Ketorolac tromethamine [“ACTIVE COMPONENT JBC”, Russia]
II	Diclofenac [Aarti Drugs Limited, India] Ibuprofen [«BASF», Germany]
III	Pyridoxine hydrochloride [DSM, Germany] Ribavirin [Jinan Mingxin Pharmaceutical Co., Ltd., China]
IV	Furosemide [“AMRI India Pvt. Ltd.”, India] Abirateron [Jiangsu Airbright Pharmaceuticals Co., Ltd., China]

Table 1
Physico-chemical properties (PEO)N/2-(PO)m-(PEO)N/2 block copolymers (Chen et al., 2022).

Copolymer	Molar mass (in Da)	Average number of EO groups in a block (N_{EO})	Average number of software groups per block (M_{PO})	Ethylene oxide content in block copolymer (M_{EO} %)	HLB	Cloud point in 1% polymer solution (℃)	CMC (mol/l)
Poloxamer 407 (P407, F127)	12,600	200.45	65.17	»70%	22	> 100	$2.8 \cdot 10^{-6}$
Poloxamer 188 (P188, F68)	8400	152.73	28.97	»80%	29	> 100	$4.8 \cdot 10^{-4}$

Table 3
Compositions of experimental samples of *in situ* systems.

	Lidocaine hydrochloride 2%	Ketorolac tromethamine 2%	Ibuprofen 2%	Diclofenac 2%	Pyridoxine hydrochloride 2%	Ribavirin 2%	Furosemide 2%	Abiraterone 2%
P407 18% + water 100 ml	L1	K1	I1	D1	P1	R1	F1	A1
P407 18% + P188 5% + water	L2	K2	I2	D2	P2	R2	F2	A2
P407 18% + P188 3% + PEG 2.5% + water 100 ml	L3	K3	I3	D3	P3	R3	F3	A3

composition based on poloxamer 407 as a reference (Table 3) were selected for the study.

In order to achieve accurate concentration of active pharmaceutical substances in the experimental samples, each tested matrix was manufactured according to a single methodology, according to which each gel component was weighed on analytical scales Mettler Toledo Balance XPR404S/A (Mettler Toledo, USA) with an accuracy of 0.0001 g. Then the gel components were mixed in a precise volume of water purified on a magnetic stirrer IKA C-mag HS 7 digital (IKA, Germany) for 20–30 min to achieve homogeneity and stability of the solution. Further prepared samples were placed in a pharmaceutical refrigerator at 4 ± 0.5 °C for 24 h to obtain a stable gel.

The dosing accuracy and homogeneity of the obtained experimental samples were proved by spectrophotometric quantification of API in the prepared gels. For this purpose, placebo solutions containing no AFI and consisting of gel-forming matrices were additionally prepared.

Quantitative determination of API content in the prepared gels was performed by UV–visible spectrophotometry on an Agilent Cary 60 spectrophotometer (Agilent Technologies Inc., USA). A placebo solution with the appropriate composition of gel forming excipients was used as a comparison solution for each sample; the wavelengths for each composition were selected according to the API contained in the test sample. To determine dosing uniformity, 1-mL samples were taken from the prepared samples in the liquid state at 4 °C using a Proline Sartorius BIOHIT single-channel pipette (Sartorius AG, Germany) from an area not touching the bottom or space near the walls of the vessel containing the experimental sample solution. The selected samples were then placed in 5 ml measuring vials, the volume of the vial was brought to the mark with purified water, and the solution was mixed thoroughly. The resulting solutions were transferred into cuvettes for spectrophotometry and measured. Each experimental sample was analyzed in at least 5 measurements.

Thus, during the analysis of homogeneity and accuracy of dosing by spectrophotometry and statistical processing of the results obtained, it was found that each of the tested gel samples contains the exact concentration of API, which is evenly distributed in the gel matrix.

Experimental samples were obtained by dispersing the components in purified water on a magnetic stirrer IKA C-mag HS 7 digital (IKA, Germany) for 20 min and further obtaining a stable gel in a pharmaceutical refrigerator at a temperature of 4 ± 0.5 °C for 24 h.

