Dielectric studies of molecular motions in glassy and liquid nicotine

Dielectric studies of molecular motions in glassy and liquid nicotine

K Kamiński[1], M Paluch[1], J Ziolo[1] and K L Ngai[2]

[1] Institute of Physics, Silesian University, ulica Uniwersytecka 4, 40-007 Katowice, Poland
[2] Naval Research Laboratory, Washington DC 20375-5320, USA

Abstract
The dielectric permittivity and loss spectra of glassy and liquid states of nicotine have been measured over the frequency range 10^{-2}–10^9 Hz. The relaxation spectra are similar to common small molecular glass-forming substances, showing the structural α-relaxation and its precursor, the Johari–Goldstein β-relaxation. The α-relaxation is well described by the Fourier transform of the Kohlrausch–Williams–Watts stretched exponential function with an approximately constant stretch exponent that is equal to 0.70 as the glass transition temperature is approached. The dielectric α-relaxation time measured over 11 orders of magnitude cannot be described by a single Vogel–Fulcher–Tamman–Hesse equation. The most probable Johari–Goldstein β-relaxation time determined from the dielectric spectra is in good agreement with the primitive relaxation time of the coupling model calculated from parameters of the structural α-relaxation. The shape of the dielectric spectra of nicotine is compared with that of other glass-formers having about the same stretch exponent, and they are shown to be nearly isomorphic. The results indicate that the molecular dynamics of nicotine conform to the general pattern found in other glass-formers, and the presence of the universal Johari–Goldstein secondary relaxation, which plays a role in the crystallization of amorphous pharmaceuticals.

1. Introduction

Nicotine is a tertiary amine composed of a pyridine and a pyrrolidine ring. It is classified as a drug and should be of interest to researchers in pharmaceutical science. Its molecular formula and chemical name are respectively $C_{10}H_{14}N_2$ and S-3-(1-methyl-2-pyrrolidinyl) pyridine. Its structure is shown in figure 1. For researchers in physics and chemistry, it is just another small molecule substance that undergoes the liquid–glass transition when supercooled. In recent years, some researchers in pharmaceutical sciences have been interested in amorphous solid and viscous liquid pharmaceuticals as viable alternatives for the manufacture of stable drugs [1–11]. It is interesting to see if the molecular dynamic properties of supercooled
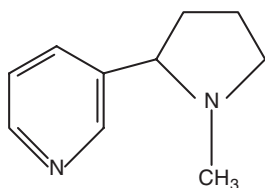
Figure 1. Molecular structure of nicotine.

pharmaceutical liquids and glasses such as nicotine are similar to those of non-pharmaceutical counterparts or not. If similar, the question that follows is to what extent their properties are similar. Nicotine can be supercooled and it is chosen as a pharmaceutical related substance for a dielectric relaxation study of molecular dynamic properties. Dielectric relaxation measurements of nicotine were made over a wide range of timescales and the data are utilized to elicit the relaxations dynamics of the glass-former. The dielectric spectra of nicotine are analysed in the same manner as conventionally done for non-pharmaceutical liquids and glasses. The molecular dynamic properties of nicotine are compared with some non-pharmaceutical liquids and glasses. Remarkable qualitative and even quantitative similarities between them are found and discussed.

2. Experimental details

The nicotine sample was purchased from Aldrich and used as received. The complex permittivity over ten decades of frequency was measured using an Alfa analyser (10^{-2}–10^7 Hz), in combination with an Agilent 4291B network analyser (10^6–10^9 Hz). In the frequency range from 10^{-2} Hz up to 10^7 Hz, the sample was placed in a parallel plate capacitor with diameter 18 mm and gap 0.15 mm. In the region 10^6–10^9 Hz the parallel plate geometry was also used but with a smaller diameter (8 mm) and a smaller gap (0.075 mm): temperature control was performed using a dry-nitrogen stream based system, thermostatted with a precision better than 0.1 K.

