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STABILITY EVALUATION OF THERMOSENSITIVE DRUG CARRIER SYSTEMS BASED ON PLURONIC® F-127 POLYMER

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Abstract: The aim of this study was to evaluate the stability of thermosensitive systems based on Pluronic® F-127 polymer, in aspects of their possible application in novel drug technology. A formulation was prepared without any active ingredient, consisting of 16% (w/w) of polymer dissolved in aqueous medium. Such preparation was autoclaved and then subjected to 3-month conditioning at elevated (40°) and reduced (5°C) temperature. Rheological parameters: viscosity, consistency and sol-gel transition characteristics were studied in 1-month interval. The significance of measured changes was evaluated by proper statistical analyses. Significant changes exceeding the established criteria (±10% of every initial value) were observed during the study. Furthermore, total involution of sol-gel transition phenomenon was observed in samples stored at 40°C. Results indicate the lack of stability in tested formulation at both of storage conditions. However, some regularity indicates that the stability at reduced temperature could be confirmed, if only the concentration of polymer and the measurements schedule were slightly modified.

Keywords: Poloxamer P 407, Pluronic® F-127, thermosensitive drug carriers, stability

Poloxamers, known by their commercial names Pluronic® or Kolliphor® are linear, triblock copolymers of ethylene oxide (EO) and propylene oxide (PO) (1). They are used as excipients in the cosmetics and food industry, but also in drug formulation technology (2). Their monographs are present for example in European (3), American (4), British (2) and Polish (5) pharmacopoeias. Poloxamers exist in more than 30 varieties, varying in average molecular mass and reciprocal proportions of PEO and PPO blocks. Those differences are responsible for their physical properties, such as state of matter, HLB value or ability to set thermosensitive systems.

Due to the presence of both hydrophilic (poly-PE) and lipophilic (poly-PO) blocks in every single molecule, Pluronics possess amphiphilic properties and act as surface acitive agents. These features allow them to be used as emulsifiers, solubilizers or stabilizers in solutions, suspensions or even micro- and macromolecular therapeutical dispersions (9, 10). An additional feature, typical only for varieties of high molecular mass and significant content of hydrophillic blocks, is their ability to form thermosensitive systems in water solutions (1, 11). In such systems, rapid viscosity growth with formation of a semisolid gel is observed as a reaction to heating of the solution, but only if a high enough concentration of proper polymer is used.

Regarding literature reports describing the relation between poloxamers structure and their potential toxicity as well as efficiency in thermosensitive systems (1), it is practical to choose Pluronic® F-127 as it is the most efficient and at the same time the least toxic. The simplicity of obtaining thermosensitive systems with this certain variety of Pluronic® (F-127) has resulted in newly invented formulations which remain liquid at room or decreased temperature, but form a gel *in situ*, in the place and time of administration. Attempts have been made to prepare such formulations intended to be administered externally (e.g., topical, upon thermal burns, ophthalmic and rectal) (9, 12-14) or by injection (intramuscular, intratumoral, intraocular, intraarterial) (9, 15). Nevertheless, no preparation using Pluronics' thermogelling mechanism is com-

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mercially available. Although some data about stability of Pluronic-based formulations could be found (16, 17), they concern complex formulations with additional excipients (e.g., polyethyleneglycol, polysorbate, ethanol). Investigation (e.g., in MEDLINE, Scopus, Elsevier, Springer and Web of Knowledge databases) showed a lack of any former studies covering stability of thermosensitive formulations based on pure Pluronic® F-127 or even of the polymer in aqueous media by itself.

The aim of this study was to evaluate the stability of thermosensitive systems based on Pluronic® F-127 polymer, during storage at different conditions, by the measurements of their rheologic parameters, i.e., viscosity, hardness, cohesiveness and phase transition characteristics.

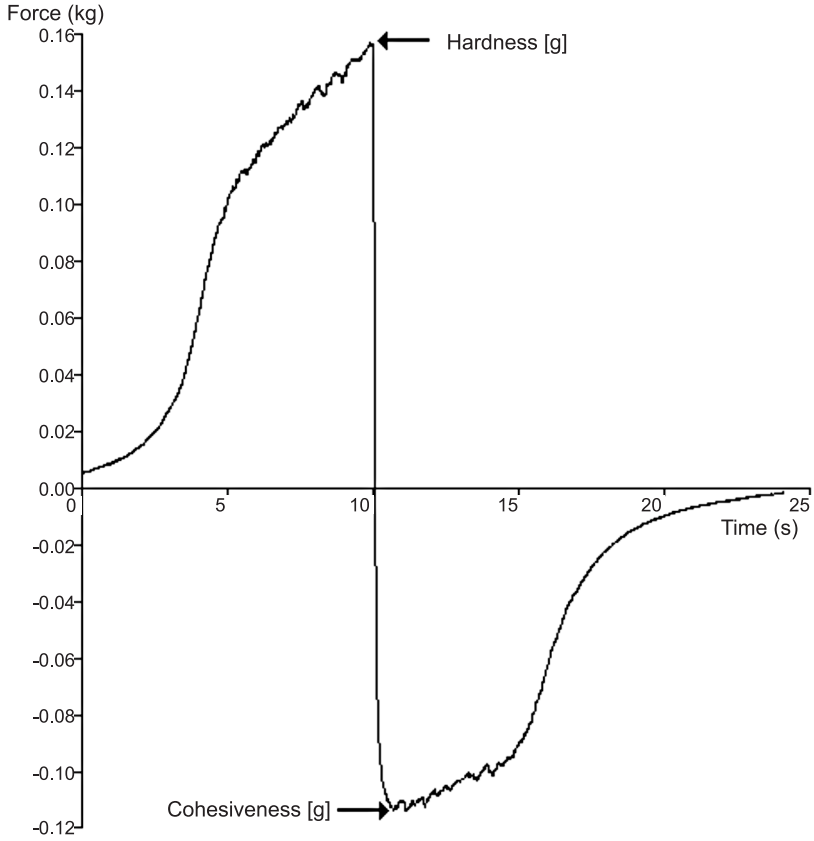

Figure 1. An example plot of force *versus* time. showing the effects of consistency analysis and explaining the method of determination of the hardness and the cohesiveness values

Table 1. Identification of data points.

