



You have downloaded a document from
RE-BUŚ
repository of the University of Silesia in Katowice

Title: Thermodynamically controlled crystallization of glucose pentaacetates from amorphous phase

Author: Patryk Włodarczyk, Łukasz Hawełek, Andrzej Hudecki, Agnieszka Włodarczyk, Aleksandra Kolano-Burian

Citation style: Patryk Włodarczyk, Łukasz Hawełek, Andrzej Hudecki, Agnieszka Włodarczyk, Aleksandra Kolano-Burian. (2016). Thermodynamically controlled crystallization of glucose pentaacetates from amorphous phase. "AIP Advances" (2016, vol. 6, iss. 8, art. no 085221), doi 10.1063/1.4962300



Uznanie autorstwa - Licencja ta pozwala na kopiowanie, zmienianie, rozprowadzanie, przedstawianie i wykonywanie utworu jedynie pod warunkiem oznaczenia autorstwa.



UNIwersYTET ŚLĄSKI
W KATOWICACH



Biblioteka
Uniwersytetu Śląskiego



Ministerstwo Nauki
i Szkolnictwa Wyższego

Thermodynamically controlled crystallization of glucose pentaacetates from amorphous phase

P. Włodarczyk,^{1,a} L. Hawelek,¹ A. Hudecki,¹ A. Włodarczyk,²
and A. Kolano-Burian¹

¹*Institute of Non-Ferrous Metals, ul. Sowinskiego 5, 44-100 Gliwice, Poland*

²*Department of Animal Histology and Embryology, University of Silesia, ul. Bankowa 9, 40-007 Katowice, Poland*

(Received 9 June 2016; accepted 23 August 2016; published online 31 August 2016)

The α and β glucose pentaacetates are known sugar derivatives, which can be potentially used as stabilizers of amorphous phase of active ingredients of drugs (API). In the present work, crystallization behavior of equimolar mixture of α and β form in comparison to both pure anomers is revealed. It was shown that despite the same molecular interactions and similar molecular dynamics, crystallization from amorphous phase is significantly suppressed in equimolar mixture. Time dependent X-ray diffraction studies confirmed higher stability of the quenched amorphous equimolar mixture. Its tendency to crystallization is about 10 times lower than for pure anomers. Calorimetric studies revealed that the α and β anomers don't form solid solutions and have eutectic point for $x_{\alpha} = 0.625$. Suppressed crystallization tendency in the mixture is probably caused by the altered thermodynamics of the system. The factors such as difference of free energy between crystalline and amorphous state or altered configurational entropy are probably responsible for the inhibitory effect. © 2016 Author(s). All article content, except where otherwise noted, is licensed under a Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>). [<http://dx.doi.org/10.1063/1.4962300>]

I. INTRODUCTION

The α and β glucose pentaacetates are known glass-forming liquids, with glass transition below room temperature.¹ Recently, these compounds are gaining attention in pharmaceutical sciences, due to their ability to stabilize amorphous state of drug.² Drugs in the amorphous state have better bioavailability and solubility, therefore there is a need for additives that can prevent active ingredient (API) from crystallization.³ Sugar peracetates are van der Waals compounds i.e. systems dominated by dipol-dipol interactions, but they have many hydrogen bond (HB) acceptor sites in the structure (oxygen atoms). Therefore, when mixed with the hydrogen bond system (with proton donors) they can create extended HB network and specific intermolecular forces becoming dominant. In their pure states, compounds crystallize fairly easy from the amorphous phase. Moreover, it was found that the kinetics of crystallization for the α and β forms of glucose pentaacetates is different.⁴ Different crystals morphology is caused by the differences in the nucleation to growth ratio for both substances. Very recently, it was shown that saccharides peracetates (mainly disaccharides) can suppress crystallization kinetics very efficiently by altering hydrogen bond dynamics. It was found that in mixtures with nifedipine, maltose octaacetate creates chemical pressure in the system and causes significant increase of hydrogen bond lifetimes between nifedipine molecules.⁵ Inhibitory crystallization effect of acetyl derivatives of carbohydrates was also found in mixtures with the celecoxib drug.⁶

Crystallization is a two stage process. The first stage is related to the nucleation and the second one to the crystal growth. Different factors control both nucleation and growth rates. Crystallization

^apatrykw@imn.gliwice.pl

factors can be divided into three different groups. First group is related to thermodynamics of a system.^{7,8} Parameters such as difference of free energy between crystalline and amorphous state or configurational entropy have major impact on nucleation rate. The second group is related to the kinetic factors i.e. molecular mobility which is correlated to the viscosity of the system.⁹⁻¹² Molecular mobility has biggest influence on crystal growth. The third group of effects is related to the molecular interactions occurring in mixtures. Different additives may for example alternate hydrogen bond pattern.¹³⁻¹⁷ Stronger hydrogen bonds can inhibit or catalyze crystallization, which depends on the system type.