To study the rheological parameters of the gels, a viscometer of the Lamy Rheology RM 200 model (France) was used using Rheomatic-T software for processing experimental data. The "cylinder in cylinder" ms-din 33 system was used for the measurement, the cell volume was 17 ml. The experiment was carried out at a constant shear rate of 100 s^{-1} in the temperature range from 15 to 55 °C. Each sample was measured at least 5 times with a half-hour relaxation between measurements.

According to the data obtained, the viscosity curves were constructed. The rheological properties of each sample were studied at 4, 12 and 24 weeks from the date of manufacture. The choice of a control point for 4 weeks of sample storage as the beginning of the experiment is based on a visual assessment of the sample – by this time the gels became completely transparent and did not have any inclusions of non-dissolved components.

3. Results and discussion

3.1. The results of the study of rheological properties

According to this method, BCS (biopharmaceutical classification system) class II and IV APIs (active pharmaceutical ingredients) did not allow obtaining a gel of satisfactory quality, since the API formed a precipitate or suspension. It was proposed to prepare these gels using a magnetic stirrer with heating up to 60 °C. However, after the API mixture cooled down, the precipitate or suspension was re-formed. This can be explained by the lack of solubilizing ability of the selected excipients. Therefore, BCS class II and IV APIs (Diclofenac and Ibuprofen (D1-3, Ib1-3), Furosemide and Abiraterone (F1-3, A1-3), respectively) were excluded from further study.

Let us compare the obtained results of rheological measurements of BCS class I representatives - lidocaine hydrochloride and ketorolac tromethamine (Fig. 1).

It can be noted that the CTG range for samples L1 and K1 is similar – 24–26 °C, as well as the end of the phase transition – 27–29 °C. The characters of the obtained curves are also similar. Maximum viscosity ratings of the compositions differ slightly.

A similar rheological profile was also found for samples L2 and K2. The temperature of the "sol-gel" transition is in the same range as for samples L1 and K1. The behavior of the viscosity curves L2 and K2 is comparable.

A different result was obtained during the rheological study of L3 and K3 gels. Compared to samples without PEG 1500, the phase transition temperature of these gels increased to the range of 36–40 °C. It should be noted that in samples with BCS class I API viscosity values remain in a certain range, so the addition of active substances does not affect the numerical viscosity index.

Let us consider the results of rheological measurements of gels with BCS class III API - ribavirin and pyridoxine hydrochloride (Fig. 2).

Similar to the samples L1 and K1, the phase transition of R1 and P1 is observed at 25–29 °C for half a year of gel storage, the maximum viscosity of all the mentioned compositions is alike. A feature in the rheological behavior of composition P1 was noted, which distinguishes it from samples with other APIs - a short plateau and the presence of a reversion - a reverse "gel-sol" transition with an increase in temperature above 33 °C. As the sample is stored, the plateau lengthens.

A different picture can be seen in samples R2 and P2. The temperature range compared to R1 and P1 has increased to 38–43 °C, and the viscosity curve reaches a stable plateau state; this rheological behavior practically does not change during 24 weeks of storage.

Regarding the compositions R3 and P3 the rheological characteristics are similar to those of R2 and P2.

