molecular pharmaceutics

Article

Cite This: Mol. Pharmaceutics 2018, 15, 4247−4256

pubs.acs.org/molecularpharmaceutics

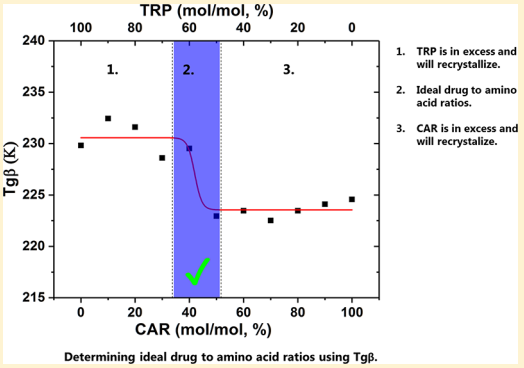
The Role of Glass Transition Temperatures in Coamorphous Drug−Amino Acid Formulations

Eric Ofosu Kissi, Georgia Kasten, Korbinian Löbmann, Thomas Rades,* and Holger Grohganz

Department of Pharmacy, University of Copenhagen, DK-2100 Copenhagen Ø, Denmark

Supporting Information

ABSTRACT: The improved physical stability associated with coamorphous drug−amino acid (AA) formulations may indicate a decrease in mobility of the amorphous drug molecules, compared to the neat amorphous form of the drug. Since the characteristic glass transition temperatures ($T_{g\alpha}$ and $T_{g\beta}$) represent molecular mobility in amorphous systems, we aimed to characterize $T_{g\alpha}$ and $T_{g\beta}$ and to determine their role in physical stability as well as their potential usefulness to determine the presence of an excess component (either drug or AA) in coamorphous systems. Indomethacin (IND)−tryptophan (TRP) and carvedilol (CAR)−TRP were used as model coamorphous systems. The analytical techniques used were X-ray powder diffractometry (XRPD) to determine the solid-state form, dynamic mechanical analysis (DMA) to probe $T_{g\alpha}$ and $T_{g\beta}$, and differential scanning calorimetry (DSC) to probe thermal behavior of the coamorphous systems. $T_{g\alpha}$ analysis showed a gradual monotonous increase in $T_{g\alpha}$ values with increasing AA concentration, and this increase in the $T_{g\alpha}$ value is not the cause of the improved physical stability. The $T_{g\beta}$ analysis for the IND−TRP sample with 10% drug had a $T_{g\beta}$ of 226.8 K, and samples with 20−90% drug had similar $T_{g\beta}$ values around 212.5 K. For CAR−TRP, samples with 10−40% drug had similar $T_{g\beta}$ values around 230.5 K, and samples with 50−90% drug had similar $T_{g\beta}$ values around 223.3 K. The similar $T_{g\beta}$ values in coamorphous systems at different drug ratios indicate that they in fact are the $T_{g\beta}$ of the component that is in excess to an ideal drug−AA coamorphous mixture. DSC and XRPD analysis showed that for IND−TRP, IND is in excess if the drug concentration is 30% or above and will eventually recrystallize. For CAR−TRP, CAR is in excess and recrystallizes when the drug concentration is 50% or above. We have proposed a means of estimating, on the basis of $T_{g\beta}$, which drug to AA ratios will lead to optimally physically stable coamorphous systems that can be considered for further development.



Determining ideal drug to amino acid ratios using Tgβ.

KEYWORDS: *glass transition temperature, physical stability, coamorphous, dynamic mechanical analysis, excess component, β-relaxation*

1. INTRODUCTION

During the development of new medicines, critical drug properties such as their aqueous solubility and dissolution rate may be directly linked to drug absorption and hence the bioavailability of a drug.[1] Amorphous drug delivery systems are used as an approach to improve the solubility and thus potentially the bioavailability of poorly water-soluble drugs.[2] Amorphization is in principle a simple method; however, formulating drugs in the neat amorphous form often becomes a challenge, as the amorphous drug molecules have the tendency to revert to their crystalline form. However, recrystallization can be avoided by formulating the amorphous drugs together with stabilizing polymers or other excipients to form the so-called amorphous solid dispersions (ASDs).[3,4] More recently, coamorphous systems, which belong to the larger group of ASDs, have been introduced to the pharmaceutical field. In contrast to drug polymer amorphous dispersions, coamorphous formulations consist of two low molecular weight, initially crystalline, materials that upon coamorphization are mixed at the molecular level to form a single amorphous phase.[5,6] Both coamorphous drug−drug[5,7] and drug−excipient combinations have been described.[8,9] Coamorphous systems may stabilize the amorphous drug by molecular interactions, i.e., formation of heterodimers between the drug and coformer,[7,10] e.g., by hydrogen bonding or even formation of coamorphous salts.[8] As a result of molecular mixing and interactions, it is likely that the molecular mobility of the drug molecules in the resulting coamorphous system differs from that of the molecules in the neat amorphous drug.

An intrinsic property of amorphous (and coamorphous) systems is their temperature-dependent molecular mobility (relaxations), which is generally classified into α-relaxation (global mobility) and β-relaxation (local mobility). Dielectric[11−15] and nuclear magnetic resonance[11] spectroscopy have confirmed the presence of α- and β-relaxations also in binary

Received: June 21, 2018
Revised: July 17, 2018
Accepted: July 18, 2018
Published: July 18, 2018

DOI: 10.1021/acs.molpharmaceut.8b00650
Mol. Pharmaceutics 2018, 15, 4247−4256

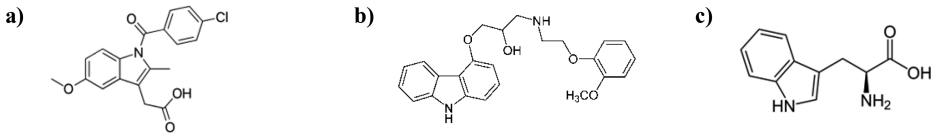


Figure 1. Chemical structures of (a) indomethacin, (b) carvedilol, and (c) L-tryptophan.

Table 1. Composition of the Binary Mixtures of Carvedilol−Tryptophan (CAR−TRP) and Indomethacin−Tryptophan (IND−TRP) Used in This Study

	CAR−TRP				IND−TRP			
molar ratio (mol/mol, %)	CAR (mg)	TRP (mg)	w_1[a]	w_2[a]	IND (mg)	TRP (mg)	w_1	w_2
0	0	1000	0	1.0	0	1000	0	1.0
10	181.09	818.91	0.18	0.82	162.94	837.06	0.16	0.84
20	332.25	667.75	0.33	0.67	304.58	695.42	0.30	0.70
30	460.32	539.68	0.46	0.54	428.84	571.16	0.43	0.57
40	570.23	429.77	0.57	0.43	538.74	461.26	0.54	0.46
50	665.58	334.42	0.67	0.33	636.62	363.38	0.64	0.36
60	749.08	250.92	0.75	0.25	724.36	275.64	0.72	0.28
70	822.82	177.18	0.82	0.18	803.45	196.55	0.80	0.20
80	888.41	111.59	0.89	0.11	875.12	124.88	0.88	0.12
90	947.12	52.88	0.95	0.05	940.36	59.64	0.94	0.06
100	1000	0	1.0	0	1000	0	1.0	0

[a] w_1 and w_2 are defined in eq 1.

amorphous systems. In the current study, we utilize dynamic mechanical analysis (DMA), which does not probe the characteristic dielectric relaxation time but readily probes the transition temperatures directly. Furthermore, differential scanning calorimetry (DSC) was used to investigate the thermal behavior and the α-relaxation of the coamorphous systems. The α-relaxation is basically responsible for the transition from the glassy to the supercooled liquid form and vice versa, and the corresponding temperature for this transition is termed the primary glass transition temperature ($T_{g\alpha}$). This transition process occurs at a comparatively high temperature where interaction and reorientation of the molecules depend on other surrounding molecules;[16] hence at $T_{g\alpha}$, the motions of the molecules become cooperative, and the degree of cooperativeness increases as the number of participating molecules increases.[17] Several studies, mostly performed above the $T_{g\alpha}$, have linked α-relaxation times (which are the inverse of the frequencies at which an α-relaxation peak is found, e.g., in dielectric spectroscopy) in amorphous drugs, including nifedipine[18] and itraconazole,[19] to the crystallization kinetics of the drug. In coamorphous systems, an increase in $T_{g\alpha}$ is usually assumed to be linked to an increase in physical stability.[20]