Sample name	Conditioning time [months]	Temperature °C
0	Zero point	
1C	1	5
1H	1	40
2C	2	5
2H	2	40
3C	3	5
3H	3	40

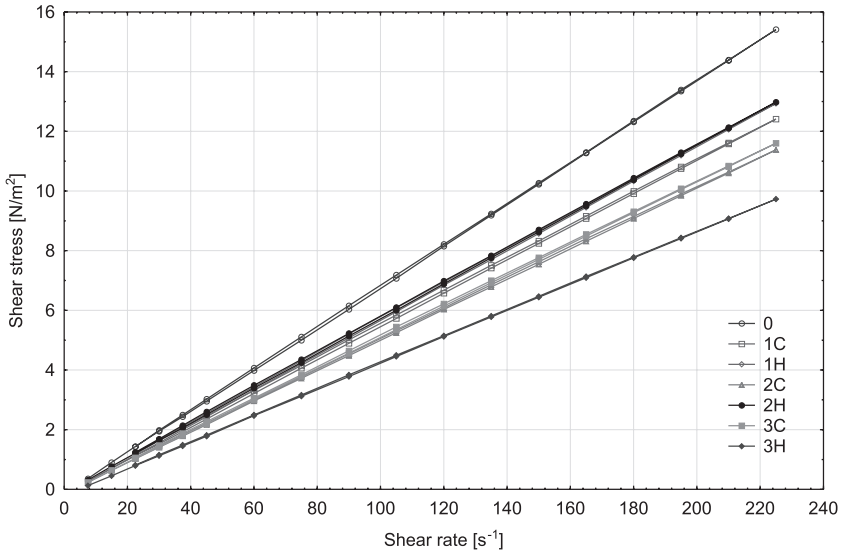

Figure 2. Mean flow curves measured at 25°C. All samples

MATERIALS AND METHODS

Materials

To prepare the formulation, polymer Pluronic® F-127 (BASF, USA) and purified water according to Aqua purificata monograph (FP IX) were used. All ingredients were weighed upon OHAUS Pioneer PA213CM/1 electronic scale (OHAUS Corporation, USA). Conditioning took place in KBF LQC-240 climatic chamber (BINDER GmbH, Germany). Rheologic parameters were measured with Brookfield RVDV III+ CP cone-plate rheometer (Brookfield Engineering Inc., USA) and TA.XT Plus Texture Analyser textuometer (Stable Micro Systems, Great Britain).

Methods

Preparation and conditioning of formulation

The aim was to prepare a formulation, which should remain liquid at room temperature, form a gel at 30-35°C and persist in the plateau of its maximal viscosity at 37°C, which is the human body temperature. According to literature (12) and manufacturer data (19), 16.0% (w/w) concentration was chosen. Initial measurements confirmed this choice as satisfying the above criteria.

Dispersion of Pluronic® F-127 was prepared according to the cool method (11). At first, proper quantities of ingredients were weighed out. About half of the necessary water amount was placed in a glass beaker, then the polymer was besprinkled upon its surface and the rest of the necessary water was added. The beaker was covered and put in the refrigerator overnight; the next day it was a clear solution inside. To ensure the homogeneity of dispersion, it was agitated with a mechanic stirrer for about 20 min. Prepared solution was split into adequate number of infusion-type hermetic glass bottles in a volume of 100 mL. Afterwards, samples filled and closed in bottles were autoclaved for 30 min at controlled temperature of 105°C.

Solutions were kept under following conditions: 1. climatic chamber: temperature 40 ± 2°C, relative humidity 75 ± 5%; 2. refrigerator: temperature 5 ± 3°C. According to the European Medicines Agency (EMA) guideline, these conditions were exact for: general accelerated stability evaluation and long-term stability evaluation specific for formulations intended to be stored in refrigerator (18). Samples were protected from direct or reflected sunlight and artificial light.

Study schedule and identification of data points

Formulation was examined and analyzed at the zero point (subsequent day after sterilization), and then in 1-month intervals at the time of 1, 2 and 3 months (± 2 days). Every time a new and freshly opened container of formulation was used. To every sample, a fixed name was given, indicating the length of the storage period (numbers 0-3) and used storage conditions (letters C/H). Details are shown in Table 1.

Table 2. Changes of dynamic viscosity $\eta_{dyn,25}$ [mPas] and apparent viscosity $\eta_{app,37}$ [mPas] values in tested samples.

Sample	Dynamic viscosity $\eta_{dyn,25}$ [mPas]				Apparent viscosity $\eta_{app,37}$ [mPas]			
	Mean	Percent	±95% c.i.	RSD	Mean	Percent	±95% c.i.	RSD
0	69.15	100.0%	1.46	2.0%	7594.40	100.0%	679.718	8.53%
1C	55.80	80.7%	2.32	4.0%	6282.64	82.7%	491.369	7.45%
1H	58.27	84.3%	1.51	2.5%	8412.09	110.8%	790.238	8.95%
2C	51.20	74.0%	1.18	2.2%	6351.68	83.6%	631.293	9.47%
2H	58.20	84.2%	0.99	1.6%	5505.94	72.5%	472.293	8.17%
3C	52.23	75.5%	0.53	1.0%	5786.42	76.2%	461.648	7.60%
3H	44.17	63.9%	0.86	1.8%	104.05	1.4%	19.373	17.74%

±95% c.i. – 95% confidence interval; RSD – relative standard deviation.

Table 3. Sol-gel transition temperature $T_{sol \rightarrow gel}$ [°C] in tested samples.

Lower sol-gel transition temperature $T_{sol \rightarrow gel}$ [°C]						
0	1C	1H	2C	2H	3C	3H
31.5	32.5	33.0	33.5	34.0	34.0	(38.0)

Table 4. Changes of hardness Hd_{25} [g] and cohesiveness Coh_{25} [g] values in tested samples.