Mixtures of glucose peracetates are very special because mixing two similar compounds (slight modification of side group alignment i.e. α versus β anomer) should not influence molecular mobility or intermolecular interactions.

In Ref. 4 authors are focused on the comparison of D-glucose to the α and β glucose pentaacetates. They explain that the different character of molecular interactions between glucose and its acetylated equivalent has major impact on crystallization kinetics. However, there have been also reported differences in crystallization kinetics in two very similar compounds α and β glucose pentaacetates. Different morphology of crystals may indicate different nucleation ratios between two anomeric forms. Cited work is a starting point for our studies. In present work, comparison of crystallization between two glucose pentaacetate anomers and their equimolar mixture will be checked.

The main aim of this work is to check the ease of crystallization of equimolar mixture of α and β anomers, their tendency to co-crystallization and to evaluate factors that control crystallization in the amorphous phase of these compounds. In the first stage, molecular dynamics of pure anomers and their equimolar mixture will be compared by use of dielectric spectroscopy in order to compare molecular mobility in pure anomers and their mixture. Isothermal crystallization undergoing at 297 K and 30-40 % humidity will be monitored by X-ray diffraction (XRD) study. Degree of crystallization will be also determined for all studied samples. In order to understand differences in crystallization kinetics between all studied samples, phase diagram of binary system of α -peracetylglucose and β -peracetylglucose will be prepared by means of differential scanning calorimetry (DSC).

II. EXPERIMENTAL

High purity compounds were bought from the Alpha Aesar company. Purity of α form was higher than 99% while β higher than 98%.

Acetylated saccharides and their mixtures were prepared in the amorphous phase by vitrification method. Molten samples were quenched on the cooper plate. Dielectric measurements were performed by Concept 81 dielectric spectrometer equipped with Alpha analyzer and Novo-cool temperature control system (Novocontrol, Germany). Measurement were carried out in the frequency range 10^{-2} – 10^6 Hz and temperatures from 173 K to 333 K. Samples were placed in acid-resistant steel capacitors with the diameter 20 mm. The sample height was 0.1 mm fixed by the teflon spacer. Dielectric spectra were fitted with Havriliak-Negami functions with use of WinFit software by Novocontrol.

The X-ray powder diffraction measurements were carried out in order to check amorphous state of supercooled samples, to verify the crystalline forms of pure acetylated sugars and their mixtures as well as the progress of crystallization in pure α and β forms and their 1:1 mixture. The sample were storage at temperature equal to 297 K and humidity in the range 30-40%. All the measurements were performed at temperature equal to 297 K using a Rigaku MiniFlex 600 diffractometer (Rigaku Corporation, Tokyo, Japan) with Cu K α radiation ($\lambda = 1.5406 \text{ \AA}$), a tube voltage of 40 kV, and a current of 15 mA using a D/teX Ultra silicon strip detector. The scan parameters were typically 0.01° step size for 5 s count times over a range $3-80^\circ 2\theta$. The samples were placed in the aluminum plate as a sample holder. All data were analyzed and displayed using the Rigaku PDXL software suite.

In order to prepare binary phase diagram of α and β glucose pentaacetate differential scanning calorimetry was used. All the measurements were performed by means of Pegasus 404C (Netzsch,

Germany) equipped with silver furnace and sample carrier equipped with E thermocouple. All the measurements were performed with use of aluminum concavus pans and under helium atmosphere (gas flow equal to 50 mL/min). As these systems can be easily undercooled, special protocol has been used to obtain both liquidus and solidus temperatures. At the beginning, crystalline samples with different mass ratios were obtain by crystallization from methanol. Then, all the crystalline samples were melted in calorimeter with different heating rates (5K/min, 10K/min and 20K/min). Onset temperatures indicate solidus temperature. In order to obtain liquidus temperature, temperatures of end of melting were extrapolated to the heating rate 0 K/min.

III. RESULTS

A. Dielectric spectroscopy

Molecular dynamics of glucose pentaacetate was recently described by Kaminski *et al.* Authors have shown dielectric spectra and derived parameters such as glass transition temperature, steepness index (to describe glass fragility) and activation energy of secondary mode. However, information about anomeric composition of glucose pentaacetate has not been provided. In the first stage of our work we have focused on the comparison of molecular dynamics of pure α anomer, pure β anomer and α - β equimolar mixture. The anomers differ by the orientation of one acetyl side group ($\text{CH}_3\text{COO}-$). In the α -anomer the group is positioned below the plane of sugar ring, while in β above the ring. The geometry of rest of molecule is intact. However, as the sugar ring exists most of the time in the chair conformation, anomeric side group in α form has equatorial position, while in β form - axial position. This small rearrangement has slight impact on molecular dynamics of whole system. In the Figure 1, comparison of three studied systems has been presented. In the left panel, dielectric loss versus temperature has been plotted for low frequency (1.5×10^{-2} Hz) in order to show differences in the behavior of structural relaxation. Secondary mode *i.e.* γ -relaxation has been compared in all studied systems by plotting the same dependence ($\epsilon'' = f(T)$) for 1×10^3 Hz