3. Results and discussion

Isothermal dielectric relaxation permittivity and loss spectra were measured at ambient pressure of 0.1 MPa. Shown in figure 2 are representative loss spectra (ε'' plotted as a function of the frequency ν) taken at 16 selected different temperatures above and below the vitrification temperature T_g at 227, 223, 219, 215, 211, 207, 203, 199, 195, 191, 187, 179, 171, 163, 155, and 147 K (from right to left). The glass transition temperature T_g is defined as a temperature at which the dielectric relaxation time τ_α is equal to 100 s. Its value is 181 K. The most prominent feature of the loss spectra is the peak originating from the structural α-relaxation. Figure 3 shows the fits to some of the α-loss peaks seen at temperatures above T_g by the one-sided Fourier transforms of the Kohlrausch–Williams–Watts (KWW) function [12–14],

$$\phi(t) = \exp[-(t/\tau_\alpha)^{1-n}]. \tag{1}$$

The KWW stretch exponent, $1 - n$, decreases slightly with decreasing temperature. Its values at some selected temperatures are 0.73 at 219 K (fit not shown), 0.71 at 195 and 191 K, and 0.70 at 187 K.

Although the KWW function fits the main α-loss peaks well, the data are in excess of the fit at frequencies sufficiently higher than ν_α, the α-loss peak frequency. The deviation, appearing
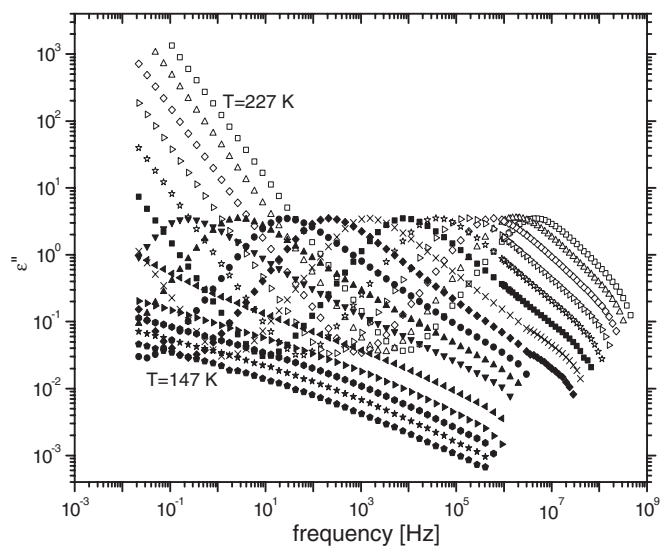
Figure 2. Frequency-dependent dielectric loss spectra of nicotine at different temperatures above and below T_g.
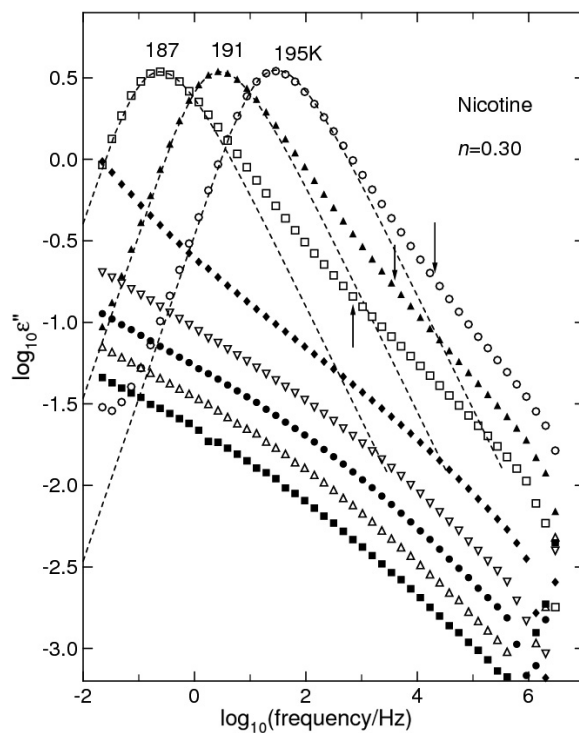
Figure 3. Representative spectra of nicotine. The dashed lines are the KWW fits with $\beta_{KWW} = 0.70$ at $T = 187$ K and 0.71 at $T = 191$ and 195 K. The vertical arrows indicate the frequencies $f_0 = (1/2\pi\tau_0)$ calculated from the CM relation at given temperatures.