Sample	Hardness Hd_{25} [g]				Cohesiveness Coh_{25} [g]			
	Mean	Percent	±95% c.i.	RSD	Mean	Percent	±95% c.i.	RSD
0	8.17	100.0%	0.046	0.54%	3.74	100.0%	0.052	1.33%
1C	8.41	103.0%	0.062	0.70%	3.66	97.8%	0.067	1.73%
1H	8.45	103.4%	0.053	0.60%	3.68	98.4%	0.038	0.99%
2C	8.71	106.6%	0.045	0.49%	3.57	95.5%	0.034	0.91%
2H	8.37	102.5%	0.053	0.61%	3.78	101.0%	0.032	0.82%
3C	8.61	105.4%	0.037	0.41%	3.68	98.4%	0.069	1.79%
3H	8.28	101.4%	0.028	0.32%	3.80	101.6%	0.030	0.76%

±95% c.i. - 95% confidence interval; RSD - relative standard deviation.

Measurements

Viscosity. Flow curves were designated at two different temperatures: 25.0°C and 37.0°C. Measurements of shear stress were done with constantly increasing and then decreasing shear rates, in the ranges of 7.5-225.0 s^{-1} (25°C) and 3.84-15.36 s^{-1} (37°C). Flow curves were used to estimate the viscosities: dynamic viscosity $\eta_{dyn,25}$ [mPas] at temp. 25°C and also apparent viscosity $\eta_{app,37}$ [mPas] measured at temp. 37°C and shear rate of $\gamma = 15.36$ s^{-1}. All measurements were repeated six times for every sample at both temperatures.

Sol-gel transition characteristics. To determinate the transition characteristics, a method similar to those found in the literature (15, 18) was used. A rheometer was used to measure the changes of apparent viscosity of formulation observed during the linear increase of temperature. Certain conditions were: shear rate: $\gamma = 0.38$ s^{-1}, temperature range: 23-43°C, temperature increase rate: 0.75°C/min, viscosity measurement interval: 0.5°C. Data were presented as a plot of viscosity versus temperature. The temperature corresponding to the first observed change of viscosity was interpreted as the sol-gel transition temperature, $T_{sol \rightarrow gel}$ (gelation temperature).

Consistency. Measurements were taken with a textuometer. Default probe was used, tipped with flat plastic disc (diameter = 35 mm, height = 5 mm),

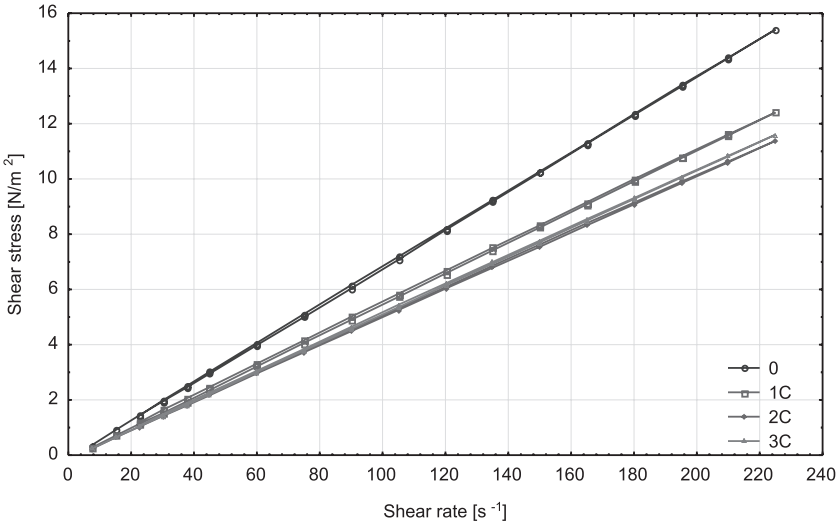

Figure 3. Mean flow curves measured at 25°C. Samples conditioned at 5°C

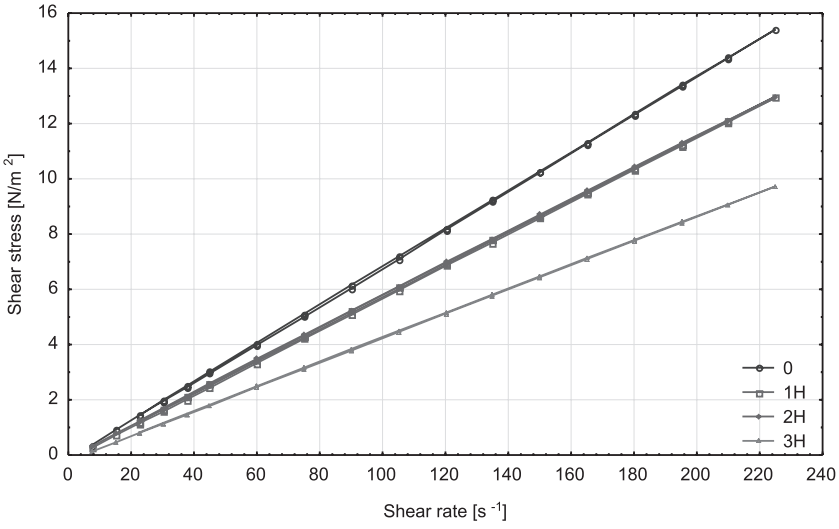

Figure 4. Mean flow curves measured at 25°C. Samples conditioned at 40°C

provided by the manufacturer. The process of this study was to measure the forces acting on the probe, when it was consecutively immersed and emerged in/from the container with the formulation. The probe was immersed to a given depth of 20 mm below the formulation surface and then emerged to the starting position, which was always about 15 mm over the surface. The position of the first contact with formulation surface was determined by the trigger force of 5.0 g. The vertical velocity of the probe in both directions was set to 2.0 mm/s.