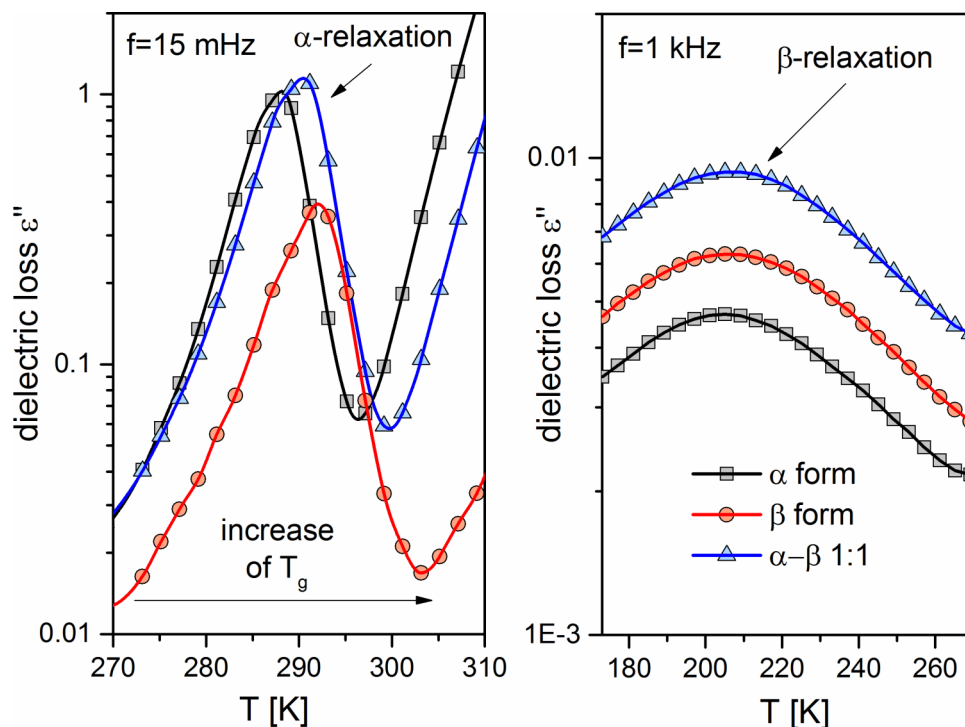


FIG. 1. Dielectric spectra presented as $\epsilon'' = f(T)$ for two different frequencies in order to compare α -relaxation (left panel) and γ -relaxation (right panel).

frequency. As one can see, dynamics in deep glass is practically the same in pure anomers and their mixture. It can be easily noticed that there is no difference in relaxation times of γ -process of all samples measured in the same temperatures. Maxima of all curves in frequency $f=1$ kHz correspond to the same temperature which is equal to $T=208$ K. The situation is different when glass is heated and approaches glass transition. In the vicinity of glass transition, structural relaxation (α -process) is observed in dielectric spectra. Curves visible in left panel of Figure 1 are related to the α -process. Maxima of curves are observed at different temperatures, which means that structural relaxation times are different for three measured samples at the same temperature. This is clear evidence that the glass transition temperature is different in case of all studied systems. It is evident that the α anomer has lower glass transition temperature than its β counterpart and as expected, their equimolar mixture has glass transition temperature between temperatures characteristic for pure α and β forms. The shape of dielectric curves for α and γ -process have been analyzed in Figure 2. In the left panel, α -relaxation curves have been superimposed in order to analyze their shape. Curves have been fitted with the use of the KWW (Kohlrausch-Williams-Watts) function which can be expressed in the form:

$$\varphi(t) = \exp \left[- \left(\frac{t}{\tau_\alpha} \right)^{\beta_{KWW}} \right],$$

Where t – time, τ_α – relaxation time, β_{KWW} – stretch exponent.

For our purpose, fits were done with use of the Fourier transforms of this function (which was initially developed for time domain measurements) plotted for relaxation time equal to $\tau_\alpha = 1$ s. As one can see, structural relaxation curve for β -anomer has been fitted with $\beta_{kww} = 0.58$, while α and mixture with $\beta_{kww} = 0.63$. Lower values of stretch exponent are related to the larger distribution of relaxation times which can be connected with higher heterogeneity of the system. Surprisingly, the equimolar mixture of α and β forms behaves like pure α anomer.