like a wing on the high frequency flank of the KWW fit (see figure 3), is commonly found in many non-pharmaceutical glass-formers with values of the KWW exponent comparable to that
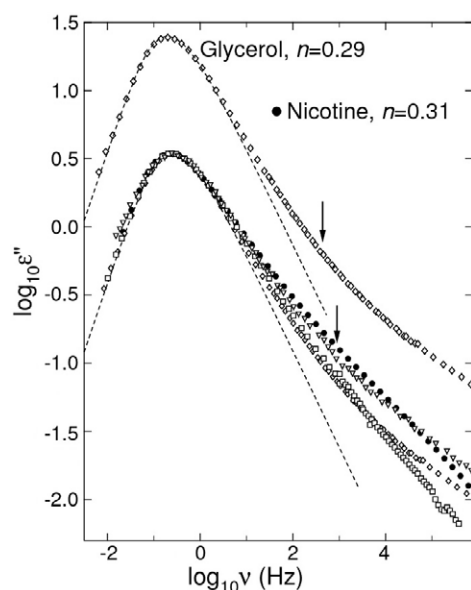
Figure 4. The comparison of the alpha dispersion of nicotine (filled circles), glycerol (open diamonds for both the original and the vertically shifted data), Aroclor (open squares) and 2-picoline (open inverted triangles). The dashed lines are the fits to the data by the one-sided Fourier transform of the KWW function. The arrows denote the locations of the calculated f_0 for nicotine and glycerol.

found for nicotine [15–21]. This general feature of the dynamics shared by nicotine is shown by comparing its $\varepsilon''(\nu)$ at 187 K in figure 4 with that of glycerol [15, 16] at 195 K, Aroclor 1242 (a chlorinated biphenol) [17] at 224 K and 2-picoline [21] at 134 K. The $\varepsilon''(\nu)$ data of the three non-pharmaceutical glass-formers have been normalized to have the same maximum loss peak height as nicotine, and small horizontal shifts all less than half a decade have been applied to bring their peak frequencies coincident with ν_α of nicotine. These non-pharmaceutical glass-formers are chosen because their loss peaks have full width at half maximum or KWW stretch exponent as that of nicotine: $(1 - n)$ is 0.71, 0.71, and 0.70 for glycerol, Aroclor 1242, and picoline respectively. It can be seen by inspection of figure 4 that the shape of the dispersion of nicotine is no different from that of the other glass-formers. The excess or 'excess wing' is contributed by modes of relaxation faster than the α-relaxation described by the KWW correlation function. Experiments including application of pressure [19, 20, 22], physical ageing [15, 16], and mixing with another glass-former [21] have shown that the excess wing is the unresolved universal Johari–Goldstein (JG) secondary relaxation [23, 24]. The JG relaxation has much weaker dielectric strength than that of the α-relaxation and it cannot be resolved when its most probable frequency ν_{JG} is not much higher than ν_α. It has been shown both empirically [14, 25] and theoretically [18–20] that, at any constant ν_α, the ratio ν_{JG}/ν_α decreases with increasing KWW exponent. This relation between ν_{JG} and ν_α was obtained theoretically by the coupling model (CM) [18–20, 26–31]. In the CM, there is a primitive relaxation which is a true precursor of the many-molecule cooperative α-relaxation. It has similar properties as the experimental JG relaxation, and hence the CM expects good correspondence between the JG relaxation time τ_{JG} and the primitive relaxation time τ_0. In the CM, there is a relation which enables τ_0 to be calculated at any temperature T and pressure P from the parameters τ_α and $(1 - n)$ of the KWW function that fits the α-relaxation. This
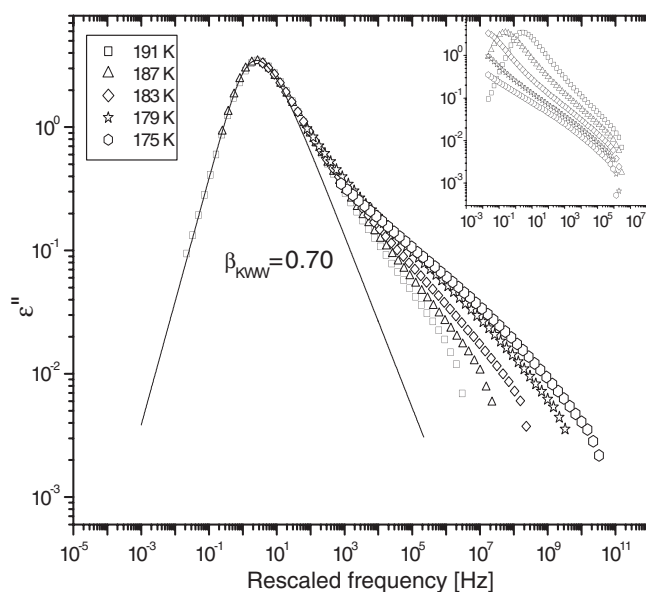
Figure 5. Superimposed dielectric loss spectra of nicotine taken at ambient pressure ($p = 0.1$ MPa) and five different temperatures. In the inset are the same spectra before superposition. Included in the figure is the KWW fit (solid line) with $\beta_{KWW} = 0.70$.