The β-relaxation is a secondary molecular mobility that can be classified as a combination of independent molecular motions[17] and has a transition temperature at $T_{g\beta}$. The $T_{g\alpha}$ and $T_{g\beta}$ are the temperatures at which the molecules have sufficient thermal energy to overcome potential energy barriers and set the molecules in motion.[21,22] The β-relaxation can be further classified into noncooperative motion of individual molecules, referred to as Johari−Goldstein (JG) β-relaxation and the movement of side chains (non-JG relaxation).[23,24] Herein, we will refer to JG β-relaxation as β-relaxation unless otherwise stated. β-relaxation in glasses is universal in nature,[23] and in the pharmaceutical field, the study of β-relaxation in amorphous drugs has gained interest because of the oftentimes unsatisfactory nature of $T_{g\alpha}$ in predicting physical stability.[25] In a study involving nine amorphous drugs or drug-like compounds, we have developed a calibration curve based on $T_{g\beta}$ values of these compounds to predict the physical stability of neat amorphous drugs,[26] highlighting the potentially high importance of the β-relaxation in the development of amorphous drugs.

When a single-phase binary amorphous system, such as a coamorphous system, is formed, the molecular mobility and mechanical properties will differ from those of the respective neat amorphous forms.[15] This is perhaps most evident in the single $T_{g\alpha}$ obtained for such one-phase systems upon calorimetric analysis (DSC), which differs from the $T_{g\alpha}$ of the individual components and varies depending on the compound ratios. In ASDs, the resulting $T_{g\alpha}$ oftentimes is predictable using theoretical models including the Gordon−Taylor (GT) equation.[27]

In the study of coamorphous systems, an important question is that of the "ideal" ratio of drug to coformer. An "ideal" ratio is the drug to coformer combination where both the drug and the coformer do not recrystallize upon long-term storage.[10,28] The presence of an excess component (which can be the drug or the coformer) might be sufficient to set the drug or the coformer to recrystallize. However, characterizing the presence of an excess component is difficult to achieve with calorimetric analysis.[29] In the current study, we have used indomethacin and carvedilol as model drugs, and tryptophan as coformer, to investigate the glass transition temperatures ($T_{g\alpha}$ and $T_{g\beta}$) in coamorphous systems by DMA. The $T_{g\beta}$ in these systems was interpreted as a qualitative measure of the presence of an excess component. We have supported this interpretation with calorimetric analysis and recrystallization studies. The $T_{g\beta}$ determines which component is in excess to the "ideal" drug to amino acid (AA) ratio, and the excess component will determine the physical stability of the coamorphous mixtures as it will eventually recrystallize.

DOI: 10.1021/acs.molpharmaceut.8b00650
Mol. Pharmaceutics 2018, 15, 4247−4256

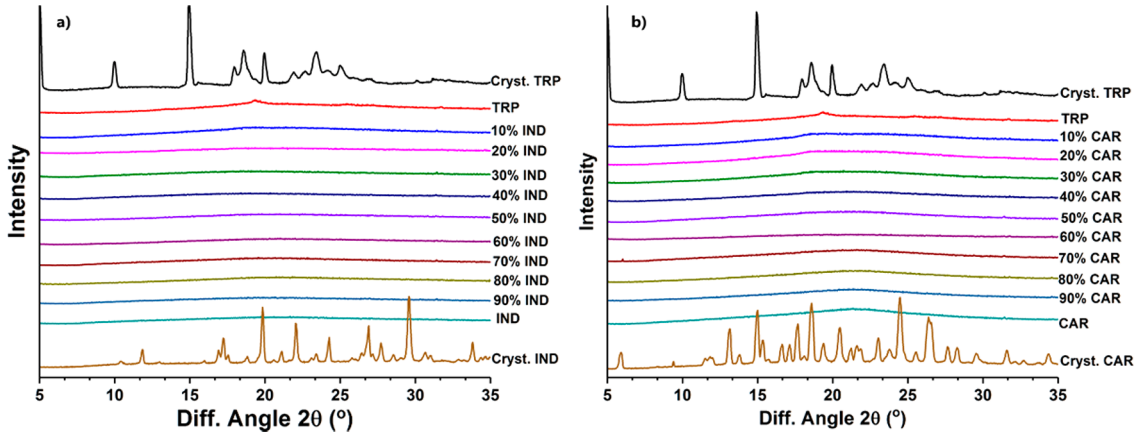


Figure 2. XRPD diffractograms for (a) IND−TRP and (b) CAR−TRP mixtures after 90 min of ball milling. The diffractograms of the starting materials before and after milling are also shown.

2. MATERIALS AND METHODS

2.1. Materials. Two drugs were used in this study: γ-indomethacin (IND, MW = 357.79 g/mol), which was purchased from Hawkins Pharmaceutical group (Minneapolis, USA), and carvedilol (CAR, MW = 406.48 g/mol), which was purchased from Cipla Ltd. (Mumbai, India). L-Tryptophan (TRP, MW = 204.23 g/mol) was used as the coformer and was purchased from Sigma-Aldrich (St. Louis, USA). All substances (see Figure 1 for their chemical structures) were of reagent grade and used as received.

2.2. Methods. *2.2.1. Preparation of Coamorphous Samples by Ball Milling.* Vibrational ball milling (BM) was used to prepare the coamorphous samples between drug and coformer. Briefly, a total of 1000 mg of powder containing the drug (CAR or IND) and the amino acid (TRP) at various molar ratios (Table 1) were milled with two 12 mm diameter stainless steel balls in 25 mL milling jars. The ball mill (Mixer mill MM400, Retsch GmbH & Co., Haan, Germany) was placed in a cold room (+ 6 °C), and the binary mixtures were milled for 90 min at a frequency of 30 Hz. In addition, BM was also used to obtain the amorphous form of the pure crystalline starting materials. All percentages of the samples expressed throughout this paper are in molar ratios (mol/mol, %).

2.2.2. X-ray Powder Diffraction (XRPD). XRPD measurements were performed using an X'Pert PANalytical PRO X-ray diffractometer (PANalytical, Almelo, The Netherlands) with Cu Kα radiation (1.54187 Å), and the acceleration voltage and current were 45 kV and 40 mA, respectively. The samples were scanned in reflectance mode between 5 and 35° 2θ, with a scan rate of 0.0625° 2θ/sec and a step size of 0.026° 2θ. The data were analyzed using the X'Pert Data Collector software (PANalytical, Almelo, The Netherlands).

2.2.3. Differential Scanning Calorimetry (DSC). DSC measurements were performed with a Discovery DSC (TA Instruments−Waters LLC, New Castle, USA), under nitrogen flow of 50 mL/min. Samples of approximately 1−6 mg were weighed into Tzero aluminum pans and sealed with Tzero lids. Thermal behavior of the coamorphous samples after BM was conducted in the modulated temperature mode, with a heating rate of 2 K/min, an amplitude of 0.212 K, and a period of 40 s. Duplicate measurements were made, and the experimental primary glass transition temperatures ($T_{g\alpha,DSC}$, midpoint) were recorded from the reversing heat flow signal. The thermal behavior of the crystalline physical mixture was measured.