In order to compare secondary mode in all studied samples, dielectric spectra measured at 173 K were fitted by the Havriliak-Negami function and further analyzed. The Havriliak-Negami complex function can be expressed in the form:

$$\varepsilon^* = \varepsilon_\infty + \frac{\Delta\varepsilon}{(1 + (i\omega\tau)^\alpha)^\beta}$$

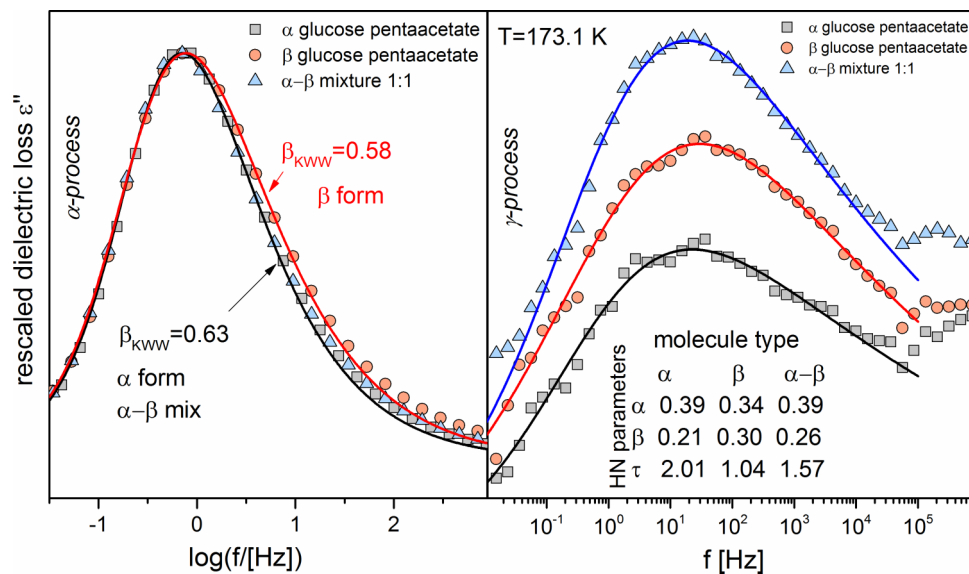


FIG. 2. Comparison of shape of dispersion curves characterizing α and γ – process in glucose peracetates. In the left panel α -relaxation curve has been fitted to the KWW equation.

Where ϵ_∞ is electric permittivity at high frequency limit, $\Delta\epsilon$ is dielectric strength, α – asymmetry parameter, β – broadness parameter, τ – the Havriliak-Negami relaxation time.

The maximum of loss peak in dielectric spectra can be estimated by the relation:

$$\omega_{max} = \left(\frac{\sin\left(\frac{\pi\alpha}{2(\beta+1)}\right)}{\sin\left(\frac{\pi\alpha\beta}{2(\beta+1)}\right)} \right)^{1/\alpha} \tau^{-1}$$

The parameters of the HN fits for secondary relaxations at 173 K are presented in the right panel of Figure 2. For all studied systems, asymmetry parameters are in the range 0.34-0.39, broadness parameters are in the range 0.21-0.30 and the HN relaxation times are in the range 1.0 – 2.0 s. All the differences are within the range of standard error, which is equal to approximately 0.05 for α exponent, 0.08 for β exponent and 1.0 s for the HN relaxation time. Therefore, it can be concluded that the local dynamics in the deep glass cannot be distinguished in α , β and $\alpha - \beta$ mixtures.

In the Figure 3, glass transition temperature, steepness index and activation energy for secondary mode has been presented for all studied samples. Thermal dependence of logarithm of structural relaxation characteristic time was fitted to the Vogel-Fulcher-Tamman equation (VFT). From the VFT fit, the glass transition temperature was evaluated with use of operational definition of glass transition which states that it is a temperature for which relaxation time is equal to 100 s. There is a slight difference in glass transition between two pure anomers. Glass transition temperature of α form is equal to 285.2 K while of β anomer is equal to 288.7 K. Glass transition temperature of 1:1 mixture lies between two pure forms and it is equal to 286.1 K. Fragility of glass was studied by evaluating steepness index of VFT fit which can be determined by the relation:

$$m = \left(\frac{d \log \tau_{max}}{d \left(\frac{T_g}{T} \right)} \right)_{T=T_g}$$

The higher the steepness index, the more fragile glass is. As one can see, α -anomer has slightly higher steepness index than two other systems ($m=95$ versus $m=87$). Higher fragility is related to the higher extent of structure reorganization when sample crosses glass transition point. Due to this