relation is given by

$$\tau_0(T, P) = t_c^n [\tau_\alpha(T, P)]^{1-n}, \qquad (2)$$

where $t_c \approx 2$ ps for molecular glass-formers [30]. The predicted correspondence between the calculated τ_0 (or $\nu_0 \equiv 1/(2\pi\tau_0)$,) and the experimental τ_{JG} (or $\nu_{JG} \equiv 1/(2\pi\tau_{JG})$,) i.e.

$$\tau_{JG}(T, P) \approx \tau_0(T, P), \qquad \nu_{JG}(T, P) \approx \nu_0(T, P) \qquad (3)$$

has been repeated verified in many glass-formers of various chemical compositions and physical structures. From equations (2) and (3) and $t_c \approx 2 \times 10^{-12}$ s, the separation between the α-relaxation frequency $\nu_\alpha \equiv 1/(2\pi\tau_\alpha)$ from ν_{JG} or ν_0 (all in Hz) on the logarithmic scale is given by

$$\log_{10}\nu_0 - \log_{10}\nu_\alpha = n(10.9 - \log_{10}\nu_\alpha) \approx \log_{10}\nu_{JG} - \log_{10}\nu_\alpha. \qquad (4)$$

This relation indicates that, for the same ν_α, the separation is smaller if n is smaller, or the KWW stretch exponent $(1 - n)$ is larger. Equation (4) also indicates that the separation between $\log_{10}\nu_{JG}$ and $\log_{10}\nu_\alpha$ increases with decreasing $\log_{10}\nu_\alpha$. This property for nicotine is demonstrated by shifting horizontally the dielectric spectra taken at several temperatures (see the inset of figure 5) to have the same peak frequency as that taken at 191 K. The result (see figure 5) clearly demonstrates that, at a lower temperature, the excess wing is further away from the α-loss peak, or the separation between $\log_{10}\nu_{JG}$ and $\log_{10}\nu_\alpha$ increases with decreasing $\log_{10}\nu_\alpha$.