2.2.3.1. Theoretical $T_{g\alpha}$ Values (Gordon−Taylor Equation). The theoretical $T_{g\alpha}$ values for the coamorphous samples were calculated using the Gordon−Taylor equation (eq 1)

$$T_{g12} = \frac{w_1 \cdot T_{g1} + K \cdot w_2 \cdot T_{g2}}{w_1 + K \cdot w_2} \quad (1)$$

where T_{g12} is the calculated $T_{g\alpha}$ value (in K) for the coamorphous samples, w_1 and w_2 are the weight ratios of the drug and the amino acid, respectively; and T_{g1} and T_{g2} are the experimentally determined $T_{g\alpha}$s of the neat amorphous components. The constant K was calculated using eq 2

$$K = \frac{T_{g1} \cdot \rho_1}{T_{g2} \cdot \rho_2} \quad (2)$$

where ρ_1 and ρ_2 are the density of the crystalline drug ($[\rho_{Crys\_CAR}$ = 1.275 g/cm$^3]$[30] or $[\rho_{Crys\_IND}$ = 1.379 g/cm$^3]$[10]) and the crystalline amino acid (ρ_{Crys_TRP} = 1.303 g/cm^3),[31] respectively. Densities of crystalline substances were used, because TRP could not be prepared in a fully amorphous form, and no literature value for the amorphous form was available.

2.2.4. Dynamic Mechanical Analysis (DMA). The transition temperatures of the coamorphous samples were measured using DMA. Details of this method have been presented elsewhere.[26] Briefly, the $T_{g\alpha}$ and $T_{g\beta}$ of the neat amorphous and coamorphous samples were investigated using a DMA Q800 (TA Instruments−Waters LLC, New Castle, DE, USA). Coamorphous samples of approximately 100 mg were loaded into the powder pocket sample holder and measured using a multifrequency strain sweep method. Duplicate DMA scans were made from 153 K to the DMA measured $T_{g\alpha}$ ($T_{g\alpha,DMA}$) using a heating rate of 3 K/min, an amplitude of 20.00 μm, and a frequency of 1 Hz.

2.2.5. Physical Stability upon Storage. Physical stability of the coamorphous samples was determined at stress conditions (for IND−TRP at 403 K and for CAR−TRP at 373 K). CAR−TRP samples were also stored under dry conditions in a desiccator at 313 K and investigated for their recrystallization tendency after 62 weeks by XRPD (see above).

3. RESULTS AND DISCUSSION

3.1. Preparation of Coamorphous Samples. The absence of peaks and the presence of the characteristic halo pattern in an XRPD diffractogram are an indication of the

DOI: 10.1021/acs.molpharmaceut.8b00650
Mol. Pharmaceutics 2018, 15, 4247−4256

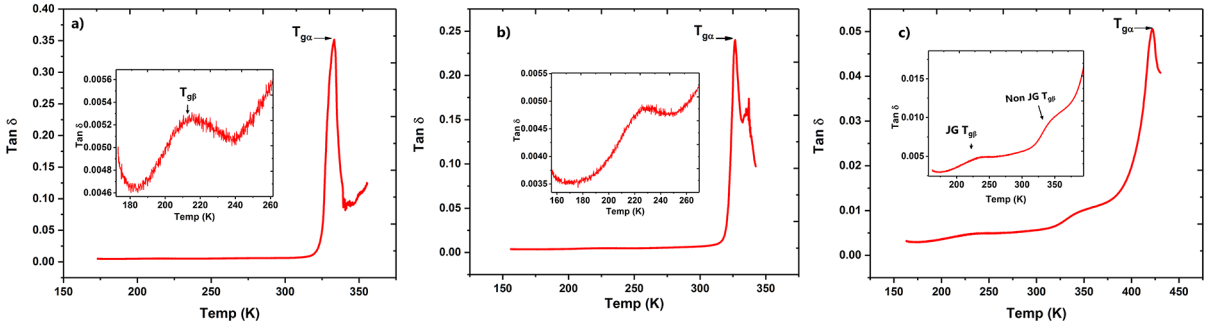


Figure 3. Transition temperatures in amorphous (a) IND, (b) CAR, and c) TRP. The insets are zoomed in sections showing the $T_{g\beta}$.

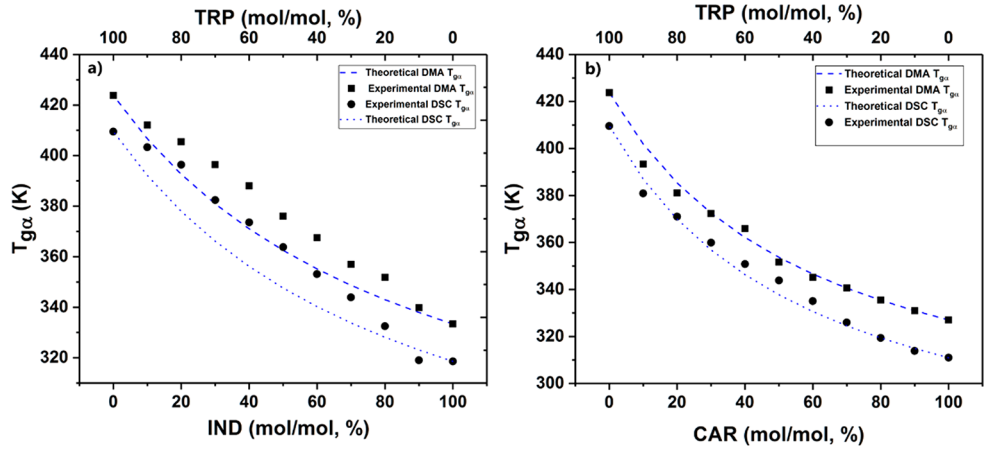


Figure 4. Evolution of $T_{g\alpha}$ in (a) IND−TRP and (b) CAR−TRP coamorphous samples (circles for DSC measured $T_{g\alpha}$, and squares for DMA measured $T_{g\alpha}$).

amorphousness of the sample. The diffractograms of the starting materials (crystalline IND, CAR, and TRP), of the neat amorphous components and of the drug−amino acid (AA) mixtures after 90 min of ball milling are shown in Figure 2a,b.

The neat crystalline drugs (CAR and IND) were fully amorphous after 90 min of ball milling, as shown by the lack of peaks in the respective diffractograms. Crystalline TRP, however, showed residual crystallinity even when subjected to 180 min of milling. The diffractograms of all drug−AA binary mixtures showed no peaks, indicating that coamorphization was successful after 90 min of ball milling.

3.2. Characterization of Transition Temperatures (T_gs) with DMA in Neat Amorphous Components. To determine the temperature range at which there is sufficient thermal energy for the molecules in the neat amorphous materials to begin noncooperative and cooperative motions, the drugs IND and CAR, and the coformer TRP (still containing some residual crystallinity) were studied.

The T_gs were determined from the temperatures corresponding to the peak maximum of the tan δ signal. IND (Figure 3a) has a $T_{g\beta}$ at around 212.8 K and a $T_{g\alpha,\mathrm{DMA}}$ at around 333.4 K, while CAR has a $T_{g\beta}$ at around 224.6 K and a $T_{g\alpha,\mathrm{DMA}}$ at around 327.0 K (Figure 3b). These results are similar to the T_gs obtained in our previous study where the samples were prepared by quench cooling,[26] and the theory behind these T_gs has been discussed in our earlier work.[22]

For TRP (Figure 3c), three T_gs could be detected between 153 and 430 K in the tan δ signal. The strongest transition at 424.2 K is the $T_{g\alpha,\mathrm{DMA}}$. At temperatures below the $T_{g\alpha,\mathrm{DMA}}$, two broad peaks were observed, and the peak maxima, at 229.8 and 343.2 K, respectively, are designated as $T_{g\beta}$s. Most neat amorphous materials studied with DMA only show a single peak below $T_{g\alpha}$, and thus, we provide an intuitive explanation why TRP has two peaks, i.e., between 185 and 273 as well as 320 and 370 K (Figure 3c). At low temperatures, between 185 and 273 K, individual TRP molecular motions are due to JG β-relaxation. However, when the temperature is around 320−370 K, the motion of the molecules results in a sufficiently large increase in free volume[32] such that the 3-methylindole side chains of TRP wiggle. As this event originates from a side chain motion, it may be ascribed to a non-JG β-relaxation. Non-JG β-relaxation can be confirmed if the transition observed in DMA is absent in terahertz spectroscopy, as the THz photon energy is not sufficient to probe side chain motions. However, further (vibrational spectroscopic) studies need to be undertaken to qualify this intuitive explanation.