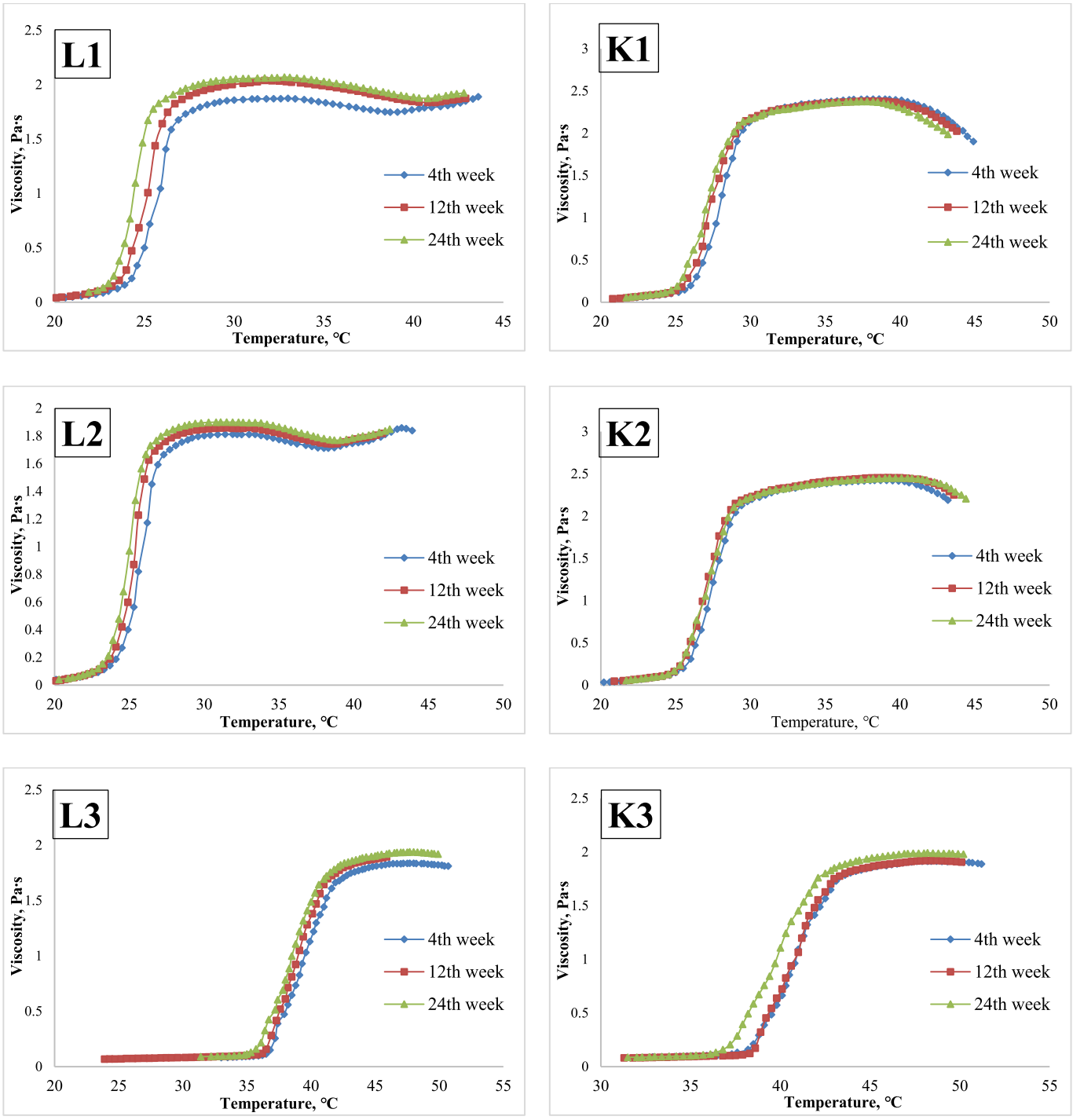

Fig. 1. Viscosity curves for compositions with API class I BCS at selected time points.

The gelation temperature correlates with the samples without PEG 1500. It should be noted that the addition of PEG 1500 significantly reduced the maximum viscosity of the samples with class III API.

Table 4 summarizes the results of long-term testing of samples. Composition P1 has a reverse "gel-sol" transition in the analysed temperature range. The combinations of K1 and K2 tend to reduce the viscosity to the initial values, but it was not possible to fix their "gel-sol" transition since it lies outside the experimental temperature range.

3.2. Discussions

During the experiments the effect of substances of various BCS classes on the gelation temperature of pure poloxamer 407, its combination with poloxamer 188 and combinations of poloxamers 407 and 188 with polyethylene glycol 1500 was studied.

To begin with, it should be noted that the addition of the F68 block copolymer increases the gelation temperature of the aqueous solution of the F127 block copolymer, which is confirmed by the work of Kai Zhang and colleagues (PJ et al., 2022).