The relaxation times τ_α of nicotine obtained from fitting the α-loss peak by the KWW function are shown in figure 6 in an Arrhenius plot against reciprocal temperature. From the parameters $(1 - n)$ and ν_α of nicotine obtained from the fits at 187, 191, and 195 K, the values of ν_0 were calculated and their locations are indicated by the vertical arrows in figure 3, each pointing at the isothermal spectrum for which it is calculated. In fact ν_0 is located within the excess wing. On the other hand, τ_{JG} or ν_{JG} of the unresolved JG relaxation can be deduced
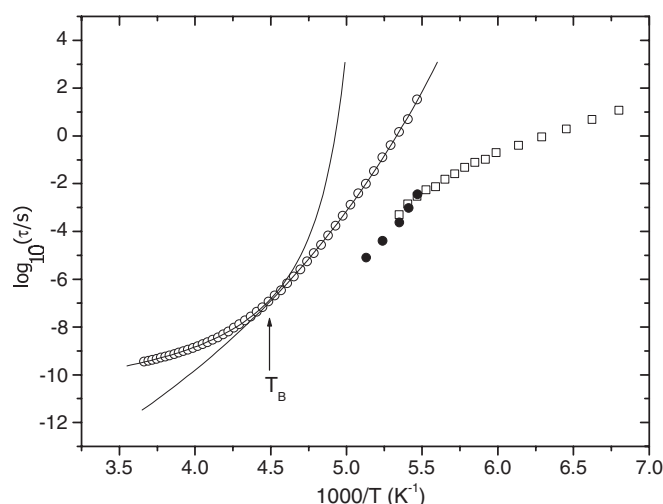
Figure 6. Relaxation map: $\log \tau$ versus $1000/T$ of the α relaxation (open circles) and JG β relaxation (open squares). Filled circles are the primitive relaxation times of the CM calculated with $n = 0.30$ at five different temperatures from the corresponding τ_α of nicotine given by the two VFTH fits (solid lines). The vertical arrow denotes the crossover temperature T_B.

operationally by fitting the dispersion by the sum of a Cole–Cole (CC) function for the JG relaxation and the Havriliak–Negami (HN) function for the α-relaxation as done in several previous works [15]:

$$\varepsilon''(\upsilon) = \mathrm{Im}\, \Delta\varepsilon_{\mathrm{HN}} \frac{1}{(1 + (\mathrm{i}2\pi f \tau_{\mathrm{HN}})^{1-\alpha_{\mathrm{HN}}})^{\gamma_{\mathrm{HN}}}} + \mathrm{Im}\, \Delta\varepsilon_{\mathrm{CC}} \frac{1}{1 + (\mathrm{i}2\pi f \tau_{\mathrm{CC}})^{1-\alpha_{\mathrm{CC}}}} \tag{5}$$

where f is the frequency in Hz, $\Delta\varepsilon_{\mathrm{HN}}$ the relaxation strength, and α_{HN} and γ_{HN} are the shape parameters.

The τ_{JG} values deduced for a number of temperatures above and below T_g are plotted in figure 6 together with the calculated τ_0 values for several temperatures. There is good correspondence between the deduced JG-relaxation frequency τ_{JG} and the calculated primitive relaxation frequency τ_0 of nicotine, as found previously in many non-pharmaceutical glass-formers that exhibit either an excess wing or a resolved JG relaxation.

Excess wings originating from unresolved JG relaxation [15, 16] as well as resolved JG relaxation [29] in non-pharmaceutical glass-formers have been found to shift to lower frequencies on physical ageing. For comparison, physical ageing experiments were performed on the excess wing found in the dielectric spectra of nicotine taken in the non-equilibrium glass state at temperature below T_g. The temperature of the sample was slowly lowered from 298 to 175 K with the cooling rate of 1 K min^{-1}. The spectra were measured at the constant temperature of 175 K in the frequency range from 10^{-2} to 10^6 Hz every 20 ks. The excess wing is observed to shift to lower frequencies on physical ageing up to 160 ks (see figure 7).