3.3. Characterization of the $T_{g\alpha}$ of Coamorphous Samples Using DSC and DMA. Single $T_{g\alpha}$ values for all coamorphous samples were observed in the DSC thermograms as well as the DMA tan δ signals of the coamorphous samples, indicating homogeneous one-phase amorphous systems.[33] Since both techniques detect $T_{g\alpha}$, it is worth discussing their differences and similarities. The techniques detect $T_{g\alpha}$ differently, as a sigmoidal change in heat capacity for DSC and as a sharp decrease in the stiffness of the sample for DMA. The temperature at which the $T_{g\alpha}$ is measured differs between the two techniques, as can be seen in Figure 4. A temperature difference between 10 and 20 K is to be expected between the DMA and DSC values,[32] because in the DMA measurements,

DOI: 10.1021/acs.molpharmaceut.8b00650
Mol. Pharmaceutics 2018, 15, 4247−4256

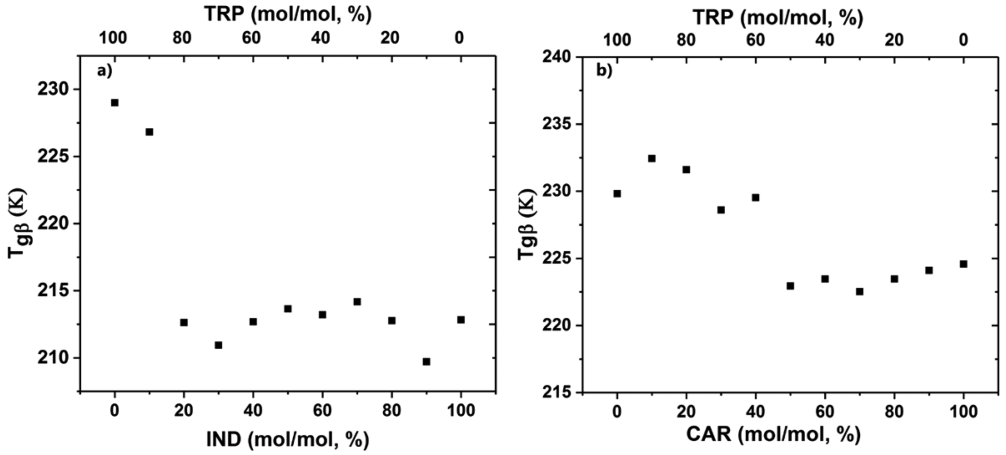


Figure 5. Evolution of $T_{g\beta}$ for (a) IND−TRP and (b) CAR−TRP coamorphous systems.

the mobility of the molecules corresponds to a relaxation time of 0.318 s at 1 Hz, while in a DSC measurement, the mobility at $T_{g\alpha}$ is generally regarded to correspond to a relaxation time of 100 s.[16] For short relaxation times, higher thermal energy is required, and the transition shifts to higher temperatures, and thus, $T_{g\alpha,DMA}$ values are higher, compared to $T_{g\alpha,DSC}$ values. However, there are also similarities in using both techniques to characterize $T_{g\alpha}$ in coamorphous samples. These include the presence of a single $T_{g\alpha}$, the fact that the samples either obey or disobey the GT equation, irrespective of the technique used (see below), and the finding that the difference in temperature of the $T_{g\alpha}$ between different materials is the same. For TRP and IND, for example, the difference in their $T_{g\alpha}$ values is approximately 90 K, using either DMA or DSC. On the basis of these similarities, it can be concluded that both techniques are adequate in characterizing the $T_{g\alpha}$ in coamorphous systems.

The $T_{g\alpha}$ values of the various coamorphous samples obtained theoretically and experimentally by DMA and DSC are shown in Figure 4a,b. The $T_{g\alpha,DMA}$ values of the coamorphous IND−TRP samples are between 337.9 and 412.1 K, and the $T_{g\alpha,DSC}$ values of these samples are between 319.0 and 403.3 K (Figure 4a). All $T_{g\alpha,DSC}$ values are in line with previous findings by Jensen et al.[29] Figure 4a also shows a deviation of the experimentally detected values from the theoretically predicted values based on the GT equation. Using the common interpretation of such deviations,[34] one will expect that there would be an interaction between IND−TRP. However, using FTIR and NMR spectroscopy, no interactions could be confirmed experimentally.[35,36] This somewhat undermines the assumption that a positive deviation from the GT equation is necessarily an indicator of intermolecular interactions. Indeed, Tobyn et al. have previously shown that the use of the GT equation is not a reliable predictor of molecular interactions.[37]

The $T_{g\alpha}$s found for the various CAR−TRP binary mixtures (Figure 4b) are between 331.0 and 393.3 K using DMA and between 313.8 and 380.9 K using DSC, and the $T_{g\alpha}$s show good agreement with the GT predictions. Irrespective of the behavior of coamorphous samples toward theoretical $T_{g\alpha}$ models, the monotonous increase in $T_{g\alpha}$ does not provide sufficient information on the solid-state properties of the amorphous forms, e.g., on their physical stability or the optimal ratio between drug and AA to form a coamorphous system (these properties are discussed in Sections 3.7 and 3.8). Therefore, it is necessary to further probe the molecular properties for the coamorphous CAR−TRP samples, which follow the GT prediction, and the coamorphous IND−TRP samples, which do not follow GT predictions, such that they can be correlated to physical stability or any other solid-state processes occurring in the system. To this end, the secondary glass transition temperature ($T_{g\beta}$) in the two sets of coamorphous samples was studied by DMA.

3.4. Characterization of the $T_{g\beta}$ in Coamorphous Samples Using DMA. Generally, the $T_{g\beta}$ in amorphous systems cannot be detected by DSC, as no signal change in the thermograms at temperatures below the $T_{g\alpha}$ can usually be found,[38] although Vyazovkin et al. upon annealing amorphous IND could detect the $T_{g\beta}$ using DSC.[39] Using DMA, $T_{g\beta}$ is readily probed, and annealing of the sample is not required. Therefore, the $T_{g\beta}$s of the various coamorphous samples were analyzed with DMA. A single broad peak was identified below the $T_{g\alpha}$ signal for all of the coamorphous samples, and the temperature corresponding to the peak maximum was taken as the $T_{g\beta}$.

The values obtained for the coamorphous IND−TRP samples are shown in Figure 5a. For the sample with 10% drug content, the $T_{g\beta}$ is at 226.8 K, while for samples with 20−90% drug content, the $T_{g\beta}$ was found between 209.7 and 214.1 K, irrespective of the drug concentration. The $T_{g\beta}$ for the sample with 10% drug content is similar to that of neat TRP, and the $T_{g\beta}$ values for the samples with 20−90% drug content are similar to that of neat IND. This indicates that at 10% drug content, the TRP molecules show a transition, while from 20 to 90% drug content, it is the IND molecules that show a transition.

The $T_{g\beta}$ values obtained for the coamorphous CAR−TRP samples are shown in Figure 5b. The $T_{g\beta}$ values obtained for samples with 10−40% drug content are between 228.6 and 232.4 K. For the samples with 50−90% drug content, the $T_{g\beta}$ is between 222.5 and 224.1 K, irrespective of the drug concentration. As for the CAR−TRP samples, the TRP molecules show a transition for samples with 10−40% drug content, while for samples with 50−90% drug content, it is the CAR molecules that show a transition.