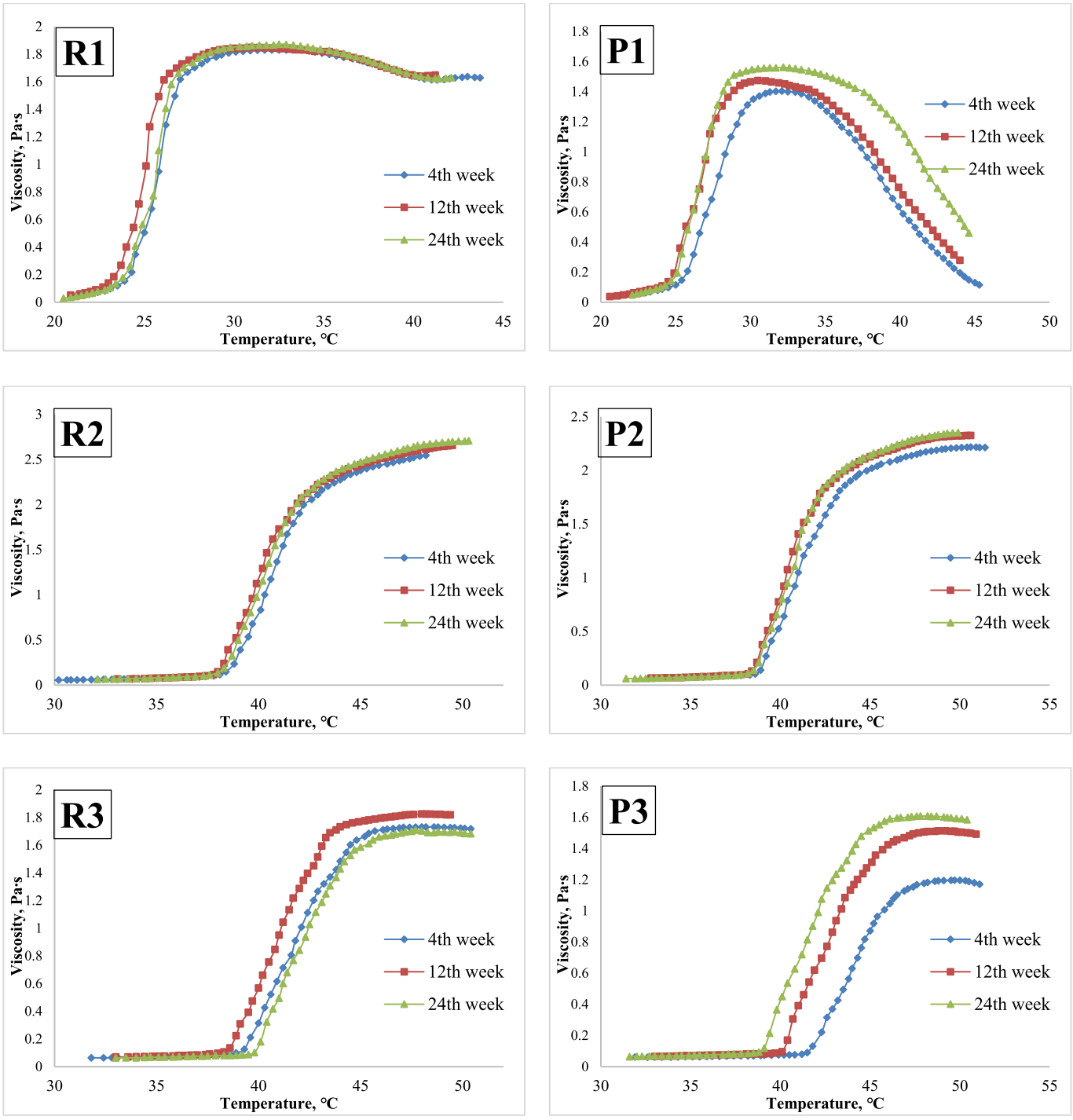

Fig. 2. Viscosity curves for formulations with API class III BCS at selected time points.

