Physical aging of polylactide-valsartan system investigated by differential scanning calorimetry

Agata Drogoń[1), *)], Marcin Skotnicki[2)], Marek Pyda[1), 3)]

Abstract: The polylactide-valsartan systems with a mass ratio of 20 : 80, 50 : 50 and 80 : 20 were obtained and characterized by standard Differential Scanning Calorimetry (DSC). The isothermal physical aging process of polylactide-valsartan with a mass ratio of 50 : 50 was investigated at the aging temperature of 50°C and 70°C for different aging times. The enthalpy of relaxation values for each of the aging times and for all investigated components were determined experimentally and fitted to the Kohlrausch-Williams-Watts equation.

Keywords: physical aging, enthalpy relaxation, polylactide, valsartan, Differential Scanning Calorimetry (DSC), Kohlrausch-Williams-Watts equation (KWW).

Proces fizycznego starzenia układów polilaktyd-walsartan badany metodą różnicowej kalorymetrii skaningowej

Streszczenie: Otrzymane układy polilaktydu z walsartanem w stosunkach masowych 20 : 80, 50 : 50 i 80 : 20 poddano analizie metodą różnicowej kalorymetrii skaningowej (DSC). Scharakteryzowano proces starzenia fizycznego mieszaniny polilaktyd-walsartan w stosunku masowym 50 : 50, prowadzony w temperaturze 50 i 70°C w różnym czasie. Z pomiarów doświadczalnych dla każdego czasu starzenia wyznaczono entalpię relaksacji, a następnie dopasowano otrzymane wielkości do równania Kohlrauscha-Williamsa-Wattsa.

Słowa kluczowe: starzenie fizyczne, entalpia relaksacji, polilaktyd, walsartan, różnicowa kalorymetria skaningowa (DSC), równanie Kohlrauscha-Williamsa-Wattsa (KWW).

Polylactide (PLA) is a biodegradable and biocompatible lactic acid polymer. It is composed of repeating mer units with a molar mass of 72.06 g/mol [Formula (I)].

PLA contains a stereogenic centre thus it can appear in the L or D configuration. Depending on the content of
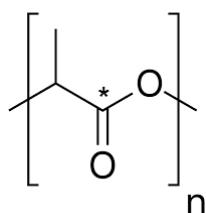
(I)

individual isomers in the chain, the polymers may differ in physicochemical properties [1–4]. The isomeric composition of PLA affects its degree of crystallinity as well as the biodegradation time. For example, studies [5, 6] have shown that the increase in the content of D-isomer in the chain results in, *i.a.*, a reduction of glass transition temperature (T_g), which has a significant impact on the physical aging process.

There are a vast array of applications for PLA, including medical, pharmaceutical and food industry. It can be used to make, among others, surgical sutures, orthopaedic and dental implants as well as foils and packaging [7, 8]. In the pharmaceutical industry, it can be used in formulations in order to modify the dissolution profile of active pharmaceutical ingredient (API) or improve its stability [8–11]. For example, Agraval *et al*. achieved sustained release of drug – sulindac up to 20 days and tetracaine up to 10 days by applying triblock copolymer [polylactide-poly(ethylene oxide)-polylactide] while the release of these drugs without polymeric carriers occurs over 4–6 h [12].

The active pharmaceutical ingredients formulated into solid dosage forms (*e.g.* tablets or capsules) following oral administration must dissolve, usually in the gastric

[1)] Rzeszów University of Technology, Department of Chemistry, al. Powstańców Warszawy 6, 35-959 Rzeszów, Poland.

[2)] Poznań University of Medical Sciences, Department of Pharmaceutical Technology, Grunwaldzka 6, 60-780 Poznań, Poland.

[3)] Poznań University of Medical Sciences, Department of Biophysics, Grunwaldzka 6, 60-780 Poznań, Poland.

[*)] Author for correspondence: agata.drogon@yahoo.pl

fluid and absorb in order to be pharmacologically active. However, about 40% of currently marketed pharmaceutical molecules and around 75% of new chemical entities exhibit significant aqueous solubility issue. Poor solubility and low dissolution rate often lead to poor bioavailability. This problem is highly relevant to poorly soluble class II (high permeability) substances according to the Biopharmaceutical Classification System (BCS). The limited bioavailability for those APIs may be enhanced by increasing the solubility and therefore the dissolution rate. An active pharmaceutical ingredient can exist in crystalline or amorphous form. The amorphous form of API is sometimes more desirable due to its usually greater apparent solubility and as a consequence bioavailability [9, 10]. However, the amorphous form (high energy form) unlike crystalline, is usually unstable. Amorphous drugs may crystallize or, in the absence of a crystalline form, undergo physical aging process during storage at a temperature below the glass transition. Aged amorphous materials are characterized by increased fragility, and the aging process may result in a slower dissolution rate of the API [11–16]. Standalone amorphous APIs are rather not used in formulation development. In most cases, amorphous APIs are formulated with excipients in order to, amongst others, provide adequate absorption and to improve their stability [17–20].

Polymeric amorphous solid dispersion (PASD) is one of the widely investigated strategies to stabilize the amorphous drug. In PASD, the improved stability of amorphous API is achieved by entrapping the drug in a high energy glassy state between the polymer chains [21, 22]. Although the excipients are often considered inert, it is known that they can interact with APIs, changing their stability, absorption and bioavailability [9, 10]. Therefore, throughout the drug development process API must be investigated during the pre-formulation studies to provide the necessary information to develop a stable formulation with adequate bioavailability [23–25]. If an amorphous drug–amorphous polymer system is completely miscible, only a single glass transition is observed with T_g value between the T_g's of individual components. If the system is immiscible, two or more T_g values may be detected [26]. The drug-polymer systems can also exhibit con-centration-dependent miscibility [27, 28]. For example, felodipine-poly(acrylic acid) systems containing 70% or 90% polymer showed only one T_g, indicating miscible sys-tem, while systems containing 30% or 50% polymer showed two glass transitions, indicating the immiscibility in the blends [25].