From the similar $T_{g\beta}$ values of the various coamorphous samples, it can be concluded that for any drug to AA ratio, it is either the drug or the coformer that will show a transition. Since the $T_{g\beta}$ is an indication of the temperature at which noncooperative molecular motions of amorphous low molecular weight compounds occurs, it can be inferred that

DOI: 10.1021/acs.molpharmaceut.8b00650
Mol. Pharmaceutics 2018, 15, 4247−4256

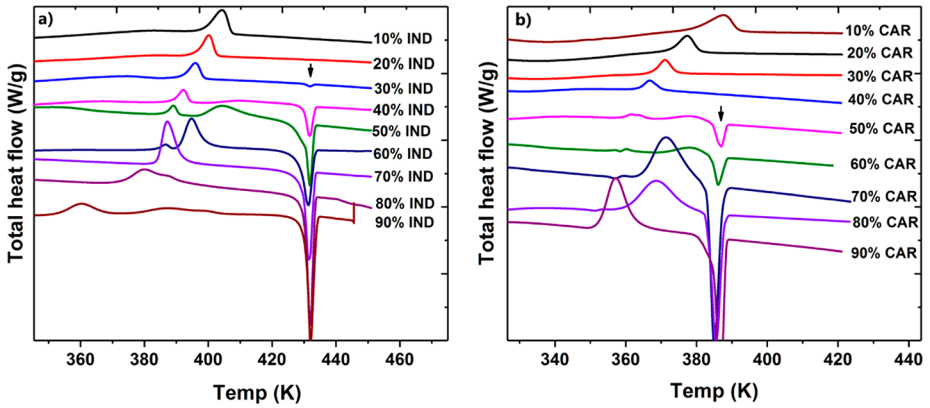


Figure 6. Thermograms of (a) IND−TRP and (b) CAR−TRP. The arrows show drug to TRP ratios from where on drug melting was observed.

depending on the drug to AA ratio, it is either the drug or the coformer (AA) molecules that begin to move in the coamorphous systems. Since these are coamorphous systems, it can be concluded that it is the drug or coformer, which is in excess that contributes to the $T_{g\beta}$ signal in the DMA analysis.

These findings, where an excess component is present in the coamorphous system, are in line with studies conducted on binary amorphous systems by Bock et al.[11] These authors studied β-relaxation using dielectric, ^{2}H, and ^{31}P NMR spectroscopy in tripropyl phosphate/polystyrene systems. They found that whereas the $T_{g\alpha}$ changes as a function of the composition, the β-relaxation processes did not change and concluded that the β-process is induced by a single component.[11]

Analyzing the $T_{g\alpha}$ of coamorphous systems using DMA gives information on the actual formation of a coamorphous form by observing a single $T_{g\alpha}$ value (in the same way that this would be possible by DSC). Additionally, the $T_{g\beta}$ measured with DMA corresponds to the motion of a single component, which may be regarded as the excess component in the coamorphous system.

3.5. Characterization of the Thermal Behavior of the Coamorphous Samples Using DSC. The presence of a melting endotherm during DSC analysis of coamorphous systems is an indication of crystallization in the initially fully amorphous samples during heating. When the drug component is stabilized by the coformer, it will remain in the amorphous form and thus not show a melting endotherm. Therefore, the presence or absence of a melting endotherm can be used as an indication of physical stability. To determine if the coamorphous samples will be physically stable, a DSC analysis was performed on the coamorphous samples.

The thermal behavior of the coamorphous samples was investigated up to approximately 20 K above the melting point (T_m) of the drugs because of degradation of the coamorphous samples (for example, using TGA analysis, 20% weight loss at 555 K was detected for CAR−TRP sample containing 45% drug, data not shown). In Figure 6a, the thermograms of the various IND−TRP samples are shown. The thermograms of the 10 and 20% drug samples do not show a melt endotherm. However, the thermograms of the 30−90% drug samples do show a melt endotherm with an onset at 430.0 K. Additionally, a gradual increase in the area under the melting peak (i.e., the melting endotherm) was observed as the ratio of the drug in the coamorphous samples increased. Crystalline IND has a T_m at 432.5 K (data not shown), which is an indication that it is indeed the IND that melts. By comparing the enthalpy (ΔH) of the melting endotherm of the drug in the crystalline physical mixture (PM) to that of the melts shown in Figure 6a, it was found that for the sample with 30% drug, approximately 2% of the drug fraction crystallized, whereas for the samples with 40−90% drug, 50−90% of the drug fraction crystallized. This would imply that IND recrystallizes out of the coamorphous IND−TRP sample and subsequently melts upon heating in a DSC measurement.

The thermograms of the CAR−TRP samples are shown in Figure 6b. The thermograms for the samples with 10−40% drug content did not show a melting endotherm. However, the thermograms of samples with 50−90% drug showed a melting endotherm with an onset at 383.8 K. Crystalline CAR has a T_m at 385.0 K (data not shown), and therefore, it is CAR that recrystallizes and melts in these samples. From the ΔH of the melting endotherm of the drug in the crystalline PM and the melts in Figure 6b, it was found that for samples with 50 and 60% drug, approximately 20 and 29% of the drug fraction crystallized, while for samples with 60−90% drug, 80−86% of the drug fraction crystallized.

In the thermograms shown in Figure 6a,b, recrystallization exotherms were observed for all the samples. However, since we are dealing with binary systems, a single recrystallization exotherm is difficult to interpret, and thus, further analysis was performed to determine what was recrystallizing. This will be discussed in the next section.

From the thermal behavior of the coamorphous samples, it can be concluded that at specific drug ratios, i.e., from 30 to 90% drug content in IND−TRP and from 50 to 90% drug content in CAR−TRP coamorphous samples, the drug recrystallizes and subsequently melts. The presence of a melt and the corresponding increase in the area under the melting peak with increasing drug concentration are indications of the presence of an excess drug component. These coamorphous samples, i.e., for IND−TRP, from 30 to 90% drug content, have a similar $T_{g\beta}$. Similarly, for CAR−TRP, from 50 to 90% drug content, the coamorphous samples again have a similar $T_{g\beta}$. So far, we can link the $T_{g\beta}$ as a qualitative measure of the mobility of the excess component to recrystallization of (excess) drug in coamorphous systems.

3.6. Characterization of the Solid-State Form upon Storage. Solid-state analysis was performed using XRPD to determine the physical stability of the coamorphous samples upon storage. The storage temperatures were selected from the recrystallization temperature of the samples with 10% drug

DOI: 10.1021/acs.molpharmaceut.8b00650
Mol. Pharmaceutics 2018, 15, 4247−4256

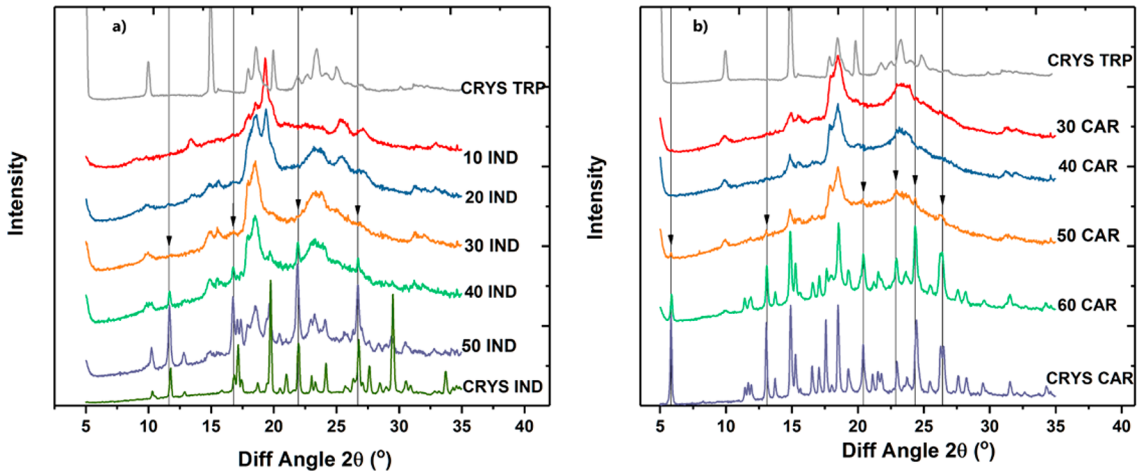


Figure 7. XRPD diffractograms of selected (a) IND−TRP samples kept at 403 K for 20 min and (b) CAR−TRP samples stored at 373 K for 20 min. The diffractograms of the crystalline starting materials are shown, and arrows in the figures show peaks of the crystallized drugs.

while considering also that the crystallized drug in the other samples should not melt during the test; hence, storage temperatures of 403 and 373 K were selected for IND−TRP and CAR−TRP, respectively. For IND−TRP, fresh samples containing 10−50% drug were kept in an oven at 403 K for 20 min, and the solid-state form was subsequently analyzed with XRPD. The diffractograms for samples with 10 and 20% drug content show that TRP recrystallizes (Figure 7) without a trace of crystalline IND peaks. In contrast, for samples with 30% drug content onward, indomethacin peaks can be identified (see arrows in Figure 7a).