Data were acquired as a plot of force against time and were used to analyze the extreme absolute values of forces noticed during every measurement cycle. The maximum positive value observed during the immersion phase was treated as hardness (Hd_{25}/Hd_{40} [g]), while the extreme absolute value in the emersion phase was treated as cohesiveness (Coh_{25}/Coh_{40} [g]) of the examined substance (see Fig. 1). The study was performed for every sample in the state of sol and gel, respectively, at 25.0 and 40.0°C. Measurement cycle was performed six

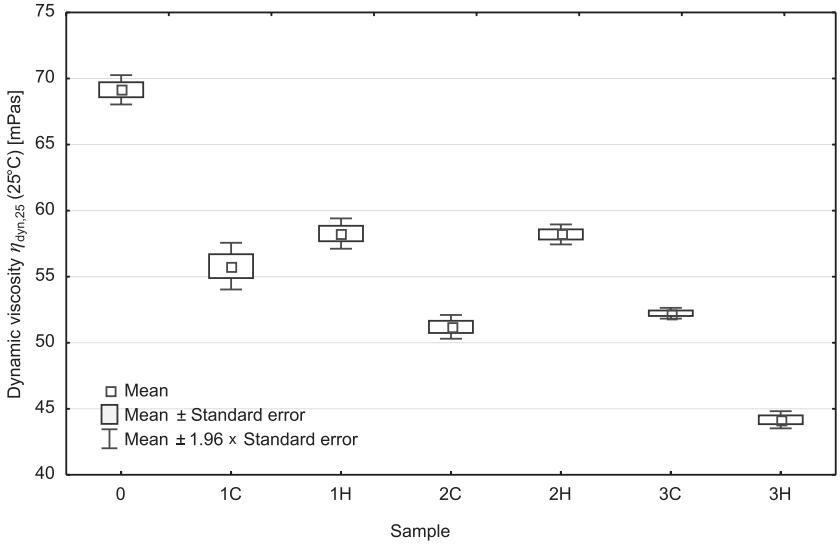

Figure 5. Box plot of average values of dynamic viscosity $\eta_{dyn,25}$ [mPas] in tested samples

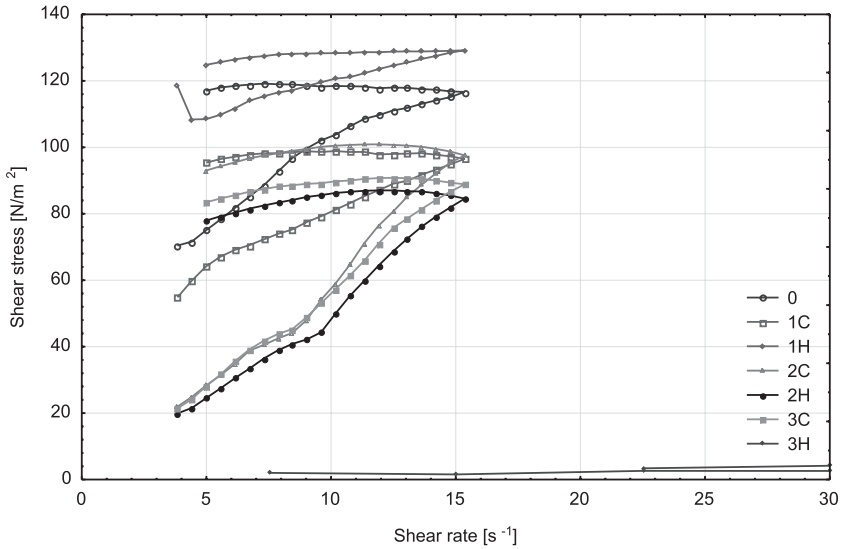

Figure 6. Mean flow curves measured at 37°C. All samples

times for every examined sample at both temperatures.

Methods for data analysis

Raw data obtained from studies of viscosity and texture were transformed logarithmically. Mean values of analyzed parameters were evaluated by ANOVA parametric analysis of variance followed by two *post-hoc* tests: NIR (LSD: Lowest Significant Difference) and Levene's test. The normality of distribution of transformed data was checked by three different statistical tests: Kolmogorov-Smirnov, Lilliefors and Shapiro-Wilk, while the homogeneity of variance was evaluated by Levene's and Brown-Forsythe tests. Correlations between some parameters were evaluated by the lowest quarter method, through the estimation of best-fit linear plot, also with care of Pearson's correlation coefficient and the confidence level, estimated by t test. In every performed analysis, the level of significance was set at 0. Statistical analysis was made with STATISTICA 10.2 PL software.

Significant changes less than ± 10% of the initial value were considered as acceptable and allowed to state the stability of the analyzed parameter.

RESULTS

Viscosity

Flow curves designated at 25°C (Figures 2-4) showed Newtonian flow characteristics. This observation was confirmed by estimation of linear equation for every obtained curve:

$$\tau = \eta \times \gamma + b$$

where: τ = shear stress [N/m^2], η = dynamic viscosity [mPas], γ = shear rate [s-1], b = yield stress/measurement error [N/m^2].

Using the above equation, it was possible to get the η dynamic viscosity value of every sample, with mean correlation coefficient reaching 0.99993 and mean error b = -0.1171 N/m^2. This value was relatively small and of negative sign, what allowed to treat it rather as negligible measurement inaccuracy in Newtonian flow model than as a yield stress typical for plastic flow model.

During the three months period, a significant decrease of dynamic viscosity was observed, reaching the level of 75.5% (3C) and 63.9% (3H) of ini-