Valsartan [VAL, Formula II)]) is a drug used in the management of hypertension and heart failure. Valsartan is marketed in a disordered form. Skotnicki *et al.* described two forms of disordered valsartan using differential scanning calorimetry solid-state nuclear magnetic resonance and powder X-ray diffractometry, *i.e.*, fully amorphous material (AM) with glass transition around 76°C (fictive temperature), whereas the as-received, marketed form

(AR) with T_g around 94°C overlapped with an enthalpy of relaxation peak [29–31]. However, it has to be noted that Guinet *et al.* described the marketed form (AR) using Raman spectroscopy, in terms of mesophase in which the long-range order of the stable crystal is limited on the length scale of tens nanometers [32]. The amorphous form of valsartan may undergo physical aging during storage of the formulation process and therefore, potentially changing its physicochemical and in consequence, therapeutic properties.
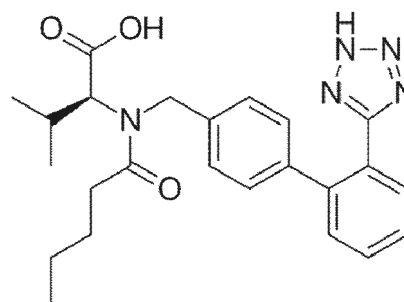
(II)

The process of physical aging applies to amorphous materials and occurs below the glass transition temperature. During the aging process, the structure of the glassy material becomes more ordered. The amorphous glass, unlike the crystal, is not in a state of thermodynamic equilibrium. The physical aging is a reversible process. During the physical aging process, there is no break nor formation of new chemical bonds. The quantity that describes physical aging is the enthalpy of relaxation (ΔH_r), which can be estimated by subtracting the difference between the total enthalpy of aged and non-aged material [33–40].

Enthalpy of relaxation (ΔH_r) resulting from the physical aging process can be estimated directly from the heat flow (Φ) or specific heat (C_p) measurements, from the difference of fields formed between heat flows or specific heats of aged and unaged sample and can be described by the Equation (1):

$$\Delta H_r = \frac{1}{q}\int_{T1}^{T2}\left(\Phi_{\mathrm{aged}}-\Phi_{\mathrm{unaged}}\right)\mathrm{d}T = \int_{T1}^{T2}\left(Cp_{\mathrm{aged}}-Cp_{\mathrm{unaged}}\right)\mathrm{d}T \quad (1)$$

where q – the heating rate, T_1, T_2 – limits of the integration temperature (where $T_1 < T_g < T_2$), Φ_{aged}, Φ_{unaged} – heat flows originating from the aged and non-aged samples respectively, Cp_{aged} and Cp_{unaged} – heat capacities of the aged and non-aged samples, respectively, dT – the temperature change.

For the characterization of the physical aging process, an equilibrium enthalpy of relaxation ($\Delta H_r^{\mathrm{inf}}$) is used, which determines the enthalpy of relaxation for infinite aging time ($t_a\rightarrow\infty$) [33–41]. The equilibrium enthalpy of relaxation is determined by measuring the

change in specific heat capacity in accordance with the Equation (2):

$$\Delta H_r^{\text{inf}} = \int_{Ta}^{Tg} \Delta C_p \, dT \approx \Delta C_p (T_g - T_a) \qquad (2)$$

where; ΔC_p – the change of heat capacity in solid-liquid transition in a given temperature, T_g and T_a – the glass transition and aging temperature, respectively.

There are several empirical models in the literature describing the kinetics of the physical aging phenomenon. One of them is the Kohlrausch-Williams-Watts (KWW) model [42, 43] described by the Equation (3):

$$\Delta H_r = \Delta H_r^{\text{inf}} \left\{ 1 - \exp[-(t/\tau^{\text{KWW}})^\beta] \right\} \qquad (3)$$

where: ΔH_r and – respectively the enthalpy of relaxation and equilibrium enthalpy relaxation, t – the aging time, τ^{KWW} – relaxation time, β – the coefficient describing the distribution of relaxation times.

Showing the Equation (3) in a different form, recovery parameter (φ) can be estimated as:

$$\varphi = \exp(-t/\tau^{\text{KWW}})^\beta = 1 - \Delta H_r / \Delta H_r^{\text{inf}} \qquad (4)$$

where all quantities in Equation (4) have the same meaning as in Equation (3).

Recovery parameter is an important quantity because it describes the kinetics of the physical aging process. From the recovery parameter correlation with aging time, it is possible to determine the departure from the equilibrium state. The recovery parameter not only shows relaxation enthalpy changes occurring during the physical aging process but also shows how much more the system can change under given conditions and how fast the material reaches equilibrium state. Recovery parameter has values from 1 for non-aged material to 0 for material whose relaxation enthalpy has reached the value of equilibrium enthalpy relaxation [42, 43].

As previously mentioned, PLA can be used as a API carrier. There is one study describing the combination of polylactide and valsartan and the aim of this study was to encapsulate valsartan within polyester microparticles, namely constituted of poly(lactic acid) (PLA) and poly(ε-caprolactone) (PCL), by using the emulsion solvent evaporation method [44].