For CAR−TRP, fresh samples containing 30−60% drug were kept at 373 K for 20 min and again analyzed with XRPD. The diffractograms for samples containing 40% drug or below showed that TRP recrystallizes, and there is no evidence of crystalline CAR peaks in the diffractograms. In contrast, CAR crystal peaks could be detected in samples containing 50% drug or more (see arrows in Figure 7b), and peaks of crystalline TRP were not visible.

The storage studies were performed at a relatively high temperature and did show that for IND−TRP the IND is stabilized in the coamorphous form when the drug ratio is below 30%. For CAR−TRP, CAR is stabilized in the coamorphous form when the drug content is below 50%. To determine if these results translate to lower storage temperatures, we stored CAR−TRP at 313 K for 62 weeks and analyzed the solid-state forms using XRPD. From Figure 8, it can be seen that the diffractograms of the samples containing 10−40% drug showed TRP peaks. Samples containing 50% or more drug showed CAR peaks, indicating that at these drug to AA ratios, CAR crystallized (enlarged version of diffractograms of samples with 20, 30, 60, and 70% drug are shown in the Supporting Information). Thus, the same tendency was observed as for the samples that were analyzed at relatively high storage temperature.

3.7. $T_{g\beta}$ and Physical Stability of Coamorphous Systems. In our previous study on neat amorphous drugs, we have shown that it is possible to predict physical stability from the $T_{g\beta}$ values of the amorphous drugs.[26] In the coamorphous systems analyzed, it is not possible to predict the physical stability solely on the $T_{g\beta}$ values. Other parameters including molecular interaction and the degree of intimate molecular mixing need to be taken into consideration. We

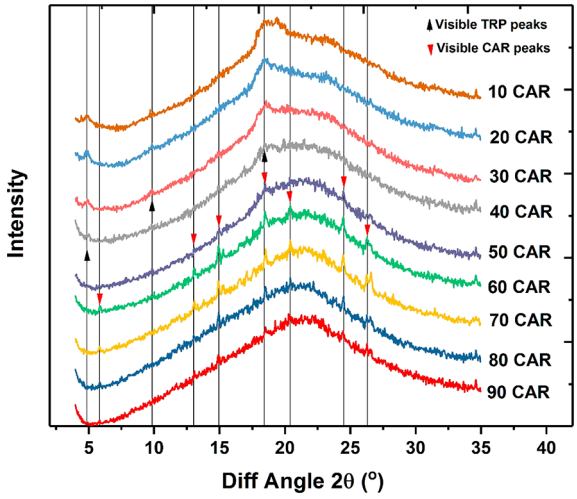


Figure 8. Diffractogram of the CAR−TRP samples after 62 weeks of storage under dry conditions at 313 K. Black arrows represent drug to AA ratios where TRP peaks are visible, and red arrows represent ratios where CAR peaks are visible.

herein discuss some factors based on the motion of the molecules that may provide a stabilization effect. The first stabilization factor is provided by hindered motion of the drug molecules because of the presence of the AA molecules. This can be seen in the increase in the temperature difference between $T_{g\alpha.DMA}$ and $T_{g\beta}$ (δT_g) shown in Figure 9. For a neat amorphous drug, the thermal energy required for a transition from a noncooperative to cooperative molecular motion is constant (data not shown). However, as AAs are added and their concentration increases, so does the thermal energy required for the transition from the noncooperative to cooperative molecular motion.

The second stabilizing factor is the motion of the coamorphous molecules; conceptualized here as two molecules that form a heterodimer[40] and move as an entity. When the coamorphous molecules are in motion, it is intuitive (and indeed has been shown, e.g., for carbamazepine−nicotinamide systems[41]) that they should nucleate and recrystallize into a respective cocrystal form. However, for the coamorphous systems studied here, and also for some coamorphous drug−drug systems,[42] there is no indication of cocrystal formation

DOI: 10.1021/acs.molpharmaceut.8b00650
Mol. Pharmaceutics 2018, 15, 4247−4256

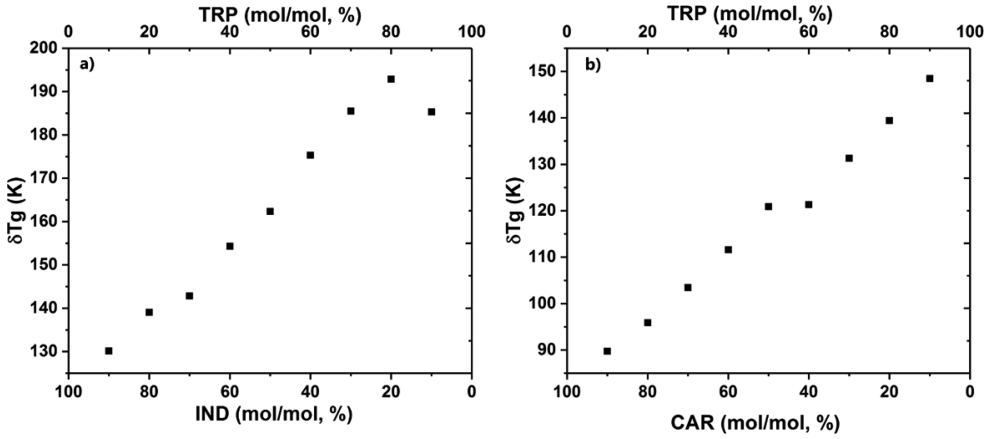


Figure 9. Temperature difference between $T_{g\alpha.DMA}$ and $T_{g\beta}$ (δT_g) for (a) IND−TRP and (b) CAR−TRP.

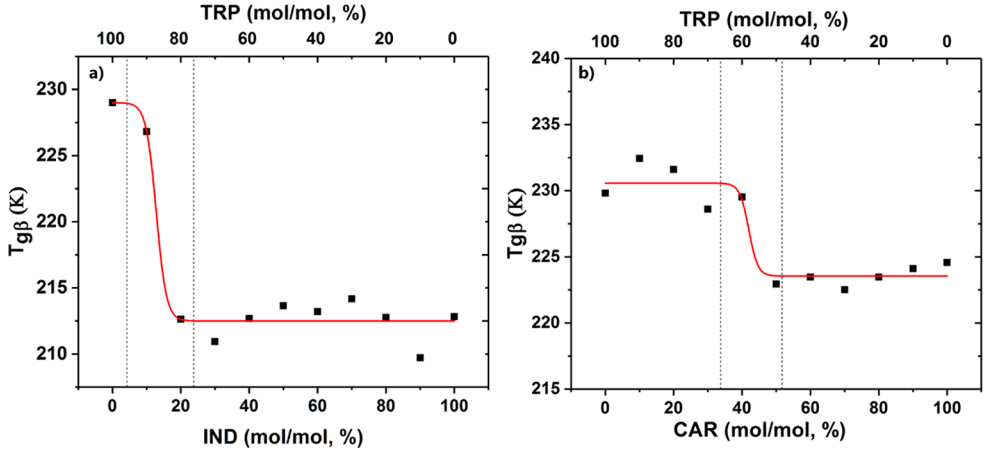


Figure 10. Predicting optimal drug to AA ratios with respect to physical stability using the $T_{g\beta}$ of (a) IND−TRP and (b) CAR−TRP coamorphous systems.

upon recrystallization. This means that the coamorphous molecules may be mobile but do not find a cocrystallizing partner, and hence, their motion will not lead to recrystallization. Therefore, in terms of the physical stability, the focus should be on the drug to amino acid ratios, in which no excess components (either the drug or the AA) are found, as those with excess component will eventually recrystallize.