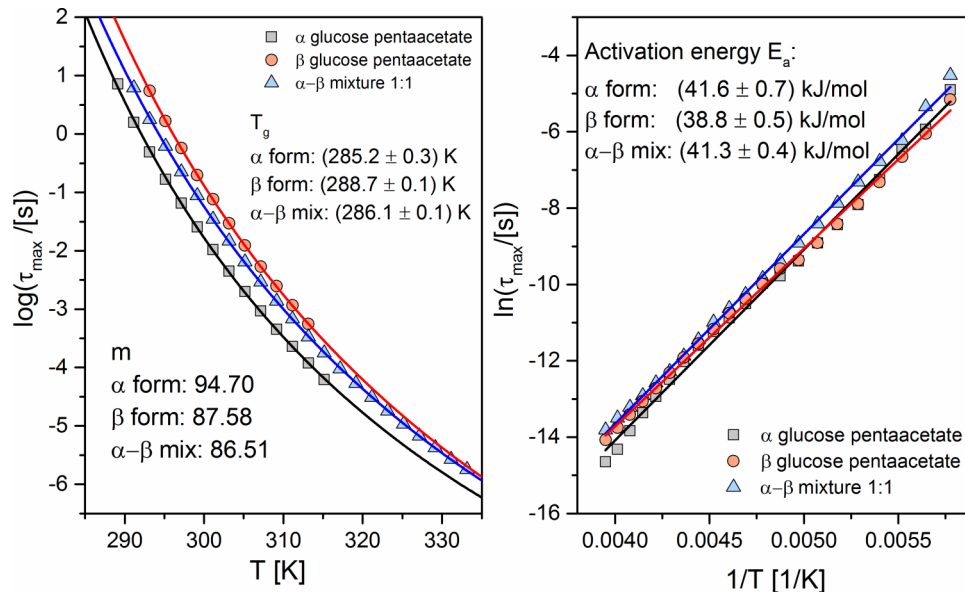


FIG. 3. In the left panel, VFT fits of structural relaxation times have been presented. From the fits glass transition temperatures as well as steepness indexes have been obtained. In the right panel, activation energies for secondary modes have been obtained for all studied samples by use of Arrhenius fits. Standard deviation of relaxation times logarithm doesn't exceed ± 0.1 . Temperature accuracy is better than 0.1 K.

fact, in theory, fragile systems have stronger tendencies to crystallization than strong systems. In case of our samples, the differences are too small to link fragility with crystallization tendencies.

Activation energy of γ -process for all studied samples is the same i.e. in the range of systematic error. The activation energy is equal to approximately 40 kJ/mol.

B. Powder X-ray diffraction study

Three vitrified samples i.e. pure α and β anomers and their equimolar mixture were investigated in order to check their tendency to crystallize from the amorphous state. The progress in crystallization has been checked by performing XRD measurements. In case of pure substances, it takes 4 days to crystallize these compounds from amorphous phase. Both anomers recrystallize to the same crystalline forms with only different diffraction peak intensity, therefore different crystallographic directions during the crystallization process are preferred (Figure 4 – left panel). All the XRD intensities for α and β anomers were indexed in $P 2_12_12_1$ space group symmetry according to crystallographic database PDF-2 ICDD-00-030-1737 and ICDD-00-030-1738, respectively. In contrary to this result, equimolar mixture is very resistant to crystallization, there was no crystallization signs in the first four days. After one week sample starts to crystallize and first diffraction peak appears around 9.5 degree in 2-theta scale. After one month, more peaks on the XRD pattern are visible (Figure 5). To elucidate the kinetic of recrystallization process the crystallinity curve have been plotted in Figure 4 (right panel) as the function of time. Crystallinity values were calculated as a ratio between the integrated area below the Bragg crystalline peaks and the total area. After 5 days the pure anomers recrystallized in almost 90%, while their mixture after 30 days in about 10%. There is no clear indications from the XRD study which anomeric form starts to recrystallize from amorphous phase. There are also small differences in the crystallization kinetics for α and β anomers. The main difference is observed in the incubation time, which is related to the transient nucleation rate.¹⁸

C. DSC

In order to understand significant differences in crystallization kinetics between pure and equimolar mixture, phase diagram for binary system of two studied anomers has been formed (see Figure 6 for details). Pure α and β anomers have their melting points at temperatures 385 and 405 K