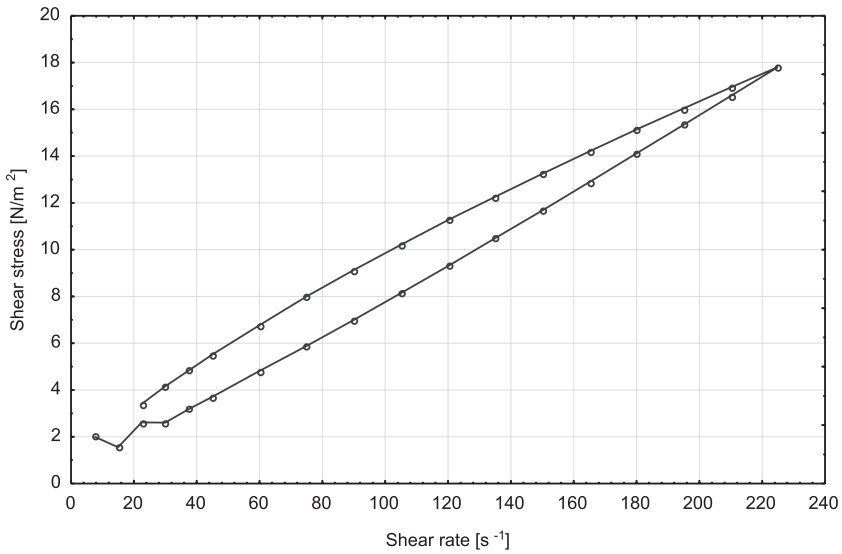

Figure 7. Mean flow curve of sample 3H measured at 37°C

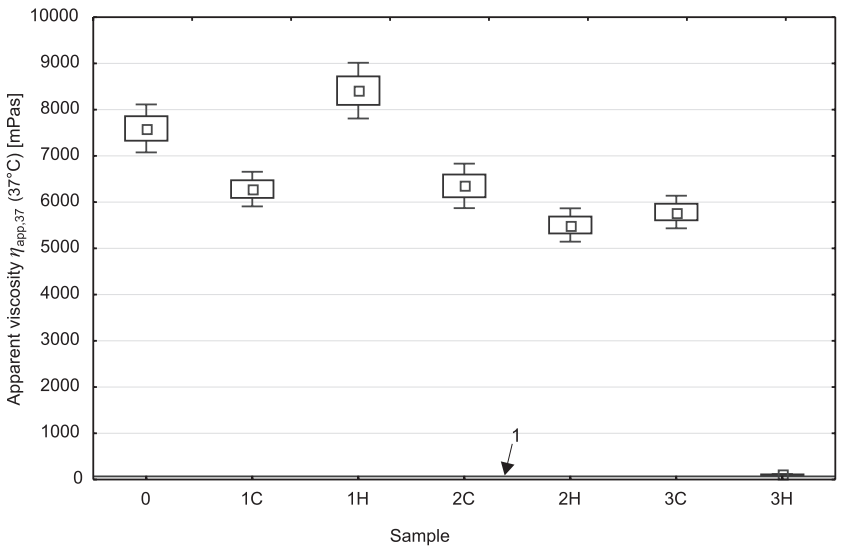

Figure 8. Box plot of average values of apparent viscosity $\eta_{app,37}$ [mPas] in tested samples. Horizontal line (1) refers to mean dynamic viscosity $\eta_{dyn,25}$ [mPas] in "zero point" sample, measured at 25°C

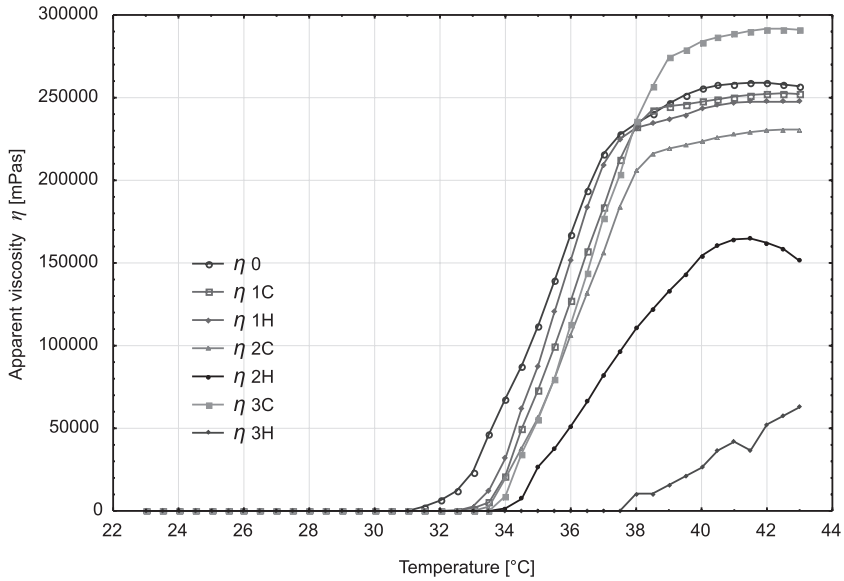

Figure 9. Phase transition characteristics in tested samples

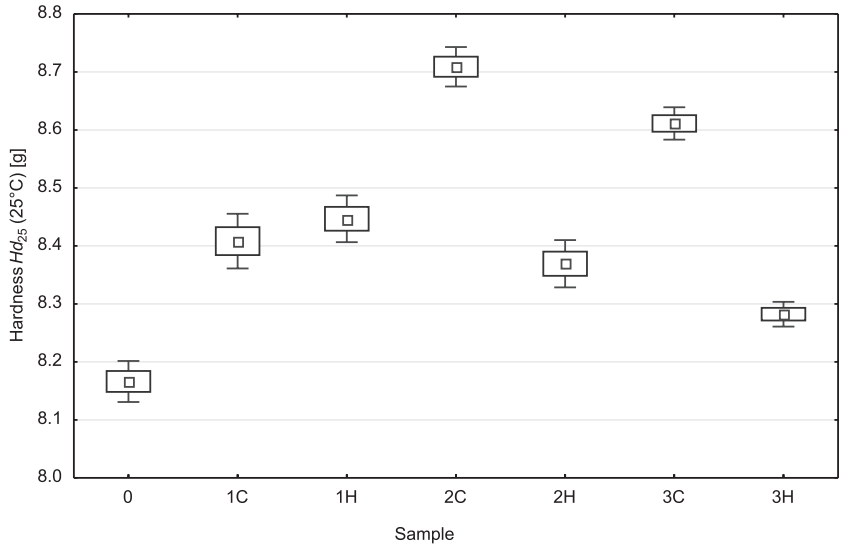

Figure 10. Box plot of average values of hardness Hd_{25} [g] in tested samples

tial value. In the first and second month, the viscosity of samples stored at elevated temperature was significantly higher than of analogical ones; in the third month the situation has inverted due to a considerable decrease of viscosity in elevated-temperature samples. Overall changes showed stronger decrease of the viscosity during storage at elevated temperature.

Flow curves designated at 37°C (Figs. 6, 7) showed explicit non-Newtonian flow characteristics. Ascending parts of curves laid concave. which showed a decrease in viscosity with increasing of the shear rate; thus pseudoplastic flow was observed. Descending parts of the same curves laid almost horizontally and higher than ascending ones. This proved that viscosity was increasing due to the process (time) of shearing, thus rheopexy (negative thixotropy) was also observed. The exception of this rule was observed in sample 3H, where the degradation of structure was so intensive. that its rheologi-

cal behavior has changed into slightly dilatant flow with lower rheopexy (Fig. 7). In this case, the apparent viscosity $\eta_{app,37}$ at 37°C reached almost the level typical for dynamic viscosity at 25°C (see: horizontal line in Fig. 8). These dramatic changes have forced a modification of measurement conditions (extension of used shear rate range). to avoid the inaccuracy that might came from improper usage of the apparatus' scope.