3.8. Prediction of the Optimal Drug to Amino Acid Ratios in Coamorphous Formulations with Regard to Physical Stability. Optimal physical stability in coamorphous systems implies ratios of drug to coformer in which the amorphous drug will be stabilized over long periods of time. Here we aim to provide a means of predicting these ratios from $T_{g\beta}$ values. As seen in Figure 10a,b, there is a sigmoidal change in $T_{g\beta}$ values with increasing drug concentration. Specifically, for IND−TRP in Figure 10a, there is a sharp change between samples containing 5−24% drug. For CAR−TRP in Figure 10b, the sigmoidal change ranges from samples containing 34−52% drug.

For coamorphous systems, the β-process originates from a single component,[11] and its mobility is characterized by the $T_{g\beta}$. From the $T_{g\beta}$ values obtained for the drug−AA mixtures studied here, the optimal IND−TRP ratios are represented by samples that contain 5−24% drug and for CAR−TRP by samples containing 34−52% drug. The optimal drug to AA ratios determined here for IND−TRP and CAR−TRP correlate well with the results of the physical stability study using XRPD (absence of crystalline drug peaks) and the thermal behavior studies using DSC (the absence of a melting endotherm).

The use of $T_{g\beta}$ values in predicting optimal drug ratios of coamorphous systems with respect to physical stability represents a novel and systematic approach in selecting drug loading ratios.

4. CONCLUSIONS

The $T_{g\alpha}$ and $T_{g\beta}$ have been investigated in two coamorphous systems (IND−TRP and CAR−TRP). For IND−TRP, the $T_{g\alpha}$ did not follow the GT equation. The $T_{g\beta}$ of coamorphous samples with 10% drug was found at 226.8 K, and for samples containing 20−90% drug, $T_{g\beta}$ values between 209.7 and 214.1 K were found irrespective of drug content. For CAR−TRP, the $T_{g\alpha}$ did follow the GT equation. Similar $T_{g\beta}$ values (between 228.6 and 232.4 K) were found for CAR−TRP samples containing 10−40% drug. For the 50−90% drug ratio, similar $T_{g\beta}$ values between 222.5 and 224.6 K were found for all samples. Similar $T_{g\beta}$ values irrespective of drug content were interpreted as a qualitative measure of an excess component in the analyzed coamorphous samples. Thermal and physical stability studies indicated that the excess components recrystallize and subsequently melt. This confirms the assumptions that $T_{g\beta}$ represents the motions of excess components.

DOI: 10.1021/acs.molpharmaceut.8b00650
Mol. Pharmaceutics 2018, 15, 4247−4256

The improved physical stability of coamorphous systems may be influenced by hindered molecular motions of the drug molecules by addition of the AA. Hindered motions were confirmed by the increase in the temperature difference between $T_{g\alpha.DMA}$ and $T_{g\beta}$ (δT_g). The motions of the coamorphous molecules (heterodimer as an entity) may not lead to crystallization because of the inability of the coamorphous molecules to crystallize to a cocrystal. Physical stability is thus controlled by the presence of an excess component, which can be determined by measuring the $T_{g\beta}$. We presented a means of determining optimal drug to amino acid ratios with respect to physical stability based on the $T_{g\beta}$ of the coamorphous samples. For IND−TRP, 5−24% drug content and for CAR−TRP, 34−52% drug content were found to be ideal ratios in terms of physical stability.

Finally, $T_{g\alpha}$ does not provide adequate information on the presence of an excess component in coamorphous systems. On the other hand, $T_{g\beta}$ is an important parameter in characterizing coamorphous drug−AA formulations and can be used to detect the presence of excess components. Once excess components are identified, the optimal drug−AA ratio needed for formulation development can be determined.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.molpharmaceut.8b00650.

Diffractograms of CAR−TRP samples with 20, 30, 60 and 70% drug after long-term physical stability study (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: thomas.rades@sund.ku.dk; Telephone: +45 35 33 60 32.

ORCID

Eric Ofosu Kissi: 0000-0001-9301-9939

Thomas Rades: 0000-0002-7521-6020

Holger Grohganz: 0000-0002-0482-1397

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Amidon, G. L.; Lennernas, H.; Shah, V. P.; Crison, J. R. A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability. *Pharm. Res.* **1995**, *12*, 413−20.

(2) Kawabata, Y.; Wada, K.; Nakatani, M.; Yamada, S.; Onoue, S. Formulation Design for Poorly Water-Soluble Drugs Based on Biopharmaceutics Classification System: Basic Approaches and Practical Applications. *Int. J. Pharm.* **2011**, *420*, 1−10.

(3) Chiou, W. L.; Riegelman, S. Pharmaceutical Applications of Solid Dispersion Systems. *J. Pharm. Sci.* **1971**, *60*, 1281−1302.

(4) Bikiaris, D. N. Solid Dispersions, Part I: Recent Evolutions and Future Opportunities in Manufacturing Methods for Dissolution Rate Enhancement of Poorly Water-Soluble Drugs. *Expert Opin. Drug Delivery* **2011**, *8*, 1501−19.

(5) Dengale, S. J.; Ranjan, O. P.; Hussen, S. S.; Krishna, B. S. M.; Musmade, P. B.; Gautham Shenoy, G.; Bhat, K. Preparation and Characterization of Co-Amorphous Ritonavir−Indomethacin Systems by Solvent Evaporation Technique: Improved Dissolution Behavior and Physical Stability without Evidence of Intermolecular Interactions. *Eur. J. Pharm. Sci.* **2014**, *62*, 57−64.

(6) Laitinen, R.; Löbmann, K.; Strachan, C. J.; Grohganz, H.; Rades, T. Emerging Trends in the Stabilization of Amorphous Drugs. *Int. J. Pharm.* **2013**, *453*, 65−79.

(7) Alleso, M.; Chieng, N.; Rehder, S.; Rantanen, J.; Rades, T.; Aaltonen, J. Enhanced Dissolution Rate and Synchronized Release of Drugs in Binary Systems Through Formulation: Amorphous Naproxen-Cimetidine Mixtures Prepared by Mechanical Activation. *J. Controlled Release* **2009**, *136*, 45−53.

(8) Huang, Y.; Zhang, Q.; Wang, J. R.; Lin, K. L.; Mei, X. Amino Acids as Co-Amorphous Excipients for Tackling the Poor Aqueous Solubility of Valsartan. *Pharm. Dev. Technol.* **2017**, *22*, 69−76.

(9) Löbmann, K.; Grohganz, H.; Laitinen, R.; Strachan, C.; Rades, T. Amino Acids as Co-Amorphous Stabilizers for Poorly Water Soluble Drugs − Part 1: Preparation, Stability and Dissolution Enhancement. *Eur. J. Pharm. Biopharm.* **2013**, *85*, 873−881.

(10) Löbmann, K.; Laitinen, R.; Grohganz, H.; Gordon, K. C.; Strachan, C.; Rades, T. Coamorphous Drug Systems: Enhanced Physical Stability and Dissolution Rate of Indomethacin and Naproxen. *Mol. Pharmaceutics* **2011**, *8*, 1919−1928.

(11) Bock, D.; Kahlau, R.; Micko, B.; Pötzschner, B.; Schneider, G. J.; Rössler, E. A. On the Cooperative Nature of the β-Process in Neat and Binary Glasses: A Dielectric and Nuclear Magnetic Resonance Spectroscopy Study. *J. Chem. Phys.* **2013**, *139*, 064508.

(12) Knapik, J.; Wojnarowska, Z.; Grzybowska, K.; Jurkiewicz, K.; Tajber, L.; Paluch, M. Molecular Dynamics and Physical Stability of Coamorphous Ezetimib and Indapamide Mixtures. *Mol. Pharmaceutics* **2015**, *12*, 3610−3619.

(13) Capaccioli, S.; Kessairi, K.; Prevosto, D.; Lucchesi, M.; Ngai, K. L. Genuine Johari−Goldstein β-Relaxations in Glass-Forming Binary Mixtures. *J. Non-Cryst. Solids* **2006**, *352*, 4643−4648.

(14) Shahin Thayyil, M.; Capaccioli, S.; Rolla, P. A.; Ngai, K. L. The Component Dynamics of Miscible Binary Mixtures of Glass Formers: *Philos. Mag.* **2008**, *88*, 4047−4055.