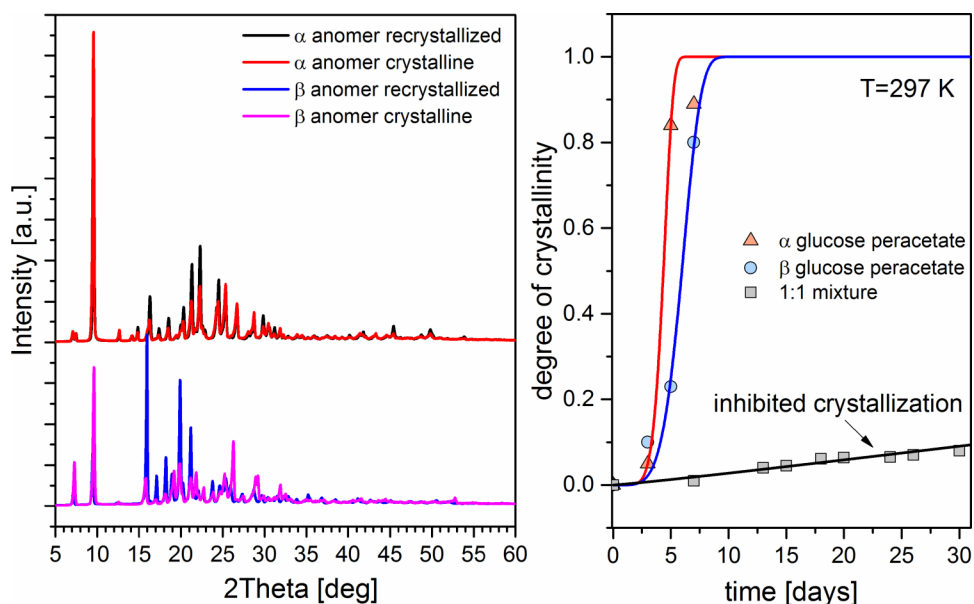


FIG. 4. X-ray diffraction patterns for crystalline and recrystallized pure anomers (left panel). The crystallinity evolution for pure anomers and α - β mixture (right panel).

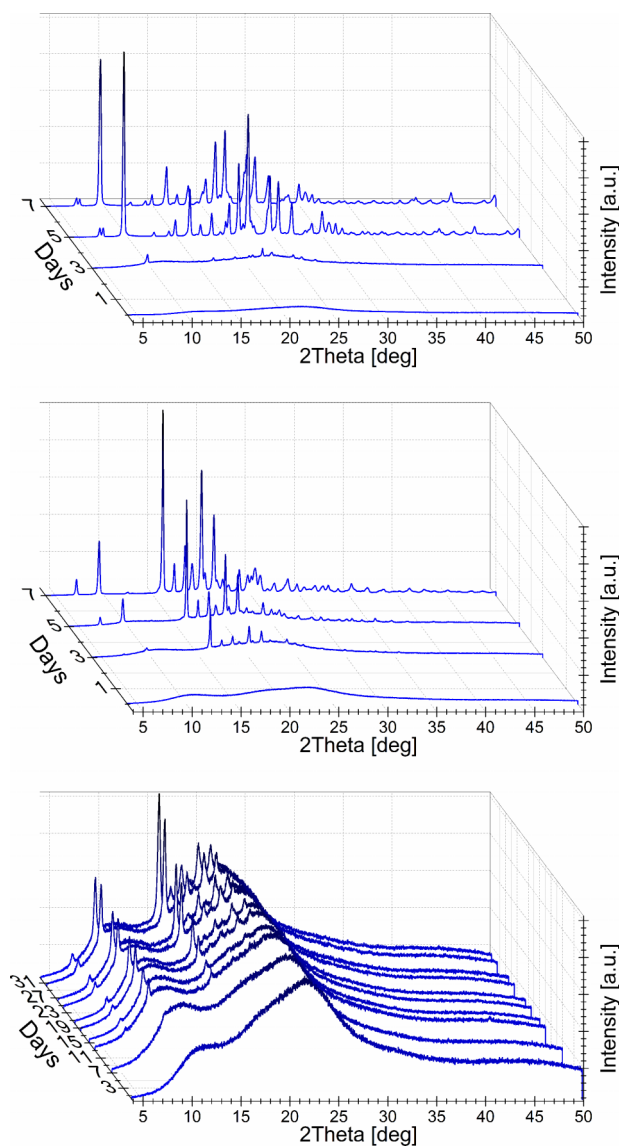


FIG. 5. Time dependent X-ray diffraction patterns of isothermal recrystallized pure α and β form and α - β mix.

respectively. For the composition where molar fraction of α is equal to 0.625, melting temperature exhibits minimum ($T=366$ K) at eutectic point. As one can see in Figure 7, there are no co-crystals formed in solid state. These substances don't have ability to form solutions in solid state. From the DSC measurements heat of fusion of pure anomers as well as eutectic mixture has been derived. It is equal to 88 J/g for α , 81 J/g for β and 60 J/g for eutectic mixture.