During three months, a statistically significant decrease of apparent viscosity had been observed, which was intensified by the elevated storage temperature. Exceptionally high degradation was observed in the third month of study, in sample stored at elevated temperature. In samples stored in the refrigerator, only moderate changes occurred in the months 2-3, despite the significant change in the first month.

Sol-gel transitions characteristics

Both the sol-gel transition temperature (gelation temperature) $T_{sol \rightarrow gel}$ and the maximal viscosity

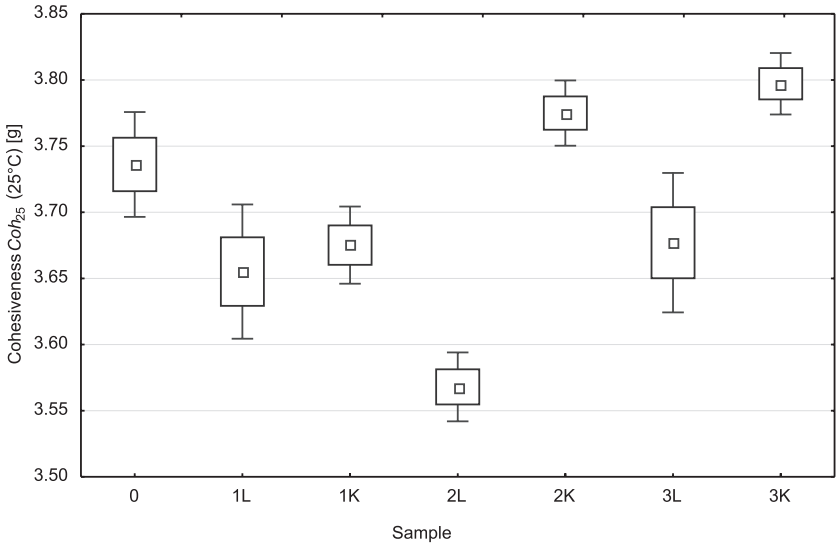

Figure 11. Box plot of average values of cohesiveness Coh_{25} [g] in tested samples

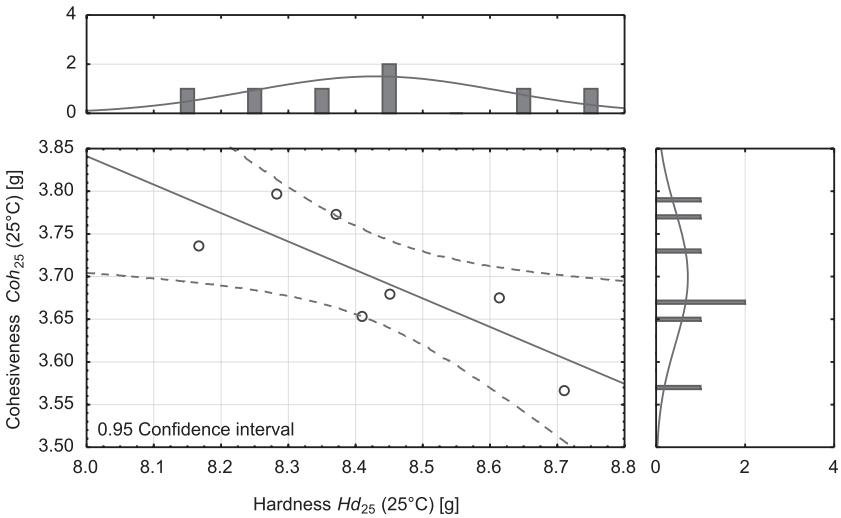

Figure 12. Correlation plot: cohesiveness (6.51 - 0.334) as a function of hardness (25°C), correlation r = -0791

Table 5. Correlation parameters between mean hardness and cohesiveness; both analyzed at 25°C.

Analyzed correlation	$Coh_{25} = f(Hd_{25})$
Corelation coefficient *r*	-0.791
Determination coefficient r^2	0.626
Statistics *t*	-2.90
Confidence level *p*	0.0341
Number of cases *n*	7
Intercept *b*	6.51
Slope *a*	-0.334

Table 6. Changes of hardness Hd_{40} [g] and cohesiveness Coh_{40} [g] values in tested samples.

Sample	Hardness Hd_{40} [g]				Cohesiveness Coh_{40} [g]			
	Mean	Percent	±95% c.i.	RSD	Mean	Percent	±95% c.i.	RSD
0	133.72	100.0%	3.612	2.57%	97.17	100.0%	1.314	1.29%
1C	123.80	92.6%	1.181	0.91%	90.86	93.5%	0.921	0.97%
1H	126.76	94.8%	1.254	0.94%	91.08	93.7%	1.271	1.33%
2C	151.06	113.0%	3.882	2.45%	111.14	114.4%	2.506	2.15%
2H	21.41	16.0%	0.845	3.76%	8.60	8.9%	0.288	3.19%
3C	128.50	96.1%	3.585	2.66%	90.42	93.1%	1.993	2.10%
3H	13.54	10.1%	0.488	3.44%	4.66	4.8%	0.240	4.90%

±95% c.i. - 95% confidence interval; RSD - relative standard deviation.

Table 7. Correlation parameters between mean *hardness* and *cohesiveness* values, both analyzed at 40°C.

Analyzed correlation	$Coh_{40} = f(Hd_{40})$
Corelation coefficient *r*	0.999
Determination coefficient r^2	0.999
Statistics *t*	70.3
Confidence level *p*	1.11E-08
Number of cases *n*	7
Intercept *b*	-6.96
Slope *a*	0.777

observed in this transition have significantly changed during the study, as shown in Figure 9 and Table 3.

Samples stored in the refrigerator showed the increase of $T_{sol \rightarrow gel}$ of about 2.5°C, but the maximal viscosity changed only slightly. In samples stored at climatic chamber, parameters deteriorated significantly after the first month. Exceptionally high degradation was observed in sample 3H: the curve showed almost linear character; area of the steep slope and the plateau in upper part of plot were not present at all (Fig. 9). The transformation observed in this case could not be called *sensu stricto* a sol-gel transition.