When PEG 1500 is added to this combination, a slight shift in the temperature range of gel formation is observed. Due to its greater hydrophilicity polyethylene glycol should form a large number of hydrogen bonds with water, thus reducing the number of iterations of the polyethylene oxide fraction of pluronics with a solvent, lowering the critical temperature of micelle formation and facilitating gel formation. However, during our observations, the opposite effect is found from the addition of PEG 1500 to the combination of excipients. This phenomenon can be explained by the incorporation of PEG into the crown of micelles due to the interaction of the terminal hydroxyl groups of PEG and EO fragments of poloxamers. This incorporation leads to an increase in the size of micelles and the distance between them, which hinders their aggregation. In this regard, a high temperature is required to increase the concentration of micelles in the solution and their aggregation into a single gel network.

This observation is confirmed by many studies, particularly in the work of Pragatiswaran and Chen, who studied the effect of PEG and PEO on gelation in aqueous solutions of P407 (Khodaei A. et al., 2022, Yuan et al., 2022, Azum and Ail 2023).

Table 4
The results of long-term testing of experimental samples.

	4th week	12th week	24th week
L1	t^{1} = 24.3–26.9; h^2_{max} = 1.89	t^{1} = 24.0–26.0; h^2_{max} = 2.03	t^{1} = 23.3–25.5; h^2_{max} = 2.07
L2	t^{1} = 24.1–26.9; h^2_{max} = 1.85	t^{1} = 23.7–26.3;h^2_{max} = 1.86	t^{1} = 23.6–26.1;h^2_{max} = 1.90
L3	t^{1} = 36.8–41.6; h^2_{max} = 1.84	t^{1} = 36.5–41.0;h^2_{max} = 1.89	t^{1} = 36.1–40.6;h^2_{max} = 1.94
K1	t^{1} = 26.0–29.5; h^2_{max} = 2.40 t'= 41.6->45.0	t^{1} = 25.4–29.0; h^2_{max} = 2.38 t'= 39.0->45.0	t^{1} = 25.1–28.9; h^2_{max} = 2.37 t'= 38.5->45.0
K2	t^{1} = 25.5–29.0; h^2_{max} = 2.42 t'= 39.5->43.0	t^{1} = 25.3–28.7; h^2_{max} = 2.45 t'= 40.4->45.0	t^{1} = 25.3–28.9; h^2_{max} = 2.45 t'= 41.5->45.0
K3	t^{1} = 38.2–43.1; h^2_{max} = 1.92	t^{1} = 38.6–42.8; h^2_{max} = 1.92	t^{1} = 36.8–41.9; h^2_{max} = 1.99
P1	t^{1} = 25.4–29.4; h^2_{max} = 1.40 t'= 34.3–43.6	t^{1} = 24.9–28.1; h^2_{max} = 1.47 t'= 34.7–44.0	t^{1} = 25.1–28.2; h^2_{max} = 1.56 t'= 37.6–44.6
P2	t^{1} = 38.9–43.3; h^2_{max} = 2.22	t^{1} = 38.7–42.2; h^2_{max} = 2.32	t^{1} = 38.8–42.3; h^2_{max} = 2.35
P3	t^{1} = 41.8–45.8; h^2_{max} = 1.20	t^{1} = 40.1–45.3; h^2_{max} = 1.51	t^{1} = 39.1–44.5; h^2_{max} = 1.61
R1	t^{1} = 24.3–27.0; h^2_{max} = 1.83	t^{1} = 23.3–26.1; h^2_{max} = 1.85	t^{1} = 24.2–26.5; h^2_{max} = 1.87
R2	t^{1} = 38.8–42.2; h^2_{max} = 2.55	t^{1} = 38.3–41.4; h^2_{max} = 2.66	t^{1} = 38.3–41.9; h^2_{max} = 2.71
R3	t^{1} = 39.3–44.3; h^2_{max} = 1.73	t^{1} = 38.6–43.3; h^2_{max} = 1.82	t^{1} = 39.8–44.2; h^2_{max} = 1.71

t^{1} –temperature range of sol–gel transition, ℃.
t' –temperature range of gel-sol transition, ℃.
h^2_{max} – maximum viscosity, Pa•s.