In this study, fully amorphous polylactide (PLA-H) was used to form the system with valsartan. The aim of the study was to obtain polylactide-valsartan systems with different mass ratios to investigate miscibility and physical aging process of the system. Valsartan belongs to class II BCS (low solubility and high permeability) and is used in this study as a model amorphous drug to investigate the effect of the added polymer on physical aging process of VAL in the system with polylactide. The obtained PLA-H-valsartan systems with mass ratios of 20 : 80, 50 : 50 and 80 : 20 were subjected to the physical aging process at 50°C (both polymer and drug underwent

aging process) and at 70°C (this is above T_g of PLA-H, therefore, only valsartan underwent physical aging process). The relaxation enthalpies values obtained for the aged components of the system were fitted to the KWW equation, which allowed the determination of relaxation times and the distribution of relaxation times.

EXPERIMENTAL PART

Materials

The investigated materials in this study were the poly-lactide-valsartan (PLA-H-VAL) systems with three set mass ratios. The first component of these systems was a non-active pharmaceutical ingredient: a biodegradable and biocompatibile polymer, polylactide (PLA-H) [see Formula (I)] which has a chiral carbon atom in the repeating unit marked in the Formula (I) with the star. PLA-H contains 16.4% of the D-isomer in its chain, and it is a fully amorphous material [45], produced by Cargill Dow Nature-Works LLC. The second component of examined systems, an active pharmaceutical ingredient (API), was valsartan (VAL) [Formula(II)] and the sample was obtained from Polpharma, Starogard Gdański, Poland.

Samples preparations

The PLA-H-VAL systems with following mass ratios of 20 : 80, 50 : 50 and 80 : 20 were prepared by a solvent evaporation method. For each mixture, 10–20 mg of VAL and PLA-H were used in adequate proportions and were dissolved in 50 cm³ of chloroform followed by evaporation of the solvent under reduced pressure at about 55–60°C in a rotary evaporator. Next, polymer-API systems were dried at 40°C for 2 days. The obtained materials were in the form of a brittle, thin film. Standalone PLA-H and standalone VAL were also dissolved in chloroform and treated in the same way as PLA-H-VAL systems.

Methods of testing

Differential Scanning Calorimetry (DSC) curves were obtained using a differential scanning calorimeters: DSC Q2500, DSC Q1000 and DSC 2920 from TA Instrument USA. The temperature and heat-flow rate measured by the DSC equipments were calibrated with indium (m.p. = 156.65°C, ΔH_f = 28.45 J/g) [33], and at least two tests were run on each sample. Sapphire (Al_2O_3) was used to calibrate heat capacity [33].

Thin film samples of the examined PLA-VAL systems (1–10 mg) were placed in a standard aluminum pan. For standard thermal analysis, the samples were heated from 5°C to 140°C with the constant heating rate of 10°C/min. Next, the samples were cooled to 5°C and then reheated to 140°C in a second run. For thermal analysis of the isothermal physical aging process, the measurements were carried out at aging temperatures T_a = 50°C (physical

aging of PLA-H and VAL) and 70°C (physical aging of VAL). Before annealing, samples were heated to 140°C to erase previous thermal history, then cooled down to chosen aging temperature and annealed for different aging times. After every tested aging time, the samples were rapidly cooled down to 5°C and then heated at a constant heating rate of 10°C/min again to 140°C. During this heating, the data for aged sample were collected.

RESULTS AND DISCUSSION

Figure 1 presents the results obtained from the standard DSC measurement as a plot of heat-flow changes with temperature for standalone valsartan (VAL), standalone polylactide (PLA-H), and for the (PLA-H-VAL) systems with different mass ratios (20 : 80, 50 : 50 and 80 : 20, respectively).

On the heat-flow as a function of temperature trace for standalone valsartan, one glass transition is observed at 71.3 ± 0.5°C which is in good agreement with literature [29–31]. PLA-H is also characterized by one glass transition around 56.5 ± 0.3°C, which is also in good agreement
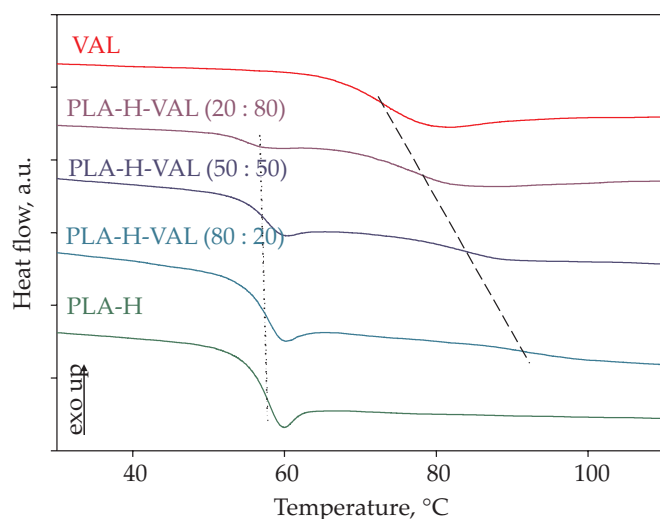

Fig. 1. Heat-flow rate dependence on temperature for: valsartan (VAL), polylactide (PLA-H) and polylactide-valsartan (PLA-H-VAL) systems with different mass ratios (20 : 80, 50 : 50 and 80 : 20) obtained from standard DSC measurements with constant heating rate of 10°C/min

with the literature [4]. In addition, a small endothermic peak of enthalpy relaxation at the glass transition region for standalone PLA-H is observed, resulting from the aging process occurring during standard DSC measurement. The examined PLA-H-VAL systems are characterized by two glass transitions – the first one derived from the PLA-H, and the second from VAL. Coexistence of these two glass transitions indicates that the system is immiscible. As a result of the glass transition analysis, the glass transition temperature, T_g, and the changes of the heat capacity, ΔC_p, at T_g were determined for PLA-H and VAL for the components of the tested systems as well as for the standalone, individual substances. The results of the glass transition analysis are presented in Table 1.