Consistency

Consistency studies performed at 25°C showed statistically significant differences between most of the samples. Changes of the hardness Hd_{25} [g] consisted of an initial increase followed by a

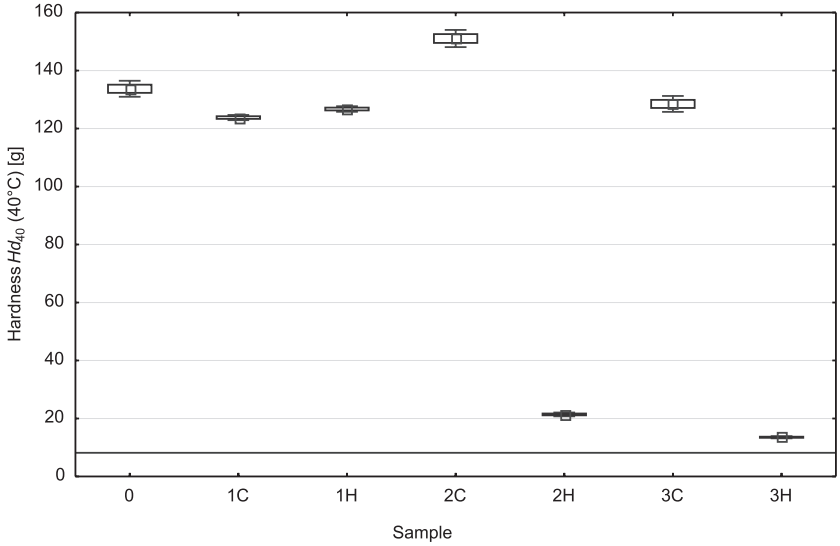

Figure 13. Box plot of average values of hardness Hd_{40} [g] in tested samples. Horizontal line refers to mean hardness Hd_{25} [g] in "zero point" sample at 25°C

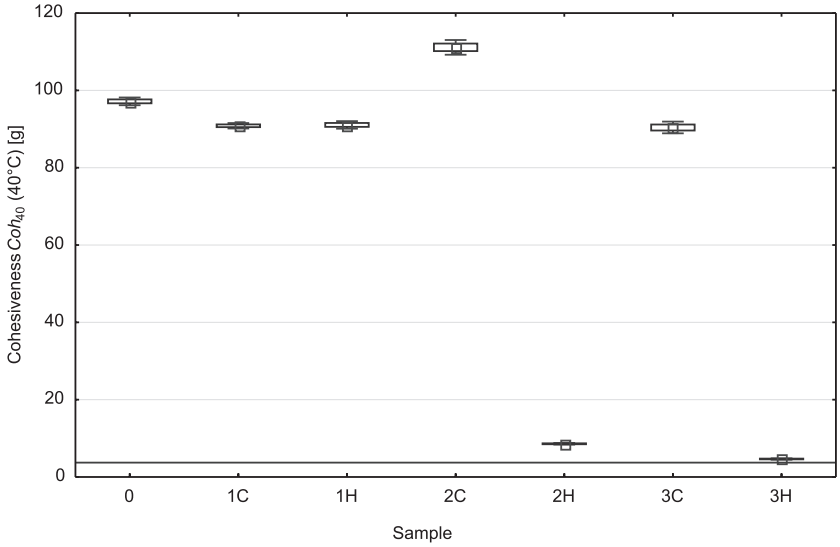

Figure 14. Box plot of average values of cohesiveness Coh_{40} [g] in tested samples. Horizontal line refers to mean cohesiveness Coh_{25} [g] in "zero point" at 25°C

moderate decrease with time (see: Fig. 10. Tab. 4). The lowest value was noticed in the zero point sample and the following measurements showed values between 101.4 and 106.6% of the initial one. In the second and third month, the hardness of samples stored in the refrigerator was significantly higher than of the analogical samples, stored at elevated temperature.

Cohesiveness studies performed at 25°C showed an exactly opposite direction of changes: initial decrease, followed by an increase with time. up to more than 100% of initial value (Fig. 11. Tab. 4). Values obtained in the second and third month were at 95.5 to 101.6% of the initial value. In the second and third month, the cohesiveness of samples stored at elevated temperature was significantly higher than of analogical samples stored in the refrigerator.

Changes observed in cases of hardness and cohesiveness. both measured at 25°C - even if they

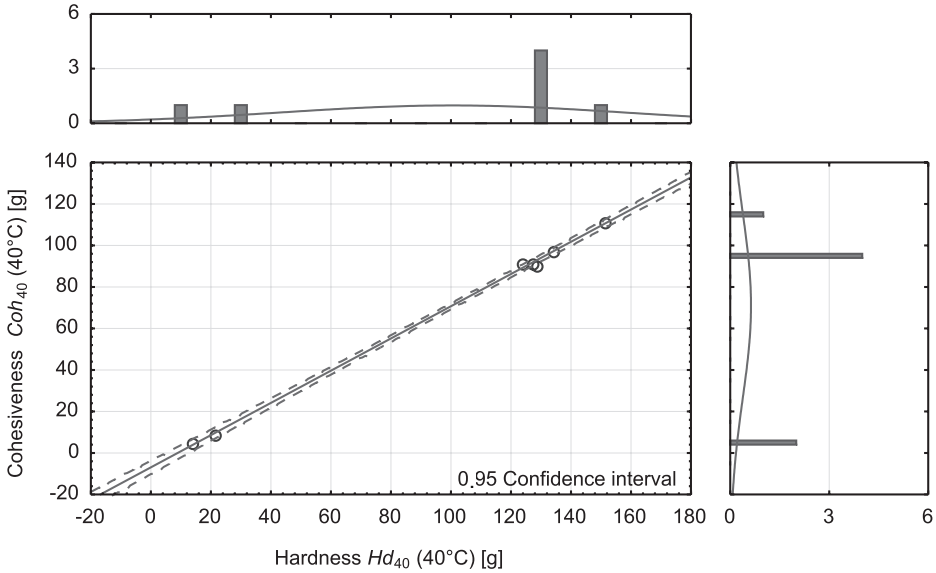

Figure 15. Correlation plot: cohesiveness (-6.995 + 0.77652) as a function of hardness (40°C), correlation r = 0.99949

were statistically significant - did not exceed the ± 10% of initial value, thus stability of those parameters under conditions used was confirmed.