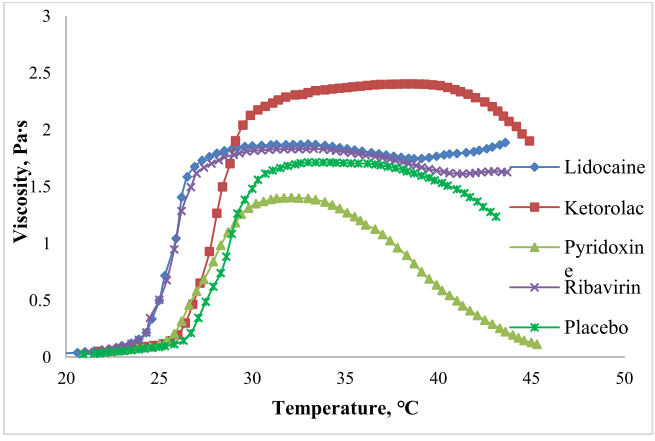

Fig. 3. Viscosity curves for samples based on poloxamer 407 with and without BCS class I and III APIs.

While investigating the effect of various active pharmaceutical ingredients on the Critical Gelation Temperature (CTG) of pure excipients and their combinations and comparing them with placebo formulations, a certain trend was noticed (Figs. 3-5):

1. Substances of BCS class I, which have good solubility in water and high permeability, reduced CTG in combination with poloxamers, but did not affect the CTG of the composition with polyethylene glycol;

2. Substances of classes II and IV did not dissolve in solutions of these excipients, since the working concentrations of surfactants in the studied samples were not enough to solubilize these APIs;

3. BCS class III substances did not affect CTG in combinations of poloxamers and poloxamers with PEG 1500.

4. The rheological properties of dosage form of pure poloxamer 407 were insignificantly affected by APIs of classes I and III.

It can be assumed that class I APIs, due to their high solubility in water, interact with P188 due to its greater hydrophilicity. Interacting with the polar functional groups of Pluronic, class I APIs hinder the formation of hydrogen bonds between micelles. It should

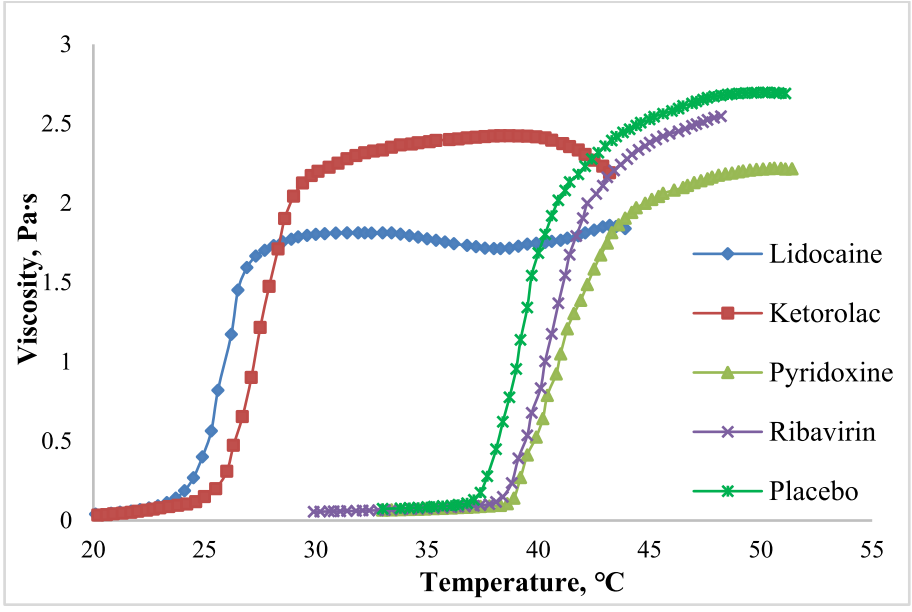

Fig. 4. Viscosity curves of samples based on poloxamers 407 and 188 with and without BCS class I and III APIs.