IV. DISCUSSION

It was found that in the glucose pentaacetates mixtures, crystallization from amorphous phase becomes inhibited in comparison to pure anomers. Dielectric spectroscopy measurements indicate that the kinetics in supercooled liquid state is very similar. Therefore, kinetic factors cannot be accounted for the improved stability against crystallization. Moreover, mixing two very similar van der Waals liquids doesn't change molecular interaction character. Therefore, difference in crystallization tendency can be explained only by the change of thermodynamic properties of mixture. Critical parameter which influence nucleation rate is the difference of free energy change between

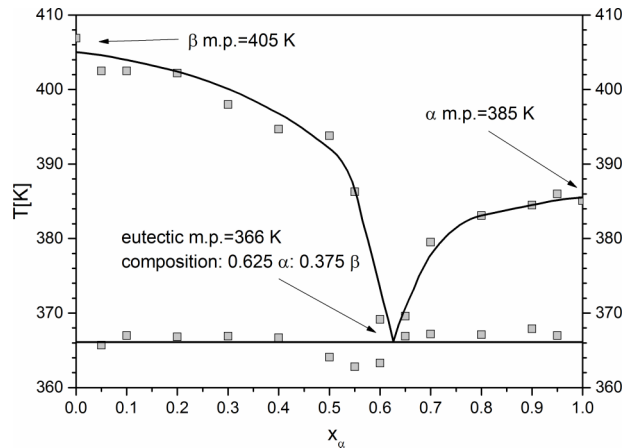


FIG. 6. Phase diagram for α and β glucose peracetate binary mixture obtained by means of differential scanning calorimetry.

crystalline and supercooled state at certain temperature. Free energy change depends on heat of fusion and heat capacities of glass and crystalline phases. For pure substances, it can be predicted by the Hoffmann equation,¹⁹ in which free energy change is proportional to the degree of supercooling and heat of fusion. Hoffmann equation can be presented in the form:

$$\Delta G = \frac{\Delta H_f (T_m - T) T}{T_m^2}$$

Where ΔH_f – heat of fusion, T_m – melting temperature, T – temperature of interest.

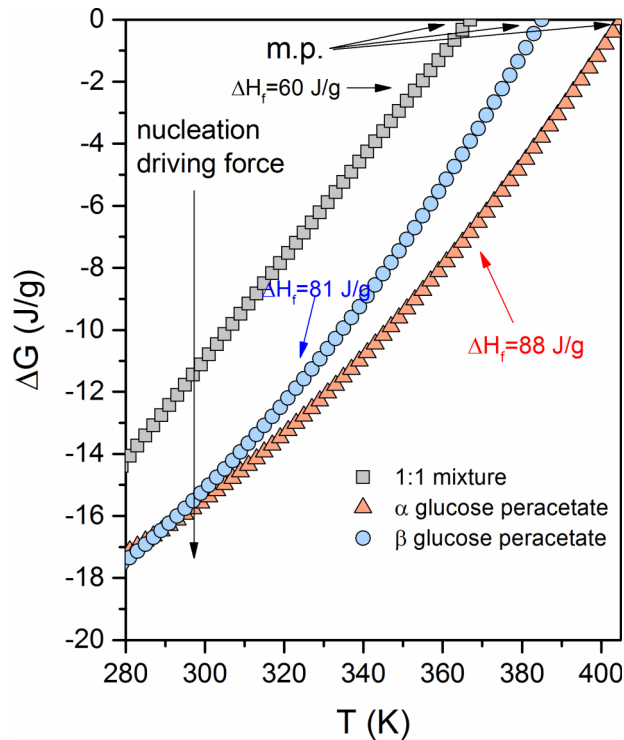


FIG. 7. Free energy difference plot for all three studied samples. The lower value of free energy difference is related to the higher stability against crystallization. Basing on the plot, at ambient temperature (298 K), ease of crystallization can be set in the following order: 1 – 1 mixture < β anomer < α anomer. For pure substances, free energy difference was calculated by use of Hoffmann equation, while for binary mixture it was estimated by similar formula based on the assumption that mixture is close to the ideal solution.

In binary mixture, one needs to take into account mixing effects. In the case when mixing enthalpy is $H_{\text{mix}} \leq 0$ and there is no miscibility gap in liquid state, free energy difference can be approximated by the equation:²⁰

$$\Delta G = \frac{\Delta H_f (T_m - T)}{T_m}$$

Our binary solution consists of molecules which are almost identical, therefore mixing enthalpy is close to 0 and the above formula is valid for our mixture.

The change of free energy for all studied samples has been presented in Figure 7. As one can see the 1:1 mixture has much lower tendency to crystallization because of the lower nucleation driving force. It is caused by the lower degree of supercooling as well as smaller heat of fusion of eutectic mixture. The Hoffmann plot indicate also that in the room temperature (297 K) crystallization in α anomer can be little bit faster than in its β counterpart. The difference in crystallization rate should be evident at elevated temperatures. This slight difference in crystallization rate between anomers was confirmed by XRD measurements (Figure 4).

The second thermodynamic factor which is of high importance is configurational entropy. In case of mixture we have two types of molecules which implies that the number of accessible conformations of the part of a system is higher. It means that mixture is characterized by higher configurational entropy, which should in consequence leads to slower nucleation rate. The part of a system has to undergo through the higher amount of configurations before it reaches optimal conformation that allows to form nucleation center. Configurational entropy could additionally influence the nucleation rate in the studied samples.