Statistically significant correlation was observed between values of hardness and cohesiveness, measured at 25°C. Parameters of this correlation are presented in Table 5, correlation plot is shown in Figure 12.

Consistency studies performed at 40°C showed exceptional degradation of gel structure in the second and third month, in samples stored at elevated temperature. The direction and level of changes of both hardness and cohesiveness were similar; even a statistically highly significant correlation was observed between those parameters (Fig. 15. Tab. 7). In both cases, the changes observed during the first month did not exceeded ± 10% of initial value,but later a significant and very considerable degradation of gel structure appeared in samples stored at elevated temperature (see Figs. 13, 14. Tab. 6). Hardness and cohesiveness of samples 2H and 3H reached almost the levels typical for a temperature of 25°C.

DISCUSSION

Parameters of consistency measured at 25°C: hardness Hd_{25} [g] and cohesiveness Coh_{25} [g] remained stable during the whole period of study, in all samples and regardless to their storage conditions. Though observed changes were in general statistically significant, none of them exceeded the range ± 10% of initial value. Between hardness Hd_{25} and cohesiveness Coh_{25}. a statistically significant correlation was observed.

Dynamic viscosity $\eta_{dyn,25}$ in every sample underwent statistically significant changes, leading to a decrease in the value below the given criteria. In samples stored at elevated temperature, the changes during the 3 months were more intensified and clearly progressive. Sample stored at 5°C showed a decrease to about 80% of initial value. but in the subsequent months this value remained constant and any changes did not exceed ± 10%. This regularity suggests that the parameter could be considered as stable, if the measurement schedule was slightly modified to introduce the time needed for the formulation structure to stabilize. It is possible that leaving a gap of 5-10 days between the sterilization of the samples and making the first measurements might bring a change leading to an overall improvement in the results of the stability evaluation of the considered parameter.

Here it should be noted that even if measurements performed at room temperature provided many information about stability, they only covered those parameters, which are important at the moment of storage and preceding the administration. Changes analyzed above, although significant, may affect only the process of administration, but they have nothing in common with effectiveness and safety of already applied preparation. Their impor-

tance should be considered in terms of being enough to state the overall lack of stability. Better information, explaining the changes in application-related behavior, could be obtained through analysis of data from tests performed at elevated temperatures, closer to that of the human body. Proper analyses are shown below.

Hardness Hd_{40} [g] and cohesiveness Coh_{40} [g] (at 40°C) in samples stored in the refrigerator remained relatively constant. only in one case (2C) exceeding the acceptance criteria. It must be noted that due to the direction of this single change, no degradation of structure could be stated. In samples conditioned at elevated temperature, the changes in hardness Hd_{40} and cohesiveness Coh_{40} were exceptionally intensified in the second and third month of study. Values of those parameters reached nearly the level typical for them when measured at room temperature (see Fig. 10, 11, 13, 14 and Tabs. 4, 6), which shows severe degradation of structure and weakening of the sol-gel transition phenomenon. The level of those changes indicated the absolute uselessness of samples 2H and 3H as a thermosensitive drug bases, intended to form a gel *in situ* at human body temperature.

Apparent viscosity $\eta_{app,37}$ [mPas] of samples stored at elevated temperature underwent substantial and statistically significant changes, leading to a value many times lesser than the initial one. In samples stored in the refrigerator, changes were less explicit and of a different nature: there was a decrease to level 82.7% of initial value in the first month, but this level remained constant for the rest of the study. Furthermore, any changes between the values from the first, second and third month were not statistically significant. Here it may be assumed as earlier (as in the case of dynamic viscosity $\eta_{dyn,25}$) that the parameter could be considered as stable, if the measurement schedule would be slightly modified to introduce an additional time between sterilization and first measurements.

Analysis of the sol-gel transition characteristics confirmed the remarks about stronger degradation of formulation's structure during storage at elevated temperature. Weakening of the sol-gel transition scale (sample 2H), leading to even a disappearance of this phenomenon (sample 3H), was clearly visible. Acquired transition curves allowed also to notice that temperature of apparent viscosity measurements (37.0°C) did not refer to the plateau of viscosity (which was achieved during the sol-gel transition). but only to the upper part of the steep slope area. This situation might have generated additional inaccuracy of measurements and thus might have been responsible for the relatively large standard deviations of measured $\eta_{app,37}$ values. Such situation should be avoided in further studies.

Analysis of the sol-gel transition temperatures, $T_{sol \rightarrow gel}$, showed a progressive increase of this temperature, appearing regardless of the storage conditions. In planning of any further studies, this phenomenon should also be considered. It is necessary to find a proper concentration of polymer, allowing for the temperature to change, but still leaving a safety margin for this parameter.

Even if the results of the above analyses showed a lack of stability, they seemed optimistic in the case of refrigerator-stored samples. Evaluation of acquired data and attempt of discovering any relations or regularities within them led to a conclusion that stability during storage at 5°C could be easily confirmed, if the polymer concentration were slightly modified and/or excipients were added, to keep the plateau of viscosity in the temperature typical for the area of application and measuremets.

CONCLUSIONS

During the study, progressive degradation of formulation's structure was observed and confirmed, regardless of the storage conditions. Observed changes debar the possibility of using it as a medicinal preparation, for which stability of rheological parameters is absolutely required.

Analysis of acquired data, performed according to given methods and criteria, allowed to declare stability only in cases of hardness Hd_{25} and cohesiveness Coh_{25}, both measured at 25°C. Stability of those parameters was observed in every sample, regardless of the storage conditions.

Conditioning at elevated temperature exerted strong, negative impact on stability of examined parameters, which led to the conclusion that Pluronic® F-127 dispersions need to be stored in a refrigerator.

Observations on changes in dynamic viscosity $\eta_{dyn,25}$ and apparent viscosity $\eta_{app,37}$ in refrigerator-stored samples during the first month of study suggest that a modification of measurements schedule is necessary. Introducing a few days of "gap" after sterilization or some additional measurement points in the first month should be considered.

Stability of thermosensitive formulation based on Pluronic® F-127 could be proved if formulations were stored at decreased temperature and the proper concentration of polymer and/or excipients were chosen, with consideration to results of above and similar studies.

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