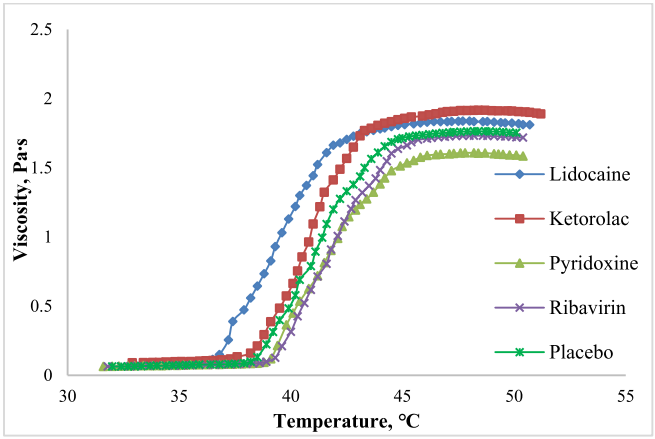

Fig. 5. Viscosity curves of samples based on poloxamers 407, 188 and PEG 1500 with and without BCS class I and III APIs.

be considered that class I APIs are amphiphilic; therefore, they can interact with non-polar PPO groups, preventing the formation of micelles themselves. Thus, class I APIs minimize the effect of P188 on the gelation of the formulation. The resulting viscosity curve is similar to that of a class I API with P407.

In the case of combining poloxamers with PEG class I API interacts more with the last, since PEG has a high hydrophilicity compared to P188. Class I APIs have a greater affinity for PEG which results in the decrease of the strength of interaction with P188. Therefore, on the rheological characteristics of the composition of the poloxamers and PEG the class I APIs affect less than on the composition of the two poloxamers.

As for BCS class III - APIs in this group usually have many polar groups, what can be assumed that they are more hydrophilic than class I APIs. Due to this property, when active substance (AS) is dissolved in water, a solvate shell is formed around the AS molecule, what prevents the interaction of class III APIs with poloxamers and PEG – the effect of the API on the gelation process is minimized and the rheological parameters are similar to placebo dosage forms.

The lack of influence of class I and III APIs on the rheological properties of P407 gel can be explained by the concentration of P407 (18% by weight), which significantly exceeds the concentration of API (2% by weight), so the presence of API in the dosage form does not prevent micelle and gel formation of poloxamer. The addition of this excipient at a lower concentration does not make sense since the effective concentration starts from 18% (Shefa et al, 2022).

4. Conclusion

As a result of an experimental study on a rotational viscometer, the presence of a characteristic rheological behavior of the compositions depending on the BCS class of the added API was established. The stability of the studied formulations in long-term storage (24 weeks) was confirmed.