In many non-pharmaceutical glass-formers in the equilibrium liquid state, the temperature dependence of τ_α cannot be fitted by a single Vogel–Fulcher–Tamman–Hesse [32–34] (VFTH) equation [35, 36]

$$\log \tau_\alpha = \log \tau_0 + \frac{B}{T - T_0}. \tag{6}$$

A determination of the crossover temperature is obtained using the model-independent derivative function introduced by Stickel *et al* [36], which for the α-relaxation time is
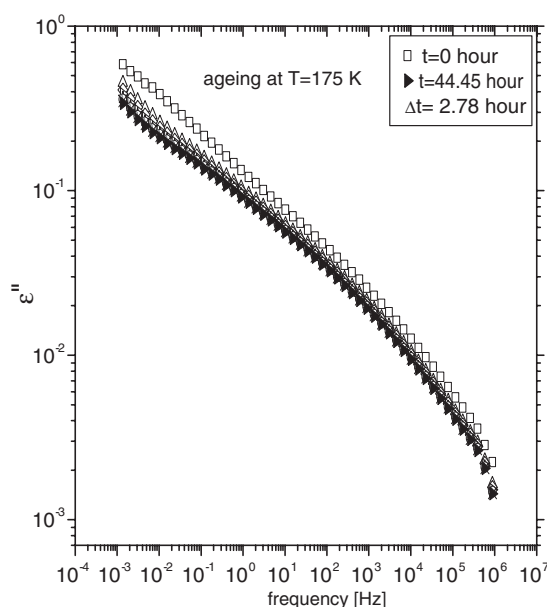
**Figure 7.** Physical ageing of nicotine at $T = 175$ K. The spectra were measured every 20 000 s.

Table 1. The parameters of the VFT equation used to fit the data of $\tau_\alpha(T)$.

Parameters	α-relaxation
VFT$_1$	
Log$_{10}\tau_{VFT}$	-11.09
D (K)	133
T_0 (K)	191
VFT$_2$	
Log$_{10}\tau_{VFT}$	-20.67
D (K)	1431
T_0 (K)	118

$\phi_T = [\mathrm{d}\log_{10}\tau_\alpha/\mathrm{d}T]^{-1/2}$. A plot of ϕ_T versus T transforms a VFTH dependence into a linear dependence on T. For nicotine, the ϕ_T calculated from τ_α (see figure 8) has two linear dependences on T, indicating two VFTH dependences are needed to fit the data in the range $-9.45 \leqslant \log_{10}\tau_\alpha \leqslant 1.51$. The values of the parameters of the two VFTH functions used to describe the whole $\tau_\alpha(T)$ dependence are collected in table 1. The crossover from one VFTH dependence to another occurs near the temperature $T_B = 223$ K. This crossover of VFTH temperature dependences of nicotine is like that found in many non-pharmaceutical glass-formers including glycerol and Aroclor [37].

The steepness or 'fragility' index, $m = \mathrm{d}\log_{10}\tau_\alpha/\mathrm{d}(T_g/T)|_{(T_g/T)=1}$ where $\tau_\alpha(T_g) = 100$ s, quantifies the rapidity of the change in τ_α as T_g is approached from above as a common means to classify glass-formers [38]. The value of steepness index of nicotine was found to be equal to 65 and is comparable with the values of other non-pharmaceutical glass-formers like glycerol ($m = 50$), Aroclor ($m = 59$) or Salol ($m = 68$). Taking into account the values of m and β_{KWW}, one can classify nicotine as an intermediate glass-forming liquid. However, these two parameters for nicotine deviate from the broad correlation between m and β_{KWW} established
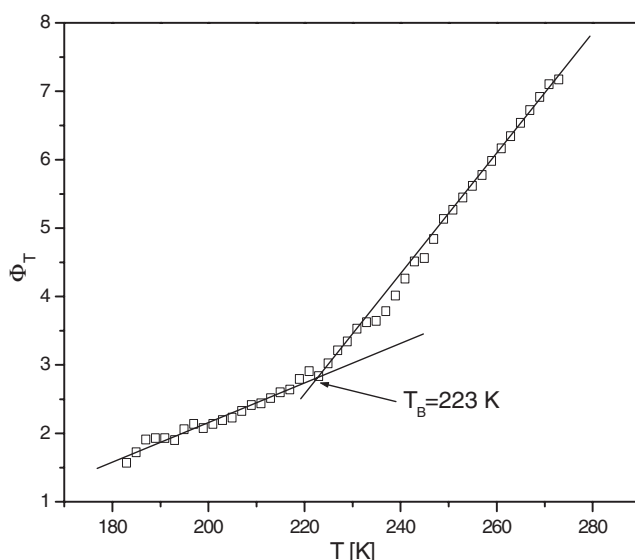
Figure 8. Derivative plot $\phi_T = [d \log_{10} \tau_\alpha / dT]^{-1/2}$ of the α relaxation times for nicotine. The intersection of the solid lines, which are linear fits to the two temperature regimes, yields the crossover temperature T_B.