V. CONCLUSIONS

By performing studies of α - glucose and β -glucose pentaacetates different mixtures, it was evaluated that for mixtures close to 1:1 molar ratio, crystallization from amorphous phase has been strongly inhibited. It was shown that molecular dynamics of mixture is very close to the dynamics observed in pure anomers, with almost the same glass transition temperature, steepness index and parameters of fast relaxation process. Despite the fact that both substances crystallize in the same space group, there are no evidence on co-crystallization or such process is extremely reduced. It was shown that crystallization tendency is significantly suppressed in the mixture due to lower change of free energy between crystalline and supercooled state and possibly also by the higher configurational entropy of the system. To conclude, it may be advantageous to modify amorphous API by adding equimolar mixture instead of pure anomers of sugar peracetates in order to stabilize amorphous state of matter.

Our studies indicate that the crystallization from amorphous phase can be satisfactorily suppressed by changing thermodynamic parameters of a system such as degree of supercooling, configurational entropy or heat of fusion. This goal can be achieved by preparing mixtures with structurally similar compounds.

ACKNOWLEDGEMENT

P. Włodarczyk, L. Hawelek and A. Kolano-Burian acknowledged for a grant from the National Science Center, Poland with contract number: UMO-2013/09/D/ST3/03758

¹ K. Kaminski, P. Włodarczyk, L. Hawelek, K. Adrjanowicz, Z. Wojnarowska, M. Paluch, and E. Kaminska, *Phys. Rev. E* **83**, 061506 (2011).

² K. Grzybowska, M. Paluch, P. Włodarczyk, A. Grzybowski, K. Kaminski, L. Hawelek, D. Zakowiecki, A. Kasprzycka, and I. Jankowska-Sumara, *Mol. Pharm.* **9**, 894 (2012).

³ P. Gupta, G. Chawla, and AK. Bansal, *Mol. Pharm.* **1**, 406 (2004).

⁴ K. Kaminski, K. Adrjanowicz, Z. Wojnarowska, M. Dulski, R. Wrzalik, M. Paluch, E. Kaminska, and A. Kasprzycka, *J. Phys. Chem. B* **115**, 11537 (2011).

⁵ E. Kaminska, M. Tarnacka, P. Włodarczyk, K. Jurkiewicz, K. Kolodziejczyk, M. Dulski, D. Haznar-Garbacz, L. Hawelek, K. Kaminski, A. Włodarczyk, and M. Paluch, *Mol. Pharm.* **12**, 3007 (2015).

- ⁶ K. Grzybowska, M. Paluch, P. Włodarczyk, A. Grzybowski, K. Kaminski, L. Hawelek, D. Zakowiecki, A. Kasprzycka, and I. Jankowska-Sumara, *Mol. Pharm.* **9**, 894 (2012).
- ⁷ D Zhou, GGZ. Zhang, D. Law, DJW Grant, and EA Schmitt, *J. Pharm. Sci.* **91**, 1863 (2002).
- ⁸ V. Andronis and G. Zografi, *J. Non-Crystalline Solids* **271**, 236 (2000).
- ⁹ V. Andronis, M. Yoshioka, and G. Zografi, *J. Pharm. Sci.* **86**, 346 (1997).
- ¹⁰ MJ. Pikal, *Drugs Pharm. Sci.* **137**, 63 (2004) (Freeze Drying/Lyophilization of Pharmaceuticals and Biological Products).
- ¹¹ A. Saleki-Gerhardt and G. Zografi, *Pharm. Res.* **11**, 471 (1994).
- ¹² SL Shamblin, BC Hancock, and MJ Pikal, *Pharm. Res.* **23**, 2254 (2006).
- ¹³ XC Tang, MJ Pikal, and LS Taylor, *Pharm. Res.* **19**, 477 (2002).
- ¹⁴ XC Tang, MJ Pikal, and LS Taylor, *Pharm. Res.* **19**, 484 (2002).
- ¹⁵ L. Gunawan, GP Johari, and RM Shanker, *Pharm. Res.* **23**, 967 (2006).
- ¹⁶ PJ. Marsac, H. Konno, and LS Taylor, *Pharm. Res.* **23**, 2306 (2006).
- ¹⁷ P Gupta, R Thilagavathi, AK Chakraborti, and AK Bansal, *Mol. Pharm.* **2**, 384 (2005).
- ¹⁸ M. Iwamatsu, *J. Chem. Phys.* **126**, 134703 (2007).
- ¹⁹ PF James, *J. Non-Cryst. Solids* **73**, 517 (1985).
- ²⁰ *Disordered Pharmaceutical Materials*, edited by Marc Descamps (Wiley VCH, 2016).