The addition of PLA-H to valsartan causes an increase in the glass transition temperature T_g of the drug from 71.3 ± 0.5°C for standalone valsartan to 91.9 ± 1.7°C in the PLA-H-VAL system with mass ratio 80 : 20. Changes of the heat capacity (ΔC_p) at the glass transition temperature (T_g) of polylactide and valsartan as components of the tested systems are proportional to the mass content of the individual components.

Increase in the glass transition temperature may potentially be a sign of increased stability [17–22]. In this case, valsartan may be incorporated as molecular dispersion in a glassy polylactide matrix, stabilized by physical separation of the molecules inside the polymer chains [46]. PLA-H in this system acts as a stabilizer by decreasing molecular mobility of VAL. The reason for this can be the strong solid-state interactions between the components [47]. In majority of the studies, the physical stability of co-amorphous systems is assigned to intermolecular interactions such as hydrogen bonds, π–π, or ionic interactions [48]. Although, the co-amorphous dispersions can increase the stability of the components even in the absence of interactions due to molecular mixing [49]. In the study [50] an inactive pharmaceutical ingredient polyvinylpyrrolidone K25 (PVP K25) was found to be effective in stabilization of ketoconazole (prevented crystallization). The absence of strong and specific drug–polymer interactions were confirmed with [13]C Nuclear Magnetic Resonance (^{13}C NMR) and Fourier Transform Infrared Spectroscopy (FT-IR). Therefore, it was concluded that the physical mechanism of the protective effect of PVP K25

T a b l e 1. Glass transition temperatures T_g and changes of the heat capacity, ΔC_p, at T_g for standalone polylactide (PLA-H), standalone valsartan (VAL), and for the PLA-H and VAL as a components of examined polymer-drug systems

Sample	Glass transition temperature T_{g1} (PLA-H), °C	Change of heat capacity at T_g ΔC_{p1} (PLA-H), J/g/K	Glass transition temperature T_{g2} (VAL), °C	Change of heat capacity at T_g ΔC_{p2} (VAL), J/g/K
PLA-H	56.5 ± 0.3	0.517 ± 0.08	–	–
Valsartan (VAL)	–	–	71.3 ± 0.5	0.379 ± 0.08
PLA-H-VAL 20 : 80	56.6 ± 0.4	0.131 ± 0.01	78.0 ± 1.3	0.266 ± 0.01
PLA-H-VAL 50 : 50	57.3 ± 0.3	0.251 ± 0.02	80.9 ± 1.5	0.128 ± 0.04
PLA-H-VAL 80 : 20	56.1 ± 0.4	0.401 ± 0.05	91.9 ± 1.7	0.073 ± 0.025

in the case of amorphous ketoconazole is not the consequence of the interactions between the polymer and the drug, but it mainly results from the polymer anti-plasticizing effect [50]. In one study [51], the FT-IR spectra were presented for standalone valsartan, PLA, polycaprolactone (PCL) and valsartan-loaded microparticles. It was noted that the PLA and PCL bands appeared in the spectra of the microparticles without any changes in their wave number, indicating no interactions between polymers and valsartan.

According to study [52], amorphous solid dispersions (ASD) can be thermodynamically stable if the drug loading of the ASD is below the solid solubility of the drug in the polymer. It was confirmed that the more physically stable the amorphous drug alone, the more physically stable the corresponding ASDs [53, 54].

The polylactide-valsartan system with mass ratio 50 : 50 was subjected to the isothermal physical aging process. As it was mentioned earlier, this process only applies to amorphous materials and occurs at temperatures below T_g. Therefore, at aging temperature $T_a = 50°C$, both components of the system undergo physical aging process, while at $T_a = 70°C$ only valsartan from the system undergoes aging process, because this is temperature above the glass transition of PLA-H and the polymer exists in such conditions as an amorphous liquid. Figure 2 shows the heat flow changes as a function of the temperature for PLA-H-VAL (50 : 50) system subjected to the isothermal physical aging process at aging temperature $T_a = 50°C$. The results were obtained for aging times from 5 min up to 28 days.

It can be seen in Fig. 2 that as the aging time increases, also the area of the endothermic relaxation peaks increase and the maxima of these peaks shift towards higher temperature values.

Figure 3 presents the dependence of the relaxation enthalpy for tested PLA-H-VAL system with 50 : 50 mass ratio versus aging time for the physical aging process
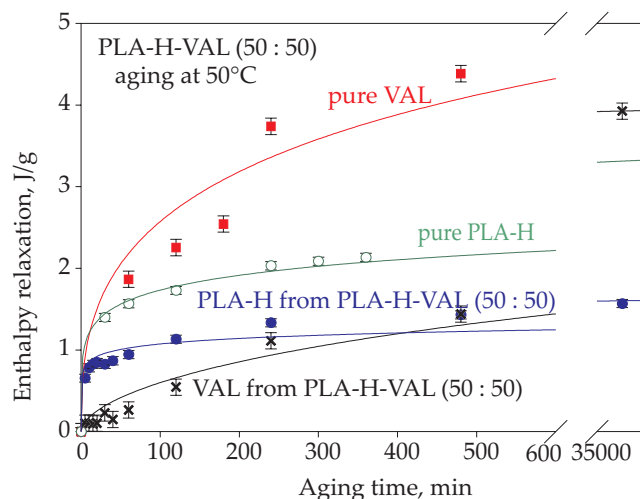
Fig. 3. Experimental enthalpy relaxation as a function of aging time for PLA-H (blue dots) and VAL (black crosses) from the PLA-H-VAL (50 : 50) system aged isothermally at $T_a = 50°C$ and their fit to the KWW equation; red squares are for standalone VAL aged at 50°C, green dots represent the values obtained from the same aging temperature for standalone PLA-H and they were taken from the literature [55]

carried out at the aging temperature $T_a = 50°C$. Enthalpy of relaxation was determined as the difference of fields created between the heat flow courses for non-aged and aged sample, according to the method described in the literature [34–39], Equation (1).