During the study of the rheological properties of stable compositions of poloxamers with APIs of different classes of BCS and comparing them to placebo dosage forms, the following dependence of these properties on the API belonging to a certain class of BCS was revealed: representatives of class I significantly reduced the temperature of the "sol-gel" transition of the matrix of P407 and P188, but did not affect the composition of poloxamers with PEG 1500; Class III APIs had little or no effect on the rheological behavior of the studied samples. Further study of the stability of the experimental formulations and a longer term study (52 weeks and beyond) of their thermoreversible properties is needed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abdirakhimov, I.E., 2021. Demulsification of oil-water emulsions. Universum: Tech. Sci. 85, 72–75. https://doi.org/10.32743/UniTech.2021.85.4-3.72-75.
Aparajay, P., Dev, A., 2022. Functionalized niosomes as a smart delivery device in cancer and fungal infection. Eur. J. Pharma. Sci. 168,. https://doi.org/10.1016/j.ejps.2021.106052 106052.
Azum, N., Ail, M., 2023. Exploring solvation behaviour of biocompatible ionic liquid 2-hydroxyethylammonium formate+ polyethylene glycols mixtures: Role of oxyethylene and hydroxyl units of PEGs. J. Mol. Liq. 382,. https://doi.org/10.1016/j.molliq.2023.121922 121922.
Bakhrushina, E.O., 2022. Application of in vitro modeling for pharmaceutical development of in situ systems. Med. Pharma. J. "Pulse" 24, 137–142. https://doi.org/10.26787/nydha-2686-6838-2022-24-6-137-142.
Bakhrushina, E.O. et al., 2022. Study of poloxamer 188 and polyethylene glycols influence on *in situ* systems thermoreversible properties. Problems Biol. Med. Pharma. Chem. 10, 16–21. https://doi.org/10.29296/25877313-2022-10-00.
Bakhrushina, E.O. et al., 2023. Block copolymers of ethylene oxide and propylene oxide: prospects for medical and pharmaceutical application in Russia. Bull. Scient. Centre Expert Eval. Med. Prod. Regul. Res. Med. Eval. 13, 333–344. https://doi.org/10.30895/1991-2919-2023-530.
Bollenbach, L., 2022. Poloxamer 188 as surfactant in biological formulations–An alternative for polysorbate 20/80? Int. J. Pharma. 620,. https://doi.org/10.1016/j.ijpharm.2022.121706 121706.
Chen, I.C. et al., 2022. Investigation and characterization of factors affecting rheological properties of poloxamer-based thermo-sensitive hydrogel. Polymers 14, 5353. https://doi.org/10.1016/S0065-2660(05)53009-8.
Chittari, S.S. et al., 2023. Investigating fundamental principles of nonequilibrium assembly using temperature-sensitive copolymers. J. Am. Chem. Soc. 145, 6554–6561. https://doi.org/10.1021/jacs.3c00883.
Dahanayake, R., 2022. Molecular structure and co-solvent distribution in PPO–PEO and pluronic micelles. Macromolecules 55, 10439–10449. https://doi.org/10.1021/acs.macromol.2c01206.
Javed, R. et al., 2022. Significance of capping agents of colloidal nanoparticles from the perspective of drug and gene delivery, bioimaging, and biosensing: An insight. Int. J. Mol. Sci. 23, 10521. https://doi.org/10.1016/j.jddst.2017.12.002.
Kelly H., 2022. " Thermo-responsive hydrogel for intratumoral administration as a treatment in solid tumor cancers." U.S. Patent No. 11,534,401. 27 Dec. 2022.
Khanliq, N.U. et al., 2023. Pluronic F-68 and F-127 based nanomedicines for advancing combination cancer therapy. Pharmaceutics 15, 2102. https://doi.org/10.3390/pharmaceutics15082102.
Khodaei, A. et al., 2022. Controlled temperature-mediated curcumin release from magneto-thermal nanocarriers to kill bone tumors. Bioact. Mater. 11, 107–117. https://doi.org/10.1016/j.bioactmat.2021.09.028.
Lupu, A. et al., 2023. Temperature induced gelation and antimicrobial properties of pluronic F127 based systems. Polymers 15, 355. https://doi.org/10.3390/polym15020355.
Pj, R.J. et al., 2022. Recent advances in drug delivery nanocarriers incorporated in temperature-sensitive Pluronic F-127–A critical review. J. Drug Delivery Sci. Technol. 72,. https://doi.org/10.1016/j.jddst.2022.103390 103390.
Rey-Rico, A., Cucchiarini, M., 2018. PEO-PPO-PEO tri-block copolymers for gene delivery applications in human regenerative medicine—an overview. Int. J. Mol. Sci. 19, 775. https://doi.org/10.3390/ijms19030775.
Saadat, Y. et al., 2023. Thermoresponsive antifouling ultrafiltration membranes from mesophase templating. J. Membr. Sci. https://doi.org/10.1016/j.memsci.2023.121861 121861.
Shefa, A.A. et al., 2022. Alpha tocopherol-nanocellulose loaded alginate membranes and pluronic hydrogels for diabetic wound healing. Mater. Des. 224,. https://doi.org/10.1016/j.matdes.2022.111404 111404.
Tobin, K.V. et al., 2023. Thermosensitive biomaterial gels with chemical permeation enhancers for enhanced microneedle delivery of naltrexone for managing opioid and alcohol dependency. Biomater. Sci. https://doi.org/10.1039/D3BM00972F.
Ward C. L. [et al.], 2023. A review of electrophoretic separations in temperature-responsive Pluronic thermal gels //Analytica Chimica Acta. 341613. doi:10.1016/j.aca.2023.341613.
Yuan, B. et al., 2022. A thin composite polymer electrolyte with high room-temperature conductivity enables mass production for solid-state lithium-metal batteries. Energy Storage Mater. 47, 288–296. https://doi.org/10.1016/j.ensm.2022.01.052.