when many different kinds of glass-forming liquids were considered together:

$$m = 250(\pm 30) - 320\beta_{KWW} \ (30 < m < 200). \tag{7}$$

For $m = 65$, equation (7) gives $\beta_{KWW} = 0.58$, which is much smaller than the value of $\beta_{KWW} = 0.70$ determined by fitting loss spectra of nicotine measured in the vicinity of the glass transition. Such deviation from equation (7) is not uncommon [44].

4. Conclusion

From the results shown in figures 2–8 and the analyses given, it is clear that the molecular dynamic properties of nicotine are similar in every respect to non-pharmaceutical glass-formers. The similarities include the following: (i) the frequency dispersion of the α-relaxation well described by the Kohlrausch–Williams–Watts (KWW) stretched exponential function; (ii) the temperature dependence of the α-relaxation time τ_α over 11 orders of magnitude needs two Vogel–Fulcher–Tamman–Hesse equations for its description; (iii) the presence of an excess wing or an unresolved Johari–Goldstein secondary relaxation in the dielectric spectra, which shifts to lower frequencies on physical ageing; and (iv) the good correspondence between the Johari–Goldstein relaxation time τ_{JG} and the calculated primitive relaxation time of the coupling model. For the same τ_α, the dielectric response of nicotine including the excess wing and the α-relaxation is nearly isomorphic to that of other non-pharmaceutical glass-formers that have the same stretched exponent $(1 - n)$ in the KWW function. This is further evidence that the Johari–Goldstein relaxation is the precursor of the many-molecule dynamics culminating in the KWW α-relaxation, and the entire dispersion is governed mainly by the stretched exponent $(1 - n)$ of the α-relaxation [39–41]. The Johari–Goldstein secondary relaxation present is instrumental in causing crystallization of amorphous pharmaceuticals [42, 43]; its characterization in nicotine is useful for further consideration in other amorphous pharmaceuticals.