Figure 3 shows experimental values of the enthalpy relaxation marked by red squares for standalone valsartan and the green circles for standalone PLA-H, both aged at 50°C. Points in Fig. 3 represent the mean values from several calculations and the error bars are standard deviation from the obtained values of enthalpy relaxation (±0.1 J/g for VAL and ±0.05 J/g for PLA-H). Results for standalone PLA-H has been obtained from the literature [55]. Solid lines in Fig. 3 represents the adjustments of the KWW equation for the obtained experimental data. It can be seen that the relaxation enthalpy values for VAL from the mixture after multiplying by 2 (since the weight proportion of valsartan in the mixture is 50%) are still lower than the results obtained from the same physical aging experiment conducted for standalone valsartan. It can, therefore, be assumed that the addition of the PLA-H to valsartan results in improved physical stability of the drug.

Figure 4 shows changes in the heat-flow rate as a function of temperature for unaged and aged PLA-H-VAL (50 : 50) system annealed at 70°C for aging times up to 600 min. According to the initial hypothesis, only valsartan coming from the examined system undergoes physical aging in the specified conditions, because at 70°C polylactide occurs in the amorphous phase of the liquid state. Analysis of the experimental results in this case, reveals an increase in the endothermic enthalpy relaxation peaks emerging in the glass transition region of VAL in the tested system and their shift towards higher
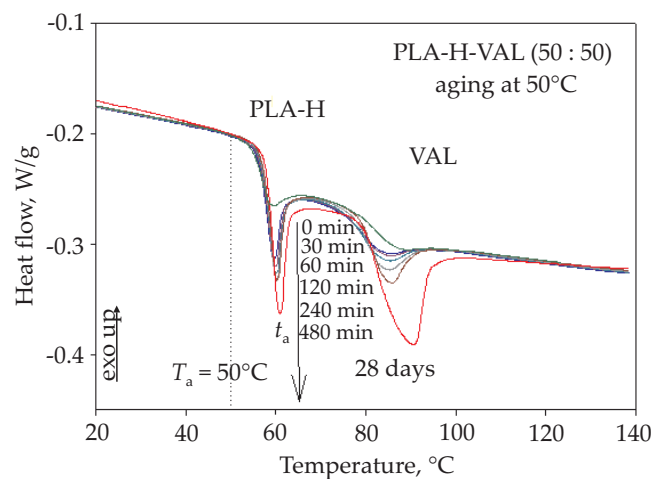

Fig. 2. Heat-flow as a function of temperature for the PLA-H-VAL system with a mass ratio of 50 : 50, obtained as a result of aging at 50°C for aging times up to 28 days
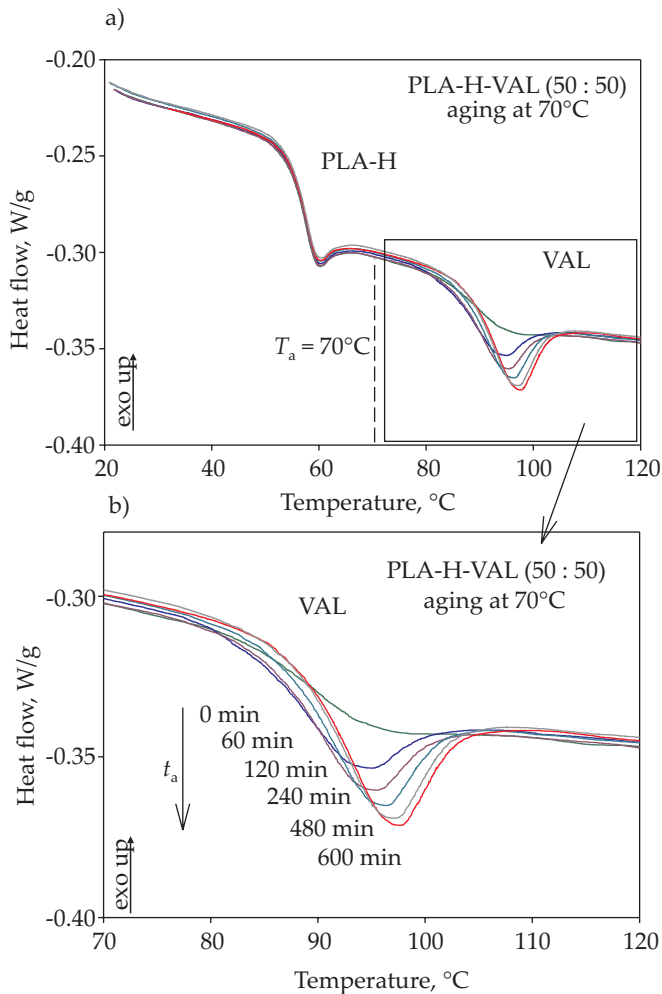
a)

b)