(15) Ngai, K. L.; Capaccioli, S. Changes of the Primary and Secondary Relaxation of Sorbitol in Mixtures with Glycerol. *J. Phys. Chem. B* **2004**, *108*, 11118−11123.

(16) Grzybowska, K.; Capaccioli, S.; Paluch, M. Recent Developments in the Experimental Investigations of Relaxations in Pharmaceuticals by Dielectric Techniques at Ambient and Elevated Pressure. *Adv. Drug Delivery Rev.* **2016**, *100*, 158−182.

(17) Ngai, K. L.; Capaccioli, S.; Shinyashiki, N.; Thayyil, M. S. Recent Progress in Understanding Relaxation in Complex Systems. *J. Non-Cryst. Solids* **2010**, *356*, 535−541.

(18) Kothari, K.; Ragoonanan, V.; Suryanarayanan, R. Influence of Molecular Mobility on the Physical Stability of Amorphous Pharmaceuticals in the Supercooled and Glassy States. *Mol. Pharmaceutics* **2014**, *11*, 3048−3055.

(19) Bhardwaj, S. P.; Arora, K. K.; Kwong, E.; Templeton, A.; Clas, S.-D.; Suryanarayanan, R. Correlation Between Molecular Mobility and Physical Stability of Amorphous Itraconazole. *Mol. Pharmaceutics* **2013**, *10*, 694−700.

(20) Dengale, S. J.; Grohganz, H.; Rades, T.; Löbmann, K. Recent Advances in Co-amorphous Drug Formulations. *Adv. Drug Delivery Rev.* **2016**, *100*, 116−125.

(21) Goldstein, M. Viscous Liquids and the Glass Transition: A Potential Energy Barrier Picture. *J. Chem. Phys.* **1969**, *51*, 3728−3739.

(22) Ruggiero, M. T.; Krynski, M.; Kissi, E. O.; Sibik, J.; Markl, D.; Tan, N. Y.; Arslanov, D.; van der Zande, W.; Redlich, B.; Korter, T. M.; Grohganz, H.; Löbmann, K.; Rades, T.; Elliott, S. R.; Zeitler, J. A. The Significance of the Amorphous Potential Energy Landscape for Dictating Glassy Dynamics and Driving Solid-State Crystallisation. *Phys. Chem. Chem. Phys.* **2017**, *19*, 30039−30047.

(23) Johari, G. P.; Goldstein, M. Viscous Liquids and Glass Transition II. Secondary Relaxations in Glasses of Rigid Molecules. *J. Chem. Phys.* **1970**, *53*, 2372−2388.

DOI: 10.1021/acs.molpharmaceut.8b00650
Mol. Pharmaceutics 2018, 15, 4247−4256

(24) Ngai, K. L.; Paluch, M. Classification of Secondary Relaxation in Glass-Formers Based on Dynamic Properties. *J. Chem. Phys.* **2004**, *120*, 857−873.
(25) Bhattacharya, S.; Suryanarayanan, R. Local Mobility in Amorphous Pharmaceuticals-Characterization and Implications on Stability. *J. Pharm. Sci.* **2009**, *98*, 2935−2953.
(26) Kissi, E. O.; Grohganz, H.; Löbmann, K.; Ruggiero, M. T.; Zeitler, J. A.; Rades, T. Glass-Transition Temperature of the β-Relaxation as the Major Predictive Parameter for Recrystallization of Neat Amorphous Drugs. *J. Phys. Chem. B* **2018**, *122*, 2803−2808.
(27) Gordon, M.; Taylor, J. S. Ideal Copolymers and the Second-Order Transitions of Synthetic Rubbers. I. Non-Crystalline Copolymers. *J. Appl. Chem.* **1952**, *2*, 493−500.
(28) Beyer, A.; Grohganz, H.; Löbmann, K.; Rades, T.; Leopold, C. S. Influence of the Cooling Rate and the Blend Ratio on the Physical Stability of Co-Amorphous Naproxen/Indomethacin. *Eur. J. Pharm. Biopharm.* **2016**, *109*, 140−148.
(29) Jensen, K. T.; Larsen, F. H.; Löbmann, K.; Rades, T.; Grohganz, H. Influence of Variation In Molar Ratio on Co-Amorphous Drug-Amino Acid Systems. *Eur. J. Pharm. Biopharm.* **2016**, *107*, 32−39.
(30) Beattie, K.; Phadke, G.; Novakovic, J. Chapter Four—Carvedilol. In *Profiles of Drug Substances, Excipients, and Related Methodology*; Brittain, H. G., Ed.; Academic Press, 2013; Vol. *38*, pp 113−157.
(31) Berlin, E.; Pallansch, M. J. Densities of Several Proteins and L-Amino Acids in the Dry State. *J. Phys. Chem.* **1968**, *72*, 1887−1889.
(32) Menard, K. P. Time−Temperature Scans: Transitions in Polymers. *Dynamic Mechanical Analysis: A Practical Introduction*, 1st ed.; CRC Press: New York, 1999.
(33) Chiou, W. L.; Riegelman, S. Pharmaceutical Applications of Solid Dispersion Systems. *J. Pharm. Sci.* **1971**, *60*, 1281−302.
(34) Qi, S. Thermal Analysis of Pharmaceuticals. In *Analytical Techniques in the Pharmaceutical Sciences*; Müllertz, A., Perrie, Y., Rades, T., Eds.; *Advances in Delivery Science and Technology*; Springer: New York, 2016; pp 363−387.
(35) Löbmann, K.; Laitinen, R.; Strachan, C.; Rades, T.; Grohganz, H. Amino Acids as Co-Amorphous Stabilizers for Poorly Water-Soluble Drugs-Part 2: Molecular Interactions. *Eur. J. Pharm. Biopharm.* **2013**, *85*, 882−888.
(36) Jensen, K. T.; Larsen, F. H.; Cornett, C.; Löbmann, K.; Grohganz, H.; Rades, T. Formation Mechanism of Coamorphous Drug−Amino Acid Mixtures. *Mol. Pharmaceutics* **2015**, *12*, 2484−2492.
(37) Tobyn, M.; Brown, J.; Dennis, A. B.; Fakes, M.; Gao, Q.; Gamble, J.; Khimyak, Y. Z.; McGeorge, G.; Patel, C.; Sinclair, W.; Timmins, P.; Yin, S. Amorphous Drug−PVP Dispersions: Application of Theoretical, Thermal and Spectroscopic Analytical Techniques to the Study of a Molecule with Intermolecular Bonds in both the Crystalline and Pure Amorphous State. *J. Pharm. Sci.* **2009**, *98*, 3456−3468.
(38) Sibik, J.; Löbmann, K.; Rades, T.; Zeitler, J. A. Predicting Crystallization of Amorphous Drugs with Terahertz Spectroscopy. *Mol. Pharmaceutics* **2015**, *12*, 3062−8.
(39) Vyazovkin, S.; Dranca, I. Probing β-relaxation in Pharmaceutically Relevant Glasses by Using DSC. *Pharm. Res.* **2006**, *23*, 422−428.
(40) Löbmann, K.; Laitinen, R.; Grohganz, H.; Strachan, C.; Rades, T.; Gordon, K. C. A Theoretical and Spectroscopic Study of Co-Amorphous Naproxen and Indomethacin. *Int. J. Pharm.* **2013**, *453*, 80−87.
(41) Seefeldt, K.; Miller, J.; Alvarez-Nunez, F.; Rodriguez-Hornedo, N. Crystallization Pathways and Kinetics of Carbamazepine-Nicotinamide Cocrystals from the Amorphous State by In Situ Thermomicroscopy, Spectroscopy, And Calorimetry Studies. *J. Pharm. Sci.* **2007**, *96*, 1147−58.
(42) Chieng, N.; Aaltonen, J.; Saville, D.; Rades, T. Physical Characterization and Stability of Amorphous Indomethacin and Ranitidine Hydrochloride Binary Systems Prepared by Mechanical Activation. *Eur. J. Pharm. Biopharm.* **2009**, *71*, 47−54.

DOI: 10.1021/acs.molpharmaceut.8b00650
Mol. Pharmaceutics 2018, 15, 4247−4256