Acknowledgments

References

[1] Hancock B C and Zografi G 1997 *J. Pharm. Sci.* **86** 1
[2] Hancock B C, Shamblin S L and Zografi G 1995 *Pharm. Res.* **12** 799
[3] Yu L 2001 *Adv. Drug. Deliv. Rev.* **48** 27
[4] Craig D Q M, Royall P G, Kett V L and Hopton M L 1999 *Int. J. Pharm.* **179** 179
[5] Shamblin S L, Tang X, Chang L, Hancock B and Pikal M 1999 *J. Phys. Chem.* B **103** 4113
[6] Alie J, Menegotto J, Cardon P, Duplaa H, Caron A, Lacabanne C and Bauer M 2004 *J. Pharm. Sci.* **93** 218
[7] Boutonnet-Fagegaltier N, Menegotto J, Lamure A, Duplaa H, Caron A, Lacabanne C and Bauer M 2002 *J. Pharm. Sci.* **91** 1548
[8] Duddu S P and Weller K 1996 *J. Pharm. Sci.* **85** 345
[9] Craig D 1995 *Dielectric Analysis of Pharmaceutical Systems* (London: Taylor and Francis)
[10] He R and Craig D 2001 *J. Pharm. Pharmacol.* **53** 41
[11] Kaushal A M, Gupta P and Bansal A K 2004 *Crit. Rev. Ther. Drug. Carrier Syst.* **21** 133
[12] Kohlrausch R 1854 *Pog. Ann. Phys. Chem.* **91** 179
[13] Williams G and Watts D C 1970 *Trans. Faraday Soc.* **66** 80
[14] Ngai K L 2000 *J. Non-Cryst. Solids* **275** 7
[15] Schneider U, Brand R, Lunkenheimer P and Loidl A 2000 *Phys. Rev. Lett.* **84** 5560
[16] Ngai K L, Lunkenheimer P, Leon C, Schneider U, Brand R and Loidl A 2000 *J. Chem. Phys.* **115** 1405
[17] Roland C M, Casalini R and Paluch M 2003 *Chem. Phys. Lett.* **367** 259
[18] Ngai K L 2003 *J. Phys.: Condens. Matter* **15** S1107
[19] Ngai K L and Paluch M 2004 *J. Chem. Phys.* **120** 857
[20] Casalini R and Roland C M 2004 *Phys. Rev.* B **69** 094202
[21] Blochowicz T 2003 *Broadband Dielectric Spectroscopy in Neat and Binary Molecular Glass Formers* (Berlin: Logos)
[22] Hensel-Bielówka S, Paluch M and Ngai K L 2005 *J. Chem. Phys.* **123** 014502
[23] Johari G P and Goldstein M 1970 *J. Chem. Phys.* **53** 2372
[24] Johari G P 2002 *J. Non-Cryst. Solids* **313** 307
[25] Ngai K L 1998 *Phys. Rev.* E **57** 7346
[26] Ngai K L 1979 *Comments Solid State Phys.* **9** 127
[27] Ngai K L and Rendell R W 1991 *J. Non-Cryst. Solids* **233** 131
[28] Tsang K Y and Ngai K L 1997 *Phys. Rev.* E **54** 3067
[29] Ngai K L and Tsang K Y 1999 *Phys. Rev.* E **60** 4511
[30] Ngai K L and Rendell R W 1997 *Supercooled Liquids, Advances and Novel Applications* (*ACS Symp. Series* vol 676) ed J T Fourkas, D Kivelson, U Mohanty and K Nelson (Washington, DC: American Chemical Society) chapter 4, p 45
[31] Prevosto D, Capaciolli S, Lucchesi M, Rolla P A and Ngai K L 2004 *J. Chem. Phys.* **120** 4808
[32] Vogel H 1921 *Z. Phys.* **22** 645
[33] Fulcher G S 1925 *J. Am. Ceram. Soc.* **8** 339
[34] Tamman G and Hesse W 1926 *Z. Anorg. Allg. Chem.* **156** 245
[35] Ngai K L, Magill J H and Plazek D J 2000 *J. Chem. Phys.* **112** 1887
[36] Stickel F, Fischer E W and Richert R 1995 *J. Chem. Phys.* **102** 6251
[37] Casalini R, Paluch M, Fontanella J J and Roland C M 2002 *J. Chem. Phys.* **117** 4901
[38] Böhmer R, Ngai K L, Angell C A and Plazek D J 1993 *J. Chem. Phys.* **99** 4201
[39] Ngai K L 2004 *3rd Int. Symp. on Slow Dynamics in Complex Systems (Sendai, Japan, Nov. 2003)* (*AIP Conf. Proc.* vol 708) ed M Tokuyama and I Oppenheim (New York: AIP) p 515
[40] Cavaille J Y, Perez J and Johari G P 1989 *Phys. Rev.* B **39** 2411
[41] Ngai K L, Casalini R, Capaciolli S, Paluch M and Roland C M 2005 *J. Phys. Chem.* B **109** 17356
[42] Johari G P, Kim S and Shanker R M 2005 *J. Pharm. Sci.* **94** 2207
[43] Tombari E, Presto S, Johari G P and Shanker R M 2005 *J. Pharm. Sci.* at press
[44] Ngai K L, Kaminska E, Sekula M and Paluch M 2005 *J. Chem. Phys.* **123** 204507