Fig. 4. Heat-flow rate as a function of temperature: a) for the PLA-H-VAL system with a mass ratio of 50 : 50, obtained as a result of an isothermal physical aging process carried out at 70°C for aging times up to 600 min, b) the enlargement of the heat-flow rate of the physical aging of valsartan (VAL) for the different aging times

temperatures as the aging time of the sample increases. It can also be observed, that although the PLA-H does not undergo aging process at 70°C, the heat-flow rate in the glass temperature region of PLA-H in the system is
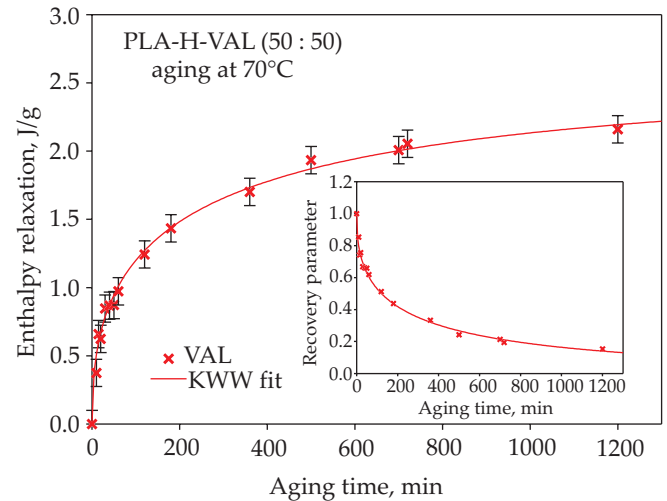

Fig. 5. Experimental enthalpy relaxation as a function of aging time for valsartan in the PLA-H-VAL (50 : 50) system aged at 70°C and fit of the KWW equation to the calculated values of ΔH_r; the inner plot presents the recovery parameter as a function of aging time

fraught with small endothermic changes due to non-isothermal aging process occurring during measurements.

In Fig. 5, the graphical representation of the enthalpy relaxation changes as the function of aging time for VAL from the PLA-H-VAL (50 : 50) system aged at $T_a = 70°C$ was showed. The solid line in Fig. 5 is the fit of the KWW equation to the experimental data. The standard deviation is ±0.1 J/g. The inner plot in Fig. 5 is the recovery parameter as the function of aging time. It can be seen that after 20 hours of annealing the PLA-H-VAL (50:50) system at 70°C, VAL from the system reaches 80% relaxation – the value of recovery parameter decreases to 0.2. Calculated parameters of the KWW equation for studied materials and aging temperatures are summarized in Table 2.

Figure 6 presents the comparison of the changes in the recovery parameter for PLA-H and VAL from the PLA-H-VAL (50:50) system aged at 50°C. The same experiment was also carried out for standalone VAL and the results for aged standalone PLA-H are taken from

T a b l e 2. Fitting parameters of experimental data to Kohlrausch-Williams-Watts equation (KWW) for PLA-H and VAL from PLA-H-VAL (50:50) mixture during the isothermal physical aging process at $T_a = 50°C$ and 70°C temperature

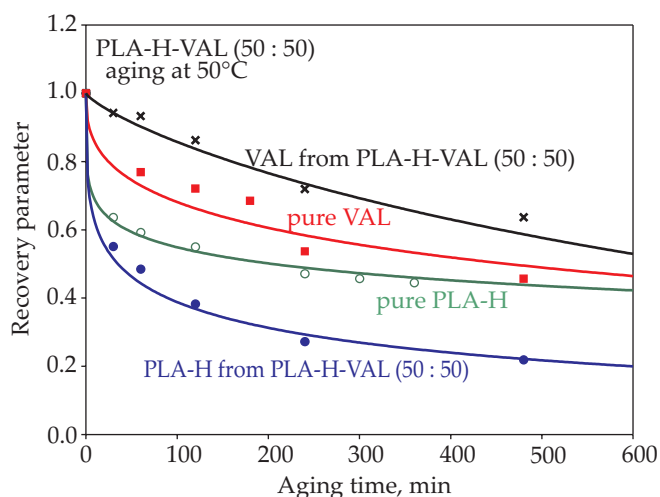|	$T_a = 50°C$			$T_a = 70°C$		
	ΔH_r^{inf} J/g	β	τ min (h)	ΔH_r^{inf} J/g	β	τ min (h)
PLA-H (from the PLA-H-VAL (50:50) system)	1.8	0.145	237.7 (3.96)	–	–	–
VAL (from the PLA-H-VAL (50:50) system)	4.0	0.567	2429.87 (40.5)	2.5	0.4548	271 (4.5)
Standalone PLA-H	3.8	0.202	1252.8 (20.88)	–	–	–
Standalone VAL	8.1	0.387	1192.34 (19.87)	–	–	–

Fig. 6. Comparison of the recovery parameter for examined PLA-H-VAL system, standalone PLA-H and standalone VAL after isothermal annealing at T_a = 50°C

the literature [54]. It can be seen that valsartan in the system with PLA-H is aging much more slowly compared to the standalone drug. The relaxation time determined by fitting the KWW equation to the obtained results for VAL in the mixture is more than twice as high as it is for standalone valsartan. The addition of PLA-H to VAL may increase the physical stability of the API in the formulation. Conversely, in the case of PLA-H, the presence of VAL in the mixture causes a 5-fold decrease in the relaxation time for PLA-H from the system aged at 50°C compared to standalone PLA-H. PLA-H from the PLA-H-VAL (50 : 50) system after storage for 200 min at 50°C reaches out 80% of the equilibrium enthalpy relaxation value for PLA-H in the system and after 28 more days at 50°C, both the enthalpy relaxation and the recovery parameter remains unchanged while the enthalpy of the relaxation for VAL in such system increases more than 3-times.

CONCLUSIONS

Using differential scanning calorimetry, the glass transition regions of obtained PLA-H-VAL systems with three specified mass ratios (80 : 20, 50 : 50 and 20 : 80) were analyzed. The presented study demonstrated that PLA-H-VAL system is immiscible, how-ever the presence of PLA-H results with an increase in the glass transition temperature of VAL in such system and hence has a significant impact on the kinetics of the physical aging process of the drug. The physical aging process of the PLA-H-VAL system with a 50 : 50 mass ratio was studied at the aging temperature T_a = 50 and 70°C. It has been shown that both components of the tested system undergo the physical aging process at 50°C, while at 70°C only valsartan from the system ages. Moreover, physical aging process at 50°C was also conducted for standalone valsartan and standalone PLA-H for comparison. The KWW equation was fitted to all of the results and the relaxation time and β parameter describing the dis-

tribution of relaxation times physical aging process were estimated. Calculated relaxation time for aging at 50°C for VAL in the 50 : 50 (w/w) system with PLA-H is twice as high as the relaxation time for standalone VAL which may result in increased stability of the drug. On the other hand, PLA-H in a mixture with VAL, compared to standalone polymer, reaches saturation relatively quickly and after 6 hours at 50°C, further changes in the enthalpy of relaxation due to physical aging are not noticeable.

REFERENCES

[1] Pyda M., Bopp R.C., Wunderlich B.: *The Journal of Chemical Thermodynamics* **2004**, *36*, 731.
https://doi.org/10.1016/j.jct.2004.05.003
[2] Magoń A., Pyda M.: *Polymer* **2009**, *50*, 3967.
https://doi.org/10.1016/j.polymer.2009.06.052
[3] Pyda M.: *Encyclopedia of Polymer Science and Technology* **2014**, 1—30.
https://doi.org/10.1002/0471440264.pst623
[4] Cai H., Dave V., Gross R.A., McCarthy S.P.: *Journal of Polymer Science: Part B: Polymer Physics* **1996**, *34*, 2701.
https://doi.org/10.1002/(SICI)1099-0488(19961130)34:16<2701::AID-POLB2>3.0.CO;2-S
[5] Kwon M., Lee S.C., Jeong Y.G.: *Macromolecular Research* **2010**, *18* (*4*), 346.
https://doi.org/10.1007/s13233-010-0410-7
[6] Aou K., Hsu S.L., Kleiner L.W. *et al.*: *Journal of Physical Chemistry B* **2007**, *111* (*42*), 12322.
http://dx.doi.org/10.1021/jp074509t
[7] "Poly(lactic acid) synthesis, structures, properties, processing, and application" (Eds. Auras R., Lim L.T., Selke S.E.M., Tsuji H., John Wiley & Sons, 2010.
http://dx.doi.org/10.1002/9780470649848
[8] Garlotta D.: *Journal of Polymers and the Environment* **2001**, *9*, 63.
https://doi.org/10.1023/A:1020200822435
[9] Hancock B.C., Parks M.: *Pharmaceutical Research* **2000**, *17* (*4*), 397.
http://dx.doi.org/10.1023/a:1007516718048
[10] Hancock B.C., Zografi G.: *Journal of Pharmaceutical Sciences* **1997**, *86* (*1*), 1.
http://dx.doi.org/10.1021/js9601896
[11] Guo J.H., Robertson R.E., Amidon G.L.: *Pharmaceutical Research* **1991**, *8*, 1500.
http://dx.doi.org/10.1023/a:1015890232106

[12] Agraval S.K., Sanabria-DeLong N., Coburn J.M. *et al.*: *Journal of Controlled Release* **2006**, *112*, 64.
https://doi.org/10.1016/j.jconrel.2005.12.024

[13] Kucera S.A., Felton L.A., McGinity J.W.: *International Journal of Pharmaceutics* **2013**, *457*, 428.
http://dx.doi.org/10.1016/j.ijpharm.2013.01.069

[14] Surana R., Pyne A., Suryanarayanan R.: *Pharmaceutical Research* **2004**, *21*, 867.
https://doi.org/10.1023/B:PHAM.0000026441.77567.75

[15] Pokharkar V.B., Mandpe L.P., Padamwar M.N. *et al.*: *Powder Technology* **2006**, *167*, 20.
https://doi.org/10.1016/j.powtec.2006.05.012

[16] Graeser K.A., Patterson J.E., Zeitler J.A. *et al.*: *European Journal of Pharmaceutical Sciences* **2009**, *37*, 492.
https://doi.org/10.1016/j.ejps.2009.04.005

[17] Julio T.A., Zamara I.F., Garcia J.S., Trevisan M.G.: *Brazilian Journal of Pharmaceutical Sciences* **2013**, *49* (*4*).
http://dx.doi.org/10.1590/S1984-82502013000400003

[18] Liechty W.B., Kryscio D.R., Slaughter B.V., Peppas N.A.: *Annual Review of Chemical and Biomolecular Engineering* **2010**, *1*, 149.
http://dx.doi.org/10.1146/annurev-chembio-eng-073009-100847

[19] Dengale S.J., Grohganz H., Rades T., Löbmann K.: *Advanced Drug Delivery Reviews* **2016**, *100*, 116.
http://dx.doi.org/10.1016/j.addr.2015.12.009

[20] Chavan R.B., Thipparaboina R., Kumar D., Shastri N.R.: *International Journal of Pharmaceutics* **2016**, *515*, 403.
http://dx.doi.org/10.1016/j.ijpharm.2016.10.043

[21] Bikiaris D.N.: *Expert Opinion on Drug Delivery* **2011**, *8* (*11*), 1501.
https://doi.org/10.1517/17425247.2011.618181

[22] Qian F., Huang J., Hussain M.A.: *Journal of Pharmaceutical Science* **2010**, *99* (*7*), 2941.
https://doi.org/10.1002/jps.22074

[23] Blasko A., Leahy-Dios A., Nelson W. *et al.*: *Monatshefte fur Chemie* **2001**, *132*, 789.
https://doi.org/10.1007/s007060170065

[24] Tiwari R., Tiwari G., Srivastava B., Raiet A.K.: *International Journal of PharmTech Research* **2009**, *1* (*4*), 1338.

[25] Sihna S., Ali M., Baboota S. *et al.*: *AAPS PharmSciTech* **2010**, *11* (*2*), 518.
http://dx.doi.org/10.1208/s12249-010-9404-1

[26] Rumondor A., Ivanisevic I., Bates S. *et al.*: *Pharmaceutical Research* **2009**, *26*, 2523.
http://dx.doi.org/10.1007/s11095-009-9970-7

[27] Newman A., Munson E.: *American Pharmaceutical Review* **2012**, *3*, 92.

[28] Al-Obaidi H., Lawrence M.J., Shah S. *et al.*: *International Journal of Pharmaceutics* **2013**, *446*, 100.
https://doi.org/10.1016/j.ijpharm.2013.02.009

[29] Skotnicki M., Gaweł A., Cebe P., Pyda M.: *Drug Development and Industrial Pharmacy* **2013**, *39*, 1508.
https://doi.org/10.3109/03639045.2012.704379

[30] Skotnicki M., Apperley D.C., Aguilar J.A. *et al.*: *Molecular Pharmaceutics* **2016**, *13* (*1*), 211.
http://dx.doi.org/10.1021/acs.molpharmaceut.5b00646

[31] Skotnicki M., Aguilar J.A., Pyda M., Hodgkinson P.: *Pharmaceutical Research* **2015**, *32*, 414.
http://dx.doi.org/10.1007/s11095-014-1471-7

[32] Guinet Y., Paccou L., Danède F. *et al.*: *International Journal of Pharmaceutics* **2017**, *526* (*1–2*), 209.
http://dx.doi.org/10.1016/j.ijpharm.2017.04.067

[33] Wunderlich B.: "Thermal Analysis of Polymeric Materials", Spring, Verlag, Berlin 2005.
https://doi.org/10.1007/b137476

[34] Struik L.C.E.: "Physical aging in amorphous polymers and other materials", Elsevier Science, 1980.
https://doi.org/10.1016/0079-6700(94)00001-I

[35] Cernošek Z., Holubová J., Cernošková E., Liška M.: *Journal of Optoelectronics and Advanced Materials* **2002**, *4*, 489.

[36] Hutchinson J.M.: *Progress in Polymer Science* **1995**, *20*, 703.
https://doi.org/10.1016/0079-6700(94)00001-I

[37] Hodge I.M.: *Journal of Non-Crystalline Solids* **1994**, *169*, 211.
https://doi.org/10.1016/0022-3093(94)90321-2

[38] Hay J.N.: *Pure and Applied Chemistry* **1995**, *67*, 1855.
https://doi.org/10.1002/masy.19991430112

[39] Koh Y.P., Simon S.L.: *Macromolecules* **2013**, *46*, 5815.
https://doi.org/10.1021/ma4011236

[40] Morris C., Taylor A.J. *et al.*: *Carbohydrate Research* **2011**, *346*, 1122.
https://doi.org/10.1016/j.carres.2011.04.009

[41] Moynihan C.T., Macedo P.B., Montrose C.J. *et al.*: *Annals of the New York Academy* of *Sciences* **1976**, *279*, 15.
https://doi.org/10.1111/j.1749-6632.1976.tb39688.x

[42] Kohlrausch R.: *Annals of Physics* **1847**, *12*, 393.

[43] Williams G., Watts D.C.: *Transactions of the Faraday Society* **1970**, *66*, 80.
https://doi.org/10.1039/tf9706600080

[44] Sadoun O., Rezgui F., G'Sell C.: *Materials Science* & *Engineering C* **2018**, *90*, 189.
http://dx.doi.org/10.1016/j.msec.2018.04.041

[45] Malmgren T., Mays J., Pyda M.: *Journal of Thermal Analysis and Calorimetry* **2006**, *83*, 35.
https://doi.org/10.1007/s10973-005-7066-0

[46] Karagianni A., Kachrimanis K., Nikolakakis I.: *Pharmaceutics* **2018**, *10* (*3*), 98.
http://dx.doi.org/10.3390/pharmaceutics10030098

[47] Laitinen R., Löbmann K., Strachan C.J. *et al.*: *International Journal of Pharmaceutics* **2013**, *453*, 65.
http://dx.doi.org/10.1016/j.ijpharm.2012.04.066

[48] Zhu S., Gao H., Babu S., Garad S.: *Molecular Pharmaceutics* **2018**, 15, 97.
http://dx.doi.org/10.1021/acs.molpharmaceut.7b00738

[49] Löbmann K., Strachan C., Grohganz H. *et al.*: *European Journal of Pharmaceutics and Biopharmaceutics* **2012**, *81*, 159.
http://dx.doi.org/10.1016/j.ejpb.2012.02.004

[50] Van den Mooter G.: *European Journal of Pharmaceutical Sciences* **2001**, *12*, 261.
http://dx.doi.org/10.1016/s0928-0987(00)00173-1

[51] Sadoun O., Rezgui F., G'Sell C.: *Materials Science & Engineering C* **2018**, *90*, 189.
https://doi.org/10.1016/j.msec.2018.04.041

[52] Qian F., Huang J., Hussain M.: *Journal of Pharmaceutical Sciences* **2010**, *99* (7), 2941.
http://dx.doi.org/10.1002/jps.22074

[53] Ng Y.C., Yang Z.Y., McAuley W.J., Qi S.: *European Journal of Pharmaceutics and Biopharmaceutics* **2013**, *84* (3), 555.

http://dx.doi.org/10.1016/j.ejpb.2013.01.008

[54] Yang Z., Nollenberger K., Albers J. *et al*.: *Pharmaceutical Research* **2015**, *32* (4), 1210.
http://dx.doi.org/10.1007/s11095-014-1527-8

[55] Drogoń A., Pyda M.: *Polimery* **2019**, *64*, 127.
http://dx.doi.org/10.14314/polimery.2019.2.6

Received 22 